

A clinical and sonographic investigation of the first
metatarsophalangeal joint in gout and asymptomatic
hyperuricaemia: A comparison with normouricaemic individuals

Sarah Stewart

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Abstract

Background: Although hyperuricaemia is required for the development of symptomatic gout, many individuals with hyperuricaemia remain asymptomatic. However, ultrasonography has identified urate deposition in people with asymptomatic hyperuricaemia. Urate crystal deposition and gout-related features have a certain propensity for the first metatarsophalangeal joint (1MTP). Despite the importance of normal structure and function of the 1MTP, it is unclear how this joint is impaired in people with gout and asymptomatic hyperuricaemia and whether this relates to underlying sonographic pathology. This thesis aimed to (i) identify clinical characteristics and (ii) sonographic features of the 1MTP in participants with gout and participants with asymptomatic hyperuricaemia; and (iii) determine the association between clinical and sonographic characteristics of the 1MTP while accounting for the diagnostic group.

Methods: This two-arm cross-sectional study involved participants with gout ($n = 23$), asymptomatic hyperuricaemia ($n = 29$), and age- and sex-matched normouricaemic controls ($n = 34$) without acute arthritis at the time of assessment. Clinically assessed characteristics included patient-reported outcomes related to foot and lower limb pain, disability and impairment; 1MTP structural and functional characteristics including joint range of motion (ROM), muscle force, hallux valgus severity and foot posture; neurovascular characteristics including temperature, vibration perception and protective sensation; and dynamic outcomes including spatiotemporal gait characteristics and barefoot plantar pressure measurements. Ultrasonography was used to assess 1MTPs for the double contour sign, tophus, erosion, effusion, synovial hypertrophy, snowstorm, synovitis and cartilage thickness.

Results: All participants were middle-aged men. Compared to controls, participants with gout reported greater 1MTP pain ($P = 0.014$), greater foot pain and disability (MFPGDI) ($P < 0.001$), decreased lower limb function for daily living ($P = 0.002$) and recreational ($P < 0.001$) activities, increased activity limitation ($P = 0.002$), reduced ROM ($P < 0.001$), reduced plantarflexion force ($P = 0.012$), increased 1MTP temperature ($P < 0.05$), more loss of protective sensation (OR 15.6, $P = 0.21$) and more severe hallux valgus (OR 0.3 $P = 0.041$). Compared to controls, participants with asymptomatic hyperuricaemia had more disabling foot pain (OR 4.2, $P = 0.013$), increased activity limitation ($P = 0.033$), decreased lower limb function for daily living ($P = 0.026$) and recreational ($P = 0.010$) activities, increased 1MTP plantarflexion force ($P = 0.004$) and a more pronated foot posture ($P = 0.036$). Compared to controls, participants with gout demonstrated increased step time ($P = 0.022$) and stance time ($P = 0.022$), and reduced velocity ($P = 0.050$). Participants with gout also walked with decreased peak pressure at the heel ($P = 0.012$) and

hallux ($P = 0.036$) and increased peak pressure ($P < 0.001$) and pressure time integrals ($P = 0.005$) at the midfoot. Compared to controls, participants with asymptomatic hyperuricaemia demonstrated increased support base ($P = 0.002$), double support time ($P < 0.001$) and cadence ($P = 0.028$), and reduced swing time ($P = 0.019$) and single support time ($P = 0.020$), as well as increased pressure at the midfoot ($P = 0.013$), first metatarsal ($P = 0.015$) and second metatarsal ($P = 0.007$). Compared to controls, participants with gout and asymptomatic hyperuricaemia had more double contour sign (odds ratio [OR] 3.91, $P = 0.011$ and OR 3.81, $P = 0.009$, respectively). Participants with gout also had more erosion (OR 10.13, $P = 0.001$) and synovitis (OR 9.00, $P < 0.001$) and had greater tophus and erosion diameters ($P = 0.035$ and $P < 0.001$, respectively). The double contour sign was associated with higher MFPDI scores ($P < 0.001$). Tophus was associated with higher MFPDI scores ($P < 0.001$), increased temperature ($P = 0.005$) and reduced walking velocity ($P = 0.001$).

Conclusions: This study has shown that urate deposition, synovitis and bone erosion are common at the 1MTP in participants with gout, even in the absence of acute arthritis. Participants with gout also demonstrated 1MTP-specific changes indicative of subclinical inflammation. Although individuals with asymptomatic hyperuricaemia lack ultrasound features of inflammation or bone changes, they demonstrate a similar frequency of urate deposition. They also report high levels of foot- and lower limb-related pain and disability. Sonographic features of urate deposition, rather than soft tissue inflammation or erosion, are associated with patient-reported foot pain and disability, while the presence of tophus is associated with impaired functional characteristics.

Table of contents

Abstract	2
List of tables.....	10
List of figures	12
Attestation of authorship	13
PhD research outputs.....	14
Peer-reviewed publications	14
Refereed conference proceedings.....	14
Acknowledgements.....	16
Chapter one: An introduction to gout and hyperuricaemia	18
1.1 Introduction	18
1.2 History.....	18
1.3 Epidemiology.....	19
1.3.1 Prevalence and incidence of gout and hyperuricaemia	19
1.3.2 Risk factors.....	20
1.3.2.1 Genetic factors.....	20
1.3.2.2 Dietary factors.....	20
1.3.2.3 Comorbidities.....	21
1.3.2.4 Medications	22
1.4 Pathophysiology.....	22
1.5 Microscopy.....	25
1.6 Classification of gout.....	26
1.7 Clinical staging.....	28
1.8 Clinical features of gout	29
1.8.1 Acute gouty arthritis	29
1.8.2 Chronic gouty arthropathy and tophaceous gout	31
1.9 The burden of gout	32
1.10 Management.....	34
1.10.1 Asymptomatic hyperuricaemia.....	34
1.10.2 Acute gouty arthritis	35
1.10.2.1 Pharmacological.....	35
1.10.2.2 Non-pharmacological.....	37
1.10.3 Long-term management of gout.....	37

1.10.3.1 Pharmacological therapy	37
1.10.3.2 Patient and practitioner education.....	39
1.10.3.3 Diet and lifestyle changes	40
1.11 Conclusion	40
Chapter two: Gout in the foot and ankle	41
2.1 Introduction	41
2.2 Joint and tendon involvement	41
2.3 Foot-related pain, disability and impairment	42
2.4 Functional and structural characteristics.....	43
2.5 Non-pharmacological management of the foot in gout.....	44
2.5.1 Footwear	44
2.5.2 Podiatric palliative care	45
2.6 Conclusion.....	45
Chapter three: The first metatarsophalangeal joint in gout: A systematic review and meta-analysis	47
3.1 Introduction	47
3.1.1 First metatarsophalangeal joint anatomy.....	47
3.1.2 The role of the first metatarsophalangeal joint during gait	48
3.1.3 Why does gout target the first metatarsophalangeal joint?	49
3.1.3.1 Temperature	49
3.1.3.2 Physical trauma	49
3.1.3.3 Biomechanical loading	50
3.1.3.4 Osteoarthritis	50
3.2 Aims.....	51
3.3 Methods.....	51
3.3.1 Search strategy	51
3.3.2 Selection criteria	52
3.3.3 Data extraction	53
3.3.4 Statistical analysis	53
3.4 Results.....	53
3.4.1 Description of studies	53
3.4.2 Epidemiology	65
3.4.3 Clinical characteristics.....	66
3.4.4 Structural characteristics	67
3.4.5 Functional characteristics	67

3.4.6 Microscopy.....	68
3.4.7 Imaging Features.....	68
3.4.7.1 Urate crystal deposition.....	68
3.4.7.2 Tophi	69
3.4.7.3 Bone disease	69
3.4.7.4 Synovial disease	70
3.5 Discussion.....	70
3.6 Conclusion.....	73
Chapter four: Imaging in gout and asymptomatic hyperuricaemia	74
4.1 Introduction	74
4.2 Conventional radiography.....	74
4.3 Conventional computed tomography.....	75
4.4 Dual-energy computed tomography.....	76
4.5 Magnetic resonance imaging.....	78
4.6 Ultrasonography	79
4.6.1 Image acquisition and interpretation	79
4.6.2 Sonographic features in gout.....	80
4.6.2.1 Synovial inflammation	80
4.6.3.2 Articular cartilage.....	82
4.6.3.3 Tophi	83
4.6.3.4 Bone	84
4.6.5 Diagnostic value	85
4.6.6 Monitoring value.....	86
4.6.7 Ultrasonography: A summary	87
4.7 Conclusion.....	87
Chapter five: Aims and hypotheses	89
5.1 Aims.....	89
5.2 Hypotheses	89
Chapter six: Methods	91
6.1 Introduction	91
6.2 Study design	91
6.3 Participants	91
6.3.1 Sample size calculation	91
6.3.2 Diagnostic group definitions	92
6.3.3 Inclusion and exclusion criteria.....	92

6.3.4 Ethical considerations	93
6.3.5 Recruitment	93
6.4 Procedure.....	94
6.4.1 Serum urate testing	94
6.4.2 Demographic and medical history	94
6.4.3 Clinical assessment	95
6.4.3.1 Equipment and procedure	95
6.4.3.2 Outcome measures	96
6.4.4 Sonographic assessment.....	108
6.4.4.1 Equipment and procedure	108
6.4.4.2 Outcome measures	109
6.5 Data analysis	112
6.5.1 Descriptive statistics	112
6.5.2 Reliability analyses	112
6.5.2.1 Intra-rater reliability.....	112
6.5.2.2 Inter-rater reliability	113
6.5.3 Inferential statistics.....	113
6.5.3.1 Participant characteristics.....	113
6.5.3.2 Data normality	114
6.5.3.3 Model selection.....	114
6.5.3.4 Aim I: Clinically assessed characteristics.....	114
6.5.3.5 Aim II: Sonographic features.....	115
6.5.3.6 Aim III: Associations between sonographic features and clinically assessed characteristics	116
6.5.3.7 Rationale for mixed-models analysis approach	117
6.5.3.8 Missing data	117
6.5.3.9 Significance levels	118
6.5.3.10 Software	118
Chapter seven: Aim I results: Clinically assessed characteristics of the 1MTP in participants with gout and asymptomatic hyperuricaemia	119
7.1 Introduction	119
7.2 Participants	119
7.2.1 Diagnostic groups.....	119
7.2.2 Participant characteristics	120
7.3 Clinically assessed characteristics	122
7.3.1 Intra-rater reliability.....	122

7.3.2 Descriptive statistics	123
7.3.4 Inferential statistics.....	125
7.3.4.1 Normality	125
7.3.4.2 Covariates	125
7.3.4.3 Patient-reported outcomes	126
7.3.4.4 Structural and functional outcomes	128
7.3.4.5 Neurovascular outcomes	129
7.3.4.6 Dynamic/gait outcomes.....	129
Chapter eight: Aim II results: Sonographic features of the 1MTP in participants with gout and asymptomatic hyperuricaemia	133
8.1 Introduction	133
8.2 Inter-rater reliability	133
8.3 Descriptive statistics	134
8.4 Inferential Statistics	141
8.4.1 Normality	141
8.4.2 Covariates	141
8.4.3 Presence of each sonographic feature	141
8.4.4 Grading of sonographic features	142
8.4.5 Tophus and erosion size and cartilage thickness.....	143
Chapter nine: Aim III results: Associations between the clinically assessed characteristics and sonographic features of the 1MTP	144
9.1 Introduction	144
9.2 Associations between the double contour sign and 1MTP clinical characteristics	144
9.3 Associations between sonographic tophus and 1MTP clinical characteristics	145
9.4 Associations between sonographic erosion and 1MTP clinical characteristics	145
9.5 Associations between sonographic synovitis and 1MTP clinical characteristics	146
Chapter ten: Discussion.....	147
10.1 Introduction	147
10.2 Participant characteristics.....	147
10.3 Aim I: Clinically assessed characteristics of the 1MTP	148
10.3.1 Patient-reported outcome measures	148
10.3.2 Structural and functional characteristics	149
10.3.3 Neurovascular characteristics.....	151
10.3.4 Dynamic outcome characteristics.....	152
10.3.5 Summary	154
10.4 Aim II: Sonographic features of the 1MTP	155

10.5 Aim III: Association between sonographic features and clinically assessed characteristics	158
10.6 Strengths and limitations	160
10.7 Clinical implications	162
10.8 Future directions.....	163
Chapter eleven: Conclusion	165
References	167
Appendices	200
Appendix 1. The impact of gout on the foot: a review	200
Appendix 2. Permission to include published article.....	208
Appendix 3. The first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a systematic review and meta-analysis	211
Appendix 4. AUTEK ethical approval.....	226
Appendix 5. Participant information sheet.....	227
Appendix 6. Participant consent form	230
Appendix 7. Clinical Report Form	231
Appendix 8. Ultrasound assessment form	237
Appendix 9. Characteristics of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a cross-sectional observational study.....	238
Appendix 10. Spatiotemporal gait parameters and plantar pressure distribution during barefoot walking in people with gout and asymptomatic hyperuricemia: comparison with healthy individuals with normal serum urate concentrations.....	246
Appendix 11. Ultrasound features of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: comparison with normouricaemic individuals	255

List of tables

Table 1.1 American College of Rheumatology (ACR) preliminary criteria for the classification of the acute arthritis of primary gout 1977	27
Table 3.1 Search terms	52
Table 3.2 Details of studies included in review	56
Table 6.1: Definitions of temporal and spatial gait parameters.....	106
Table 7.1. Demographic characteristics	120
Table 7.2. Medical, laboratory and clinical characteristics	121
Table 7.3. Gout disease characteristics	121
Table 7.4. Intra-rater reliability for rom and muscle force in.....	122
Table 7.5. Intra-rater reliability for gait parameters in	122
Table 7.6. Descriptive statistics for patient-reported outcomes.....	123
Table 7.7. Descriptive statistics for structural and functional outcomes	123
Table 7.8. Descriptive statistics for neurovascular outcomes	124
Table 7.9. Descriptive statistics for gait parameters	124
Table 7.10. Descriptive statistics for peak plantar pressure (kPa)	124
Table 7.11. Descriptive statistics for pressure time integral (kPa*sec).....	125
Table 7.12. Inferential analysis of patient-reported outcomes.....	127
Table 7.13. Inferential analysis of structural and functional outcomes	128
Table 7.14. Inferential analysis of neurovascular outcomes	129
Table 7.15. Peak plantar pressure (kPa).....	130
Table 7.16. Pressure time integrals (kPa*s).....	131
Table 7.17. Spatial and temporal gait parameters	132
Table 8.1. Inter-rater reliability for the presence of sonographic features at the 1MTP.....	133
Table 8.2. Inter-rater reliability for the grading, size and thickness of sonographic features at the 1MTP.....	134
Table 8.3. Descriptive statistics for sonographic features at the dorsal 1MTP	135
Table 8.4. Descriptive statistics for sonographic features at the medial 1MTP	136
Table 8.5. Descriptive statistics for sonographic features at the plantar 1MTP	137
Table 8.6. Descriptive statistics for sonographic features at the 1MTP.....	138
Table 8.7. Odds ratios for the presence of sonographic features at the 1MTP	142
Table 8.8. Odds ratios for grading of sonographic features at the 1MTP	142
Table 8.9. Linear regression for size and thickness of sonographic features at the 1MTP	143

Table 9.1. Association between clinical characteristics and presence of the double contour sign	144
Table 9.2. Association between clinical characteristics and presence of tophus	145
Table 9.3. Association between clinical characteristics and presence of erosion.....	145
Table 9.4. Association between clinical characteristics and presence of synovitis.....	146

List of figures

Figure 1.1: Pathophysiology of gout.....	23
Figure 1.2 Staging of hyperuricaemia and gout according to Dalbeth et al [110].....	28
Figure 1.3 Acute gouty arthritis of the right 1MTP showing localised erythema and swelling (original image)	30
Figure 1.4 Examples of chronic tophaceous gout: (a) multiple tophi within finger joints; (b) intra-tendinous tophus within Achilles tendon; (c) intra-dermal tophus at lateral heel; and (d) intra-bursal tophus within the olecranon bursa. (Original images).....	32
Figure 3.1 First metatarsophalangeal joint anatomy - plantar view (original image)	48
Figure 3.2 PRISMA flow chart of included studies.....	54
Figure 3.3 Forest plot of pooled prevalence of acute 1MTP arthritis in gout	66
Figure 6.2 Goniometer measurement of 1MTP dorsiflexion.....	99
Figure 6.3 Muscle force testing for plantarflexion strength (a) and dorsiflexion strength (b)	100
Figure 6.4 Manchester Scale for hallux valgus grading. Image from Garrow et al 2001 [484].	101
Figure 6.5 Temperature measurements of dorsal (a), medial (b), and plantar (c) aspects of the first metatarsophalangeal joint	102
Figure 6.6 Biothesiometer probe placement.....	103
Figure 6.7 Application of 10g Semmes-Weinstein monofilament.....	104
Figure 6.8 GAITRite walkway system	105
Figure 6.9 TekScan MatScan® platform (a), and masking of the seven plantar regions (b).....	107
Figure 6.1 Sonographic assessment of A) the plantar aspect, and B) the dorsal aspect of the 1MTP in the longitudinal plane.....	108
Figure 7.1 Flow chart of participants	119
Figure 7.2 Box plots of random effects associated to each diagnostic group showing no marked difference between ethnicities	126
Figure 8.1 Sonographic examples of the double contour sign on the dorsal first metatarsal head (a); tophus at the dorsal aspect of the 1mtp (b, c); tophus and erosion at medial first metatarsal head (d); effusion (e); and effusion with focal synovial hypertrophy (f).	139
Figure 8.2 Sonographic examples of mild synovial hypertrophy (a); severe synovial hypertrophy (b, c); erosion and synovitis at the medial first metatarsal head (d); synovial hypertrophy with synovitis (e); and measurement of cartilage thickness at the dorsal first metatarsal head (f).	140

Attestation of authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

A handwritten signature in black ink, appearing to read 'Sarah Stewart', with a stylized, flowing script.

Sarah Stewart

4th November 2016

PhD research outputs

Peer-reviewed publications

Stewart, S., Dalbeth, N., Vandal, A. C., Rome, K. (2015). Characteristics of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a cross-sectional observational study. *Journal of Foot and Ankle Research* 8:41 doi: 10.1186/s13047-0150091-8

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"The patient goes to bed and sleeps quietly until about two in the morning when he is awakened by a pain which usually seizes the great toe The pain resembles that of a dislocated bone ... and this is immediately succeeded by a chillness, shivering and a slight fever ... the pain ..., which is mild in the beginning, grows gradually more violent every hour ... so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein".

- Thomas Sydenham (1683) [1]

Chapter one: An introduction to gout and hyperuricaemia

1.1 Introduction

Gout is a painful rheumatic disease resulting from abnormally high levels of urate in the blood, termed hyperuricaemia, and deposition of monosodium urate (MSU) crystals within musculoskeletal structures. It has a particular propensity to affect peripheral structures of the lower limbs. This chapter reviews the history and current epidemiology of the disease before describing the pathophysiology, clinical staging and characteristics. Current management recommendations for individuals with gout and asymptomatic hyperuricaemia are also reviewed.

1.2 History

Gout is one of the oldest recognised diseases and was first documented as a painful condition affecting the great toe by Egyptians in 2640 BC [2, 3]. Hippocrates described this 'unwalkable disease' in the 5th century BC, which he referred to as podagra (from *pous* meaning foot and *agra* meaning prey - literally a 'foot-trap') [2]. Hippocrates also recognised the link between gout and the intemperate lifestyle dominated by rich foods and excessive alcohol. This led to the popular notion of gout as an affliction of the privileged, or 'the disease of kings' [3]. In some eras gout was even considered as desirable [2, 4]. The word gout was first used in the medieval period and was derived from the Latin word *gutta*, meaning 'drop', which referred to the prevailing belief that gout resulted from an imbalance of the four main bodily humours in which one of the humours would drop or accumulate in joints as a result of an overindulgent lifestyle [5].

It was not until 1776 that the chemical identity of uric acid was first established by a chemist, Karl Scheele [6]. This led to the discovery of hyperuricaemia (abnormally high serum urate) as the root cause of gouty arthritis by Sir Alfred Garrod in 1848 [7]. In 1961 McCarty and Hollander initiated the use of polarising light microscopy to examine joint fluid for MSU crystals [8] and the roles of excessive urate production and impaired excretion in the pathogenesis of hyperuricaemia were described [9]. By the end of the 20th century, gouty arthritis could be successfully managed through pharmacological interventions used in combination with lifestyle and dietary changes, which addressed these root causes of hyperuricaemia.

1.3 Epidemiology

1.3.1 Prevalence and incidence of gout and hyperuricaemia

In recent decades, the diet and lifestyle that predispose to gout and hyperuricaemia have become increasingly widespread [10, 11]. This is reflected in epidemiological studies which report an increase in the prevalence and incidence of gout and hyperuricaemia globally, including in America [12-16], Europe [17-22], Asia [23-25] and Australasia [26-28]. One in ten adults is estimated to have hyperuricaemia at least once in their lifetime [29], with the incidence of gout increasing exponentially with rising serum urate levels [21, 30-34]. A large five year epidemiological study found that men with serum urate between 0.39 and 0.47 mmol/l were 11.2 times more likely to develop gout compared to those with normal serum urate concentrations, while the odds ratio for gout development in those with hyperuricaemia > 0.56 mmol/l was 624.8 [32].

The pooled global prevalence of gout has recently been estimated at 0.6%, however, heterogeneity is high, with age, sex and continent significantly influencing gout prevalence [35]. The male to female ratio of gout is approximately 4:1 in those aged under 65 years of age, and reduces to 3:1 in adults over 65 years [36]. Although gout is uncommon in younger women, older women are at greater risk as a result of the reduction in renal clearance of uric acid following the menopause-related decline in oestrogen [37-39].

Compared to European countries, including the United Kingdom [17], Germany [17] and Italy [20], the prevalence of gout is higher in the United States [15, 40], Australia [26] and New Zealand [27]. In fact, New Zealand has one of the highest prevalence rates of gout in the world due to the increased susceptibility of Māori and Pacific Island inhabitants, who, as a result of genetic factors, are more susceptible to hyperuricaemia [41-43]. Approximately 59% of Māori and Pacific Island New Zealanders with gout report a family history of the disease [44]. Random community samples of the New Zealand population reported a prevalence of 0.3% in Europeans and 2.7% in Māori in 1958 [45], which increased to 0.9% in Europeans and 6.0% in Māori in 1966 [46]. A similarly conducted survey in 1992 reported a prevalence of 2.9% in Europeans and 6.4% in Māori [28]. More recently, a study using nationwide health system data sets determined the prevalence of gout in the entire New Zealand population in 2009 to be 2.3% in Europeans, 6.1% in Māori, and an even higher 7.63% in those of Pacific Island ethnicity [27].

1.3.2 Risk factors

Aside from the demographic risk factors of increasing age and male sex, there are several genetic, behavioural and biomedical factors that play important roles in serum urate homeostasis. The development of hyperuricaemia and gout likely result from a complex interplay between several risk factors.

1.3.2.1 Genetic factors

Genetic factors play an important role in the pathogenesis of gout through regulation of serum urate homeostasis, with one in four people with gout reporting a family history of the condition [47]. The increased prevalence of genetic variants associated with urate regulation contribute to the high level of hyperuricaemia and gout observed in some populations including Taiwanese Aborigines, Pacific people and New Zealand Māori [27, 48-50]. Most genes associated with hyperuricaemia and gout encode proteins that are involved in renal urate-transport, making the renal handling of uric acid strongly heritable [51]. Twin studies have shown high heritability for both fractional excretion of uric acid [51] and uric acid renal clearance [52]. Even single polymorphisms in urate transporter proteins can alter the structure and function of the protein resulting in a disruption to urate homeostasis [47]. Genes regulating urate transport have received significant interest in genetic research surrounding gout and hyperuricaemia [53]. A genome wide association study identified 28 genetic loci involved in renal and gut transportation of uric acid associated with hyperuricaemia [54]. Genes encoding urate transporters GLUT9 (SLC2A9) [54-59] and ABCG2 (ABCG2) [49, 54, 57] play the greatest roles in serum urate regulation and the incidence of gout [54].

1.3.2.2 Dietary factors

Dietary factors, particularly consumption of foods high in purine and excessive alcohol intake, have long been associated with the development of gout [60]. While an increased intake of meat and seafood, which are high in purines, are strongly associated with an increased risk of incident gout [11], studies have found no association between the risk of gout and intake of purine-rich vegetables, which may be related to their lower purine content and metabolic bioavailability [11, 61]. Contrastingly, a recent study found that consumption of tomatoes was positively associated with serum urate levels [62]. In fact, fructose, which is found in fruit as well as sugar-

sweetened beverages, has been associated with an increased gout risk [63, 64]. Fructose has been shown to increase serum urate through enhancing the metabolism of purine nucleotides and increasing purine synthesis [65, 66].

Alcohol consumption is perhaps the most well-known contributor to the development of gout. The ethanol component of alcohol has been shown to increase uric acid production [67, 68], while the dehydration and metabolic acidosis associated with alcohol consumption decrease urinary excretion [69]. Alcohol intake has been shown to significantly increase the risk of incident gout in both men and women [21, 60, 70]. Beer intake poses a larger risk for incident gout than spirits [21, 60], whereas moderate wine intake has no effect [60]. This difference may be explained by the higher purine content found in beer [71].

1.3.2.3 Comorbidities

People with gout often present with several comorbidities including obesity, hypertension, and renal disease. The average person with gout is reported to have four comorbidities [72], with the number related to the gout disease severity [73]. The metabolic syndrome (the co-occurrence of obesity, hypertension, dyslipidaemia, insulin resistance and hyperglycaemia) is present in 62.8% of people with gout [74]. In fact, several components of the metabolic syndrome have been shown to be independent risk factors for gout, including obesity and renal disease.

The risk of incident gout has been found to increase as body mass index (BMI) increases [20, 75] with a 28% incidence of gout in those with a BMI of greater than 25 kg/m² [20]. Hypertension has also been shown to be an independent risk factor for incident gout [21, 75-77]. In men, the risk of gout in those with hypertension was found to be twice that of those without hypertension [75]. Associations between renal disease and gout are also well recognised due to the loss of glomerular filtration and resulting promotion of hyperuricaemia [72, 75-77]. In people with a low glomerular filtration rate the risk of incident gout was 2.4 times that of those with a normal rate [77]. Despite the presence of both insulin resistance and hyperglycaemia in the metabolic syndrome, several studies have shown that the presence of diabetes reduces the risk of incident gout [78, 79]. A case-control study found that men with type two diabetes had a relative risk for incident gout of 0.67 compared to men without diabetes, independent of other risk factors [78]. It is believed that the urate lowering effect of glycosuria (renal excretion of glucose) present in diabetes, or the impaired inflammatory response may contribute to this reduced incidence of gout [80].

1.3.2.4 Medications

The use of medications has been associated with the development of gout, particularly the use of diuretics, which are used in several comorbid conditions including hypertension and renal disease [21, 33, 75, 81-83]. Men taking diuretics have been found to be 3.4 times more likely to develop gout, while women taking diuretics are 2.4 times more likely [21]. This risk increases with dosage and duration of diuretic therapy [83]. Other anti-hypertensive drugs, namely β -blockers, ACE inhibitors and angiotensin II receptor blockers (with the exception of losartan), have also found to increase the risk of incident gout by 1.5, 1.2 and 1.3 times, respectively [83]. Aspirin, particularly in low doses, also has effects on the renal handling of uric acid [84] and has been shown to increase the risk of recurrent acute gout if used in the preceding 48 hours [85].

1.4 Pathophysiology

Urate exists at a physiological pH as the ionised form of uric acid, which is the final metabolite of exogenous (dietary) and endogenous (metabolic) purine sources [86]. Humans have around ten times as much serum urate concentrations as most other mammals [87, 88] because they lack the uricase enzyme, which degrades purines to the highly soluble allantoin which can easily be removed from the body [89]. The loss of this purine metabolic pathway in humans occurred 10 to 25 million years ago as a result of several uricase gene mutations [90]. It is postulated that this reflected an evolutionary advantage at the time through compensating for vitamin C deficiency through antioxidant activity, regulating blood pressure in situations of low dietary sodium, and stimulating an immune response to injured cells [91-93]. However, today, this makes humans susceptible to abnormally high levels of urate – termed hyperuricaemia – a condition that plays an important role in the pathogenesis of gout.

Urate concentrations are dependent on a balance between dietary intake, synthesis and excretion [94]. In humans, purines in the liver produce uric acid, which enters the bloodstream. Around 70% of the uric acid produced is excreted by the kidneys while the remaining 30% is broken down by colonic bacteria in the intestines and excreted by the gastrointestinal tract [95, 96]. In 90% of people, hyperuricaemia results from inefficient excretion rather than overproduction of uric acid [95] (**Figure 1.1**).

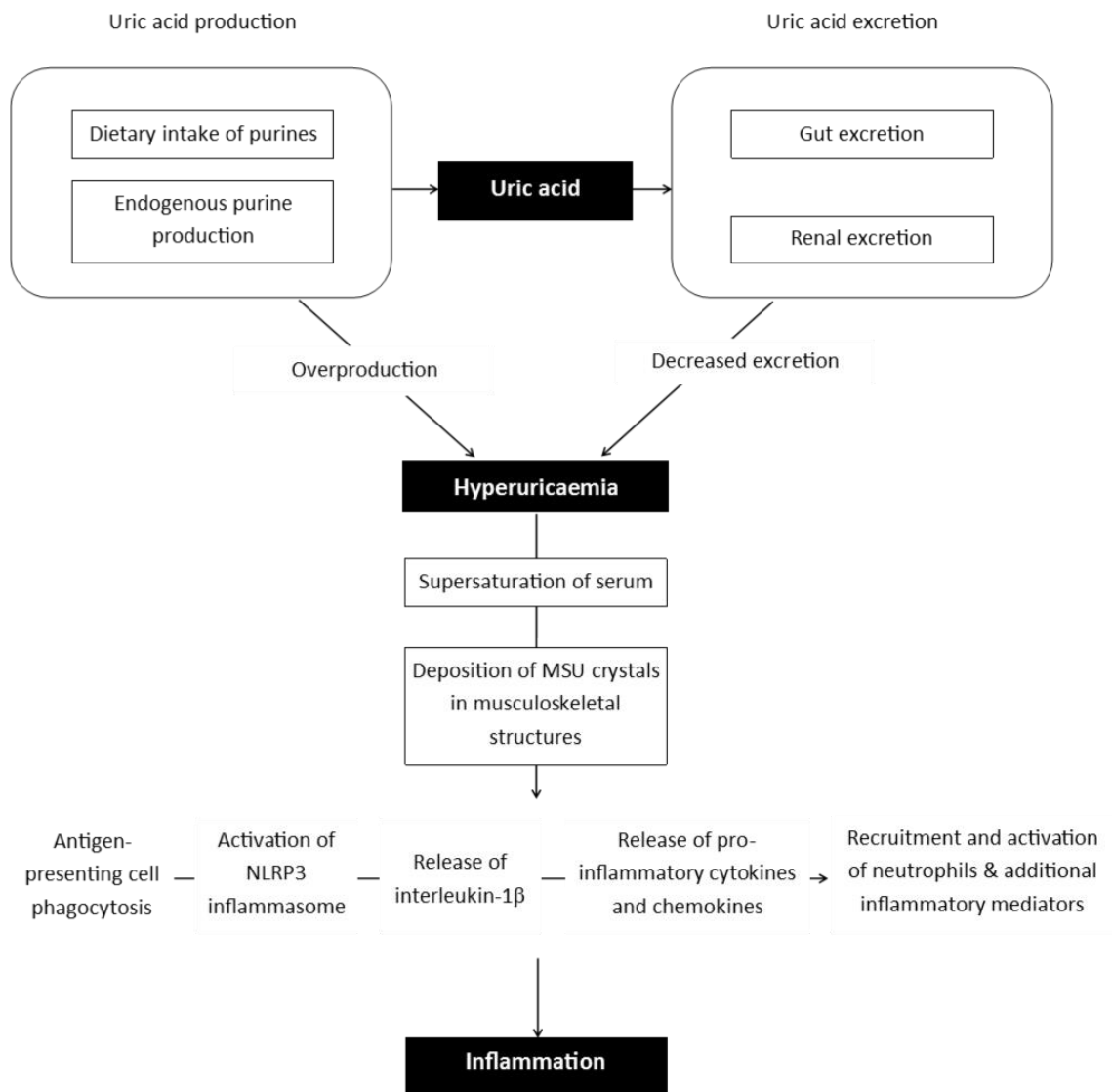


Figure 1.1: Pathophysiology of gout. Adapted from Shmerling, 2012 [97].

Due to the non-normal distribution of serum urate levels in most of the population, the physiochemical definition of hyperuricaemia is preferred, which is based on the solubility limit of urate in body fluid at 37°C as estimated by the automated enzymatic (uricase) method [98]. This corresponds to ≥ 0.41 mmol/l [99]. At this point, urate concentration exceeds its solubility, which increases the risk for supersaturation and consequent crystallisation of urate as a monosodium salt [94, 100, 101]. The nucleation and deposition of MSU crystals can occur in any musculoskeletal structure with a preference for cooler peripheral joints [98].

In the presence of synovial fluid, MSU crystals become pro-inflammatory stimuli that can initiate, intensify and sustain strong inflammatory responses [94, 102] seen clinically as acute gouty arthritis [103]. Although it is not completely clear how asymptomatic MSU crystal

deposition transitions to acute gouty arthritis, there are several recognised triggers including: excessive alcohol intake, illness, dehydration, starvation, surgery, trauma, and initiation of medications that rapidly increase or decrease serum urate levels [33, 104]. Such circumstances may facilitate the disruption of aggregated MSU crystals and the shedding of preformed crystals into the synovial fluid where they come in to contact with inflammatory cells [105]. The inflammatory response seen in acute gouty arthritis involves the phagocytosis of MSU crystals by monocytes and macrophages [106, 107]. This activates the NLRP3 inflammasome and triggers the release of interleukin-1 and other cytokines and consequently the infiltration of neutrophils [108]. As MSU crystals within cartilage and fibrous tissue are relatively protected from contact with these inflammatory mediators, it may be several years before the presence of MSU crystals results in acute arthritis [109]. Many individuals with hyperuricaemia and underlying MSU crystal deposition may remain completely asymptomatic, a condition referred to as “asymptomatic hyperuricaemia” [110].

While monocytes are involved in stimulating an acute response, differentiated macrophages have been shown to inhibit leukocyte and endothelial activation and play a central role in terminating an episode of acute arthritis [111]. However, even during these asymptomatic periods, low-grade inflammation persists due to the on-going intra-articular phagocytosis of the MSU crystals by leukocytes [112].

The persistent accumulation of MSU crystals can form masses called tophi, which histologically comprise of needle-shaped crystals surrounded by chronic mononuclear and giant cell reactions [113]. Tophi may contribute to chronic inflammation leading to persistent joint effusion and chronic swelling, which are characteristic features of chronic tophaceous gout [114]. In advanced gout, the inflammatory cells surrounding MSU crystal deposits may also promote tendon degradation [115] by directly interacting with tenocytes to reduce their viability and function [116].

Cartilage loss and bone erosion may also result from this crystal-induced inflammation [117]. MSU crystals have been shown to reduce the osteoblastic activity of bone, which is responsible for bone formation [118]. Furthermore, enhanced osteoclast development has been observed in participants with gout in close proximity to sites of crystal deposition within tophus and bone [119]. The resulting promotion of osteoclastogenesis and bone resorption further contributes to bone erosion.

1.5 Microscopy

Since the microscopic identification of MSU crystals in 1961 [8], the demonstration of MSU crystals in synovial fluid or tophus aspirates remains the definitive 'gold standard' diagnosis for gout [112, 120]. MSU crystals have been identified in samples taken from not only inflamed joints during periods of acute arthritis [121], but also from un-inflamed joints during asymptomatic periods [122, 123], and from joints that have never been subject to acute arthritis [124]. Furthermore, MSU crystals are also present in people with asymptomatic hyperuricaemia who have never experienced symptoms of gout [125, 126].

MSU crystals are best visualised under compensated polarized light microscopy [127]. Ideally samples should be examined within six hours of arthrocentesis, as the handling of samples and the reduction in number and size of the crystals with time may influence reliability of the diagnosis [128, 129]. The crystals appear as long needle-shaped rods ranging from 2 to 20 μm in length, showing strong light intensity and a negative sign of birefringence meaning the crystals appear yellow when parallel to the microscope compensator and blue when perpendicular [127, 130-132].

The reproducibility of synovial fluid analysis is performed poorly in some laboratories and there is great variability between examiners [133-135]. A false positive rate of 24% was reported in a study of 25 laboratories in which 19 identified crystals correctly [136]. Another study reported that MSU crystals were incorrectly detected in 11 out of 50 samples [135]. This may be due to the small size of the crystals or a low concentration of crystals [128], however recent centrifugation techniques are known to concentrate the crystals within the synovial fluid and increase the yield, and therefore, the accuracy of diagnosis [101].

Unfortunately, microscopy is not routinely performed in gout diagnosis with only 11% of patients undergoing aspiration in daily outpatient clinics [60, 137]. In many cases synovial fluid or tophus aspiration may not be possible [131, 132, 138, 139]. Practitioner inexperience, time constraints during clinical visits, inaccessibility or inconvenience of microscopy are amongst the reasons. Sometimes joints are inaccessible or detectable joint effusions or visible tophaceous deposits are absent. In addition, some patients may be unwilling to undergo aspiration.

1.6 Classification of gout

A reliable and accurate classification of a patient as having gout is crucial in clinical research. However, as microscopy is not always possible, clinical classification criteria are necessary. Several clinical criteria have been proposed for the classification of gout, the earliest of which were the Rome criteria in 1963 [140] and the New York criteria in 1966 [141]. Although both included important clinical features of gout, neither criteria was developed through observed prospective data. Limited validation testing has consistently demonstrated poor sensitivity for both the Rome criteria (0.64 to 0.82) and New York criteria (0.64 to 0.80) [142, 143].

In 1977 the American College of Rheumatology (ACR) published the Preliminary Criteria for the Classification of the Acute Arthritis of Primary Gout [144] (**Table 1.1**). This tool states that for a classification of gout, either aspirate proven crystals should be present or 6 of the 12 clinical criteria should be met. Unfortunately, the ACR criteria were not developed with reference to the gold standard MSU crystal identification. Limited external validity of the criteria has since been demonstrated against synovial fluid analysis with sensitivity ranging from 0.70 to 0.80 and specificity from 0.64 to 0.79 [139, 145]. The ACR criteria fails to recognise that gout is occasionally polyarticular and may involve virtually any joint including those in the upper limb, particularly in chronic stages in which the criteria are still widely used [146]. The inclusion of tophi may also influence the usefulness of this tool for the diagnosis of acute gout as less than 25% of people with gout have tophi, which do not occur until advanced stages of the disease [137]. Most importantly, the biological hallmark of gout - hyperuricaemia - may not be evident during an acute flare with as many as 42% of people with gout demonstrating normal serum urate [147-151]. It is believed that the acute inflammation present during flares influences the renal tubular response resulting in over-excretion of uric acid into the urine [148].

Table 1.1 American College of Rheumatology (ACR) preliminary criteria for the classification of the acute arthritis of primary gout 1977

- A. The presence of urate crystals in joint fluid;
and/or
- B. The presence of a tophus prove to contain urate crystals;
and/or
- C. Six of the following:
 - i. More than one attack of acute arthritis;
 - ii. Maximum inflammation developed within one day;
 - iii. Monoarthritis attack;
 - iv. Redness observed over joints;
 - v. First metatarsophalangeal joint painful or swollen;
 - vi. Unilateral first metatarsophalangeal joint attack;
 - vii. Unilateral tarsal joint attack;
 - viii. Tophus (proven or suspected);
 - ix. Hyperuricaemia;
 - x. Asymmetric swelling within a joint on x-ray;
 - xi. Subcortical cysts without erosions on x-ray;
 - xii. Joint fluid culture negative for organisms during attack.

Recent international research collaborations have resulted in the development of the 2015 ACR/EULAR Classification Criteria, which address the limitations of the 1977 ACR Criteria [152]. The first phase of this project identified items that demonstrated strong associations with the microscopic presence of urate crystals [153]. The final classification specified an entry criterion that determined which individuals the criteria could be applied to, defined as the occurrence of at least one episode of swelling, pain or tenderness in a peripheral joint or bursa. A sufficient criterion was also provided (defined as the presence of MSU crystals in synovial fluid or tophus) and if met, would classify an individual as having gout without applying the remaining criteria. The criteria itself included items relating to the pattern of joint/bursa involvement, characteristics of symptomatic episodes of acute arthritis, clinical evidence of tophi, serum urate levels, and imaging evidence of urate deposition using ultrasound, dual energy computed tomography or conventional radiography [152]. Each criterion score was assigned a weight with a maximum possible score in the final criteria of 23. A threshold score of ≥ 8 classifies an individual as having gout. This new classification criteria performed better than existing published criteria with a sensitivity of 0.92 and specificity of 0.89 [152].

1.7 Clinical staging

Traditionally, hyperuricaemia and gout have been considered under four progressive stages: asymptomatic hyperuricaemia, acute gouty arthritis, intercritical gout, and chronic gouty arthropathy [154]. However, this system fails to recognise the demonstration of MSU crystal deposition in asymptomatic individuals who have hyperuricaemia but no history or clinical evidence of gout. Furthermore, by not acknowledging the continuous deposition of MSU crystals in the asymptomatic periods between acute gouty arthritis, this staging system defines gout as a condition of recurrent flares interspersed with remissive periods, where in fact it is a chronic disease of MSU crystal deposition [110].

A new staging system has recently been proposed [110] (**Figure 1.2**). This staging system recognises the pathological phases of gout as a chronic and progressive disease of MSU deposition. *Stage A* includes those with asymptomatic hyperuricaemia but without any symptoms or evidence of MSU crystal deposition, while *Stage B* includes individuals with asymptomatic hyperuricaemia who do demonstrate MSU crystals – whether via microscopy, or advanced imaging. Individuals with MSU deposition and symptomatic gout are identified under *Stage C* if they have a history of, or are currently experiencing, an episode of acute gouty arthritis, or under *Stage D* if they demonstrate features of advanced gout including tophaceous disease or chronic arthropathy. Progression through the stages generally occurs linearly, but individuals with asymptomatic hyperuricaemia with MSU crystal deposition (*Stage B*) may also progress directly to *Stage D* without experiencing acute gouty arthritis [110].

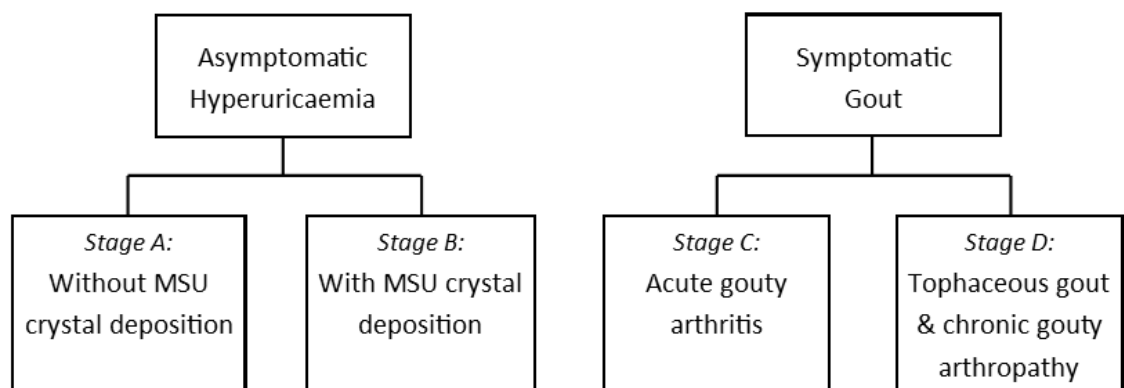


Figure 1.2 Staging of hyperuricaemia and gout according to Dalbeth et al [110]

1.8 Clinical features of gout

1.8.1 Acute gouty arthritis

Acute gouty arthritis is defined as a 'flare' or 'attack' characterised by a sudden onset of severe musculoskeletal pain as a result of acute inflammation induced by MSU crystal deposition [155]. Acute flares involve mainly synovial structures of the musculoskeletal system including joints, tendon sheaths and bursa, resulting in acute arthritis, tendonitis and bursitis [105]. Peripheral structures are most commonly involved with 83% of flares reported to occur in the lower limbs [156]. The first metatarsophalangeal joint (1MTP) is the most frequently involved structure in initial flares, followed by the midfoot, ankle and knee joints [153, 156, 157]. The olecranon bursa of the elbow is the most common structure involved in the upper limb [105], while the wrists and finger joints are often affected in older adults and those with long-standing disease duration [158-160]. Acute gouty arthritis in centrally located joints, including the hips, shoulders, and the axial skeleton is rare but may occur in people with well-established gout [161, 162]. Although 90% of initial flares are mono-articular [113, 156, 163], oligo-articular and poly-articular patterns of joint involvement may occur in the elderly, or those with long-standing and poorly-controlled hyperuricaemia [163-166].

The severe inflammatory symptoms of acute gouty arthritis may be preceded by premonitory signs known as gouty "aura" consisting of mild pain, discomfort and functional limitation [167]. However, the occurrence of flares are generally unpredictable and episodic. A recent meta-analysis examining seasonal variations in episodes of acute gouty arthritis reported that flares most frequently occur from spring, which may be attributed to the increase in physical activity, dehydration and variation in cortisol levels [168]. A large prospective study recently confirmed the historical notion that acute flares often develop during the night or early hours of the morning [169]. The authors reported the incidence of nocturnal flares were 2.4 times higher than during the day, which they attributed to diurnal variation in body temperature and serum cortisol levels as well as sleep apnoea-induced purine synthesis [169]. Due to the frequency of nocturnal flares, the rapid development of intense pain will often wake the patient from sleep [170]. The pain usually reaches its maximum in 6 to 24 hours and is associated with diffuse erythema, swelling, limited joint motion, tenderness, and warmth of the joint and peri-articular soft tissue [153, 167, 170-173] (**Figure 1.3**). During a flare, the patient is usually unable to fully weight bear or tolerate the weight of bed sheets or clothes on the affected area [174].

Although less common, systemic features of inflammation, including fever, leucocytosis and increased serum C-reactive protein levels, may occur as a reflection of the intense inflammatory reaction to MSU crystals [105, 156, 157, 164, 175]. Acute gouty arthritis is self-limiting and spontaneously resolves without treatment in one to two weeks [153, 170, 172]. As the inflammatory process begins to subside, extensive exfoliation of the skin overlying the joint may occur [86].



Figure 1.3 Acute gouty arthritis of the right 1MTP showing localised erythema and swelling (original image)

The asymptomatic phases between acute gouty arthritis generally range from a few months to several years [176]. Shorter asymptomatic periods accompanied by more frequent, prolonged and disabling flares occur in people with long-standing gout and untreated hyperuricaemia [176-179]. People with an earlier onset of gout (between the ages of 12 and 24 years) have also been shown to have shorter asymptomatic periods [180]. Some people with established gout may not experience any asymptomatic periods due to flares recurring before previous flares have completely resolved [105]. However, the majority of people with gout experience three to four flares per year with asymptomatic periods lasting several months [180]. Despite the absence of symptoms during the asymptomatic period, studies have demonstrated not only continued deposition of MSU crystals, but also a persistence of low-grade inflammation [181, 182].

1.8.2 Chronic gouty arthropathy and tophaceous gout

Chronic gouty arthropathy is characterised by the persistent clinical manifestations of inflammation accompanied by tophus formation, deformity, and joint dysfunction. The development of tophi is associated with the degree and duration of untreated hyperuricaemia [183]. In a cohort of participants with untreated gout, tophi developed in 12% of participants within 5 years and 55% after 20 years [184].

Palpable tophi, referred to as subcutaneous tophi, are often located within the synovial joint capsule, intra-dermally, or within tendons or bursa [185] (**Figure 1.4**). Tophi are frequently seen around the knees, over the olecranon process at the elbow, the Achilles tendon, and within and around the toe and finger joints - particularly over osteoarthritic Herbeden's or Bouchard's nodes [186]. They are often located in areas exposed to excessive pressure or friction [105]. Intra-dermal tophi appear as white or yellowish deposits beneath taut overlying skin [113, 187, 188]. Although rare, spinal involvement can lead to nerve compression [102, 189] and deposition in the median nerve can lead to carpal tunnel syndrome [190, 191]. Skin overlying tophi may ulcerate and extrude white, chalky material, and although rare, may become infected [165].



Figure 1.4 Examples of chronic tophaceous gout: (a) multiple tophi within finger joints; (b) intra-tendinous tophus within Achilles tendon; (c) intra-dermal tophus at lateral heel; and (d) intra-bursal tophus within the olecranon bursa. (Original images).

Although tophi are generally asymptomatic, tophaceous gout results in prominent joint damage and musculoskeletal disability [192-194]. The presence of clinically-evident tophi is highly correlated with structural joint damage as well as the presence of subclinical tophi within bone and peri-articular structures. [195, 196]. Joint limitation is an important characteristic of gouty arthropathy and may be a consequence of tophus presence within joints or surrounding ligaments and tendons, which can disrupt normal joint biomechanics [197].

1.9 The burden of gout

The substantial impact of gout on health-related quality of life (HRQoL) has been well documented in the literature [198-205]. Current research highlights not only the decreased mental wellbeing [203, 204, 206], but also the poorer physical functioning [198, 201, 203-206] components of HRQoL experienced by people with gout. HRQoL in gout appears to be a result

of a complex interplay between sociodemographic variables, comorbidities and gout-specific factors.

Poorer HRQoL has been associated with lower education, older age and the female gender [204]. Race may also play a part in the patient experience of gout including those of African American [207] and Māori and Pacific [202] ethnicities who report poorer HRQoL. The presence of comorbid conditions, including diabetes, renal disease, cardiovascular disease and obesity, have been shown to significantly reduce HRQoL in people with gout [198, 201, 203-205, 208, 209].

Gout-specific features are significantly correlated with reduced HRQoL, including more severe poly-articular joint involvement [203-205], a greater frequency of episodes of acute arthritis [203, 205, 206], a greater number of tender and swollen joints [205], and the presence of tophi [204, 206, 209, 210]. HRQoL also appears to improve during asymptomatic periods [204, 211]. The association between increased serum urate concentrations and decreased HRQoL has been demonstrated in some studies [209, 210], but not others [198, 205, 212, 213]. Furthermore, urate lowering therapy is not perceived by people with gout to improve HRQoL [192, 198]. Serum urate may have an indirect influence on HRQoL through its association with other gout-specific features including the frequency of acute arthritis and tophus presence [176, 192, 206]. It is currently unknown how asymptomatic hyperuricaemia affects HRQoL.

The high degree of physical disability experienced by people with gout is reflected in their substantial employment-related problems [214, 215]. The loss of productivity and work-related impairment results in an inability to maintain employment positions requiring strenuous activity [214-216]. Even in non-laborious occupations, the unpredictable nature of acute arthritis means people with gout take time off work [174]. Employees with gout experience significantly greater sick leave compared to employees without gout with an average of almost five more days of work lost per year [215]. A greater frequency of gout flares further contributes to this loss of work productivity [216]. Productivity loss is further pronounced in people with gout refractory to conventional therapy [205, 217, 218] who have an average annual workday loss of 25 days [218]. Many people with gout become self-employed, resign, or become reliant on sickness or unemployment benefits for financial support because they cannot meet the demands of a full time job [174].

Gout also poses a major economic burden to the healthcare systems [219-221]. Although the utilisation of primary care outpatient clinics and inpatient healthcare is largely attributable to gout [201, 218], comorbidities and sociodemographic characteristics also play a role [201, 214, 218, 222]. Functional limitations, cardiovascular disease and female gender have been reported as strong contributors to increasing healthcare costs associated with gout [214]. Disease-specific

characteristics also play a role in increased medical and pharmacy costs, including flare frequency, uncontrolled hyperuricaemia and tophi [206, 216, 220, 223].

1.10 Management

1.10.1 Asymptomatic hyperuricaemia

Despite the association between hyperuricaemia and gout there is currently an absence of data addressing the treatment of asymptomatic hyperuricaemia with either lifestyle modifications or pharmacological therapy as measures for preventing the development of acute gouty arthritis [224]. The serum urate target to prevent the progression to symptomatic gout in individuals with hyperuricaemia is also unknown [225]. Although recent guidelines do not address the use of urate lowering therapy for hyperuricaemia in the absence of symptoms, they do recommend advice regarding lifestyle modifications [226-229]. Lifestyle interventions would mirror those recommended for people with gout including dietary changes, weight loss and regular exercise [60, 75, 230]. However, further research is required to determine whether lifestyle modifications alone are sufficient to reduce the risk of gout in people with asymptomatic hyperuricaemia [225].

Decisions regarding pharmacological treatment for asymptomatic hyperuricaemia should be based on each person's individual risk of developing associated comorbidities and the potential benefits and risks of treatment. There are certain circumstances when pharmacological treatment of asymptomatic hyperuricaemia may be needed, including those with very high levels of serum urate [29], in those with excessive urinary excretion of uric acid (> 1100 mg/day), which is associated with a 50% greater risk of developing uric acid calculi [231, 232], and in those who are receiving chemotherapy or radiation therapy for cancer in which urate lowering therapy would prevent uric acid nephropathy [231].

Although pharmacological treatment is generally not recommended, due to the rare but severe side effects [233, 234], individuals identified as having asymptomatic hyperuricaemia should be treated for associated comorbidities and educated on the potential urate-elevating effects of certain medications including diuretics, β -blockers and ACE inhibitors [83, 227].

1.10.2 Acute gouty arthritis

The goal for treatment of acute gouty arthritis is to rapidly and effectively resolve pain and underlying MSU crystal-induced inflammation [227]. The current ACR guidelines recommend a combination of pharmacological and non-pharmacological treatment to achieve this [228].

1.10.2.1 Pharmacological

The initiation of pharmacological therapy within 24 hours of the onset of acute gouty arthritis is recommended to optimise patient outcomes [226, 228]. Three agents are recommended by ACR for primary use in treating acute gouty arthritis: oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), oral colchicine, and oral and intra-articular corticosteroids [228].

The choice of agent is based on the severity of pain and joint involvement. In patients with mild to moderate pain with involvement of one or a few small joints or one to two large joints, then monotherapy with one of the three agents is recommended. For individuals with severely painful polyarticular arthritis, or those not responding to monotherapy, polytherapy can be successful. NSAIDs used in combination with either colchicine or oral corticosteroids, or intra-articular corticosteroids used in combination with either oral corticosteroids, NSAIDs, or colchicine are approved [228].

Consideration of comorbidities is also advised in the treatment of acute gouty arthritis due to drug toxicities and between-drug interactions [235, 236]. The multiple comorbidities often present in people with gout, including hypertension, chronic kidney disease, diabetes, congestive heart failure and hepatic disease, often result in contraindications to one or more gout medications [236]. Although other agents, including biologic interleukin-1 (IL-1) inhibitors [237] and canakinumab [238, 239], may be options for severe acute symptoms refractory to other agents, the risk versus benefit of these drugs is uncertain.

1.10.2.1.1 NSAIDS

NSAIDs, which include non-selective agents such as indomethacin, diclofenac and naproxen are effective in treating acute gouty arthritis [240, 241]. In those with gastrointestinal contraindications or intolerance to NSAIDs, cyclooxygenase-2 (COX2) inhibitors such as

celecoxib and etoricoxib are also beneficial [242, 243]. NSAIDs decrease inflammation and associated pain during acute gout by reducing the production of pro-inflammatory prostaglandins and thromboxanes [244]. ACR recommends continuing initial treatment at full approved doses until the acute symptoms have completely subsided [228]. However, lower doses should be used in patients taking diuretics or ACE inhibitors and may be contraindicated in those with significant cardiac or renal disease [244].

1.10.2.1.2 Colchicine

Colchicine, although not a direct analgesic, relieves pain through interfering with the pro-inflammatory pathways in acute gout by inhibiting MSU crystal-activation of the NLRP3 inflammasome [108], blocking the release of IL-1 β [108] and suppressing the expression of genes involved in cell regulation, including TNF- α [245] and NF- κ B [246]. In addition, colchicine also increases levels of anti-inflammatory mediators such as TGF- β 1 [247, 248]. Three daily 0.5 mg doses of colchicine are recommended [228] and have been shown to decrease pain within 24 to 48 hours following administration [249, 250]. However, gastrointestinal effects are common, and can be severe even at lower doses, meaning colchicine is often poorly tolerated by patients and may require additional gastro-protection [227]. Furthermore, colchicine is contraindicated in patients with significant renal impairment [251].

1.10.2.1.3 Corticosteroids

Corticosteroids can be administered orally, intra-muscularly or intra-articularly. Corticosteroids have a long-acting anti-inflammatory action by reducing both vascular and cellular components of the inflammatory response. Intra-articular corticosteroids, such as triamcinolone acetonide, are useful when only one or two joints are involved and can be used in combination with oral corticosteroids [227, 228]. For more widespread involvement oral prednisone at 0.5 mg/kg doses for 5 to 10 days is recommended [228]. Oral prednisone has been shown to be as effective as NSAIDs in the treatment of acute gouty arthritis [252]. In patients with diabetes, in which colchicine and NSAIDs are often contraindicated due to renal impairment, corticosteroids may be useful [244].

1.10.2.2 Non-pharmacological

Management of acute gouty arthritis should also include patient education, particularly regarding the importance of initiating treatment upon the first signs and symptoms of acute gout [228]. Patients should also be educated on dietary and other triggers of acute arthritis. In conjunction with pharmacological interventions, the ACR guidelines also recommend topical ice therapy, by application of ice packs to the joint [228], which has been shown to significantly reduce pain during an acute flare [173]. Other oral complementary therapies, including cherry juice, ginger and celery root, lack sufficient evidence in the treatment of acute gouty arthritis and are therefore considered inappropriate [228].

1.10.3 Long-term management of gout

The long-term goal of gout management is to prevent acute gouty arthritis and joint damage through the reduction of serum urate levels. The target serum urate level for patients with gout is < 0.36 mmol/l [227], however in patients with tophaceous gout this target reduces to < 0.30 mmol/l [226], which is required for reduction in tophus size [253, 254]. Although serum urate is regarded as a key biological outcome measure for urate lowering therapy [255], reduction of subcutaneous and articular tophaceous deposits can also be monitored [254].

The long-term management of gout should also include appropriate treatment for comorbidities, especially those associated with hyperuricaemia, including hypertension, cardiovascular disease and diabetes [226-228, 256]. Removal or replacement of drugs used in the treatment of existing comorbidities, including thiazide and loop diuretics, which can influence serum urate levels, should also be considered [228].

Successful long-term management of gout involves the use of pharmacological therapy in combination with patient and practitioner education, and dietary and lifestyle changes.

1.10.3.1 Pharmacological therapy

As gout does not always progress, urate lowering therapy, which involves a lifelong use of pharmacological agents, is not always recommended after a single episode of acute gouty arthritis. Pharmacological management is recommended in patients with recurrent acute gout

(\geq two episodes per year), patients with chronic kidney disease (stages two to five, or end stage renal failure), or patients with a history of urolithiasis [228]. Urate lowering therapy can be initiated during an episode of acute gouty arthritis as long as effective prophylaxis therapy is also provided [228].

Xanthine oxidase inhibitors (XOIs), which include allopurinol and febuxostat, are considered first line therapies for serum urate reduction. In patients who do not tolerate XOIs, the use of uricosurics, including probenecid, are an alternative first line therapy [228]. In patients failing to achieve their serum urate target, then combination therapy can be used with one XOI and one uricosuric agent [254, 257]. In patients refractory or intolerant to appropriate doses of these first line drugs, the use of pegloticase as a second line drug has been shown to be effective in reaching serum urate targets and reducing tophus size [258, 259].

1.10.3.1.1 Xanthine oxidase inhibitors

XOIs reduce serum urate levels and the production of uric acid by preventing the transformation of hypoxanthine to xanthine and of xanthine to uric acid through inhibiting xanthine oxidase [184]. Allopurinol has been regarded as the primary urate lowering agent for over three decades and remains the most commonly used in gout [227]. The ACR guidelines recommend a daily starting dose of ≤ 100 mg to reduce early episodes of acute arthritis and the risk of allopurinol hypersensitivity syndrome [227, 260, 261], which has a mortality rate of 20 to 25% [262, 263]. In those with \geq stage four chronic kidney disease, a lower starting dose of 50 mg/day is recommended [228]. The dosage can be increased every two to five weeks until the serum urate target is achieved. Allopurinol has been shown to reduce serum urate by 33% from a baseline of 0.50 mmol/l with a 300 mg daily dose, which increases to 49% with a 600 mg daily dose [264]. The maximum approved daily dose of allopurinol in New Zealand is 900 mg [591].

Febuxostat is a non-purine XOI that is often used in patients who fail to achieve the target serum urate with allopurinol, if they have renal impairment, or if there are concerns about allopurinol hypersensitivity syndrome. Febuxostat has demonstrated excellent efficacy in lowering serum urate and resolving tophi [261, 265, 266]. Febuxostat is generally well tolerated with the most common adverse effects including abnormal liver function tests, headache, and gastrointestinal symptoms [267]. In patients refractory to treatment, ACR recommends increasing febuxostat to a daily dose of 120 mg to achieve serum urate targets.

1.10.3.1.2 Uricosurics

Uricosurics decrease serum urate levels through increasing the excretion of uric acid by inhibition of tubular reabsorption of urate. Probenecid is the first choice uricosuric agent. However, it is contraindicated in those with a history of urolithiasis [268] and is not recommended in those with creatinine clearance of below 50 ml/min [228]. Achievement of serum urate targets have been reported in 33% of patients taking low-dose probenecid and in 37% of those taking it in combination with allopurinol [269]. Benzbromarone, another uricosuric agent, has also been shown to be effective in lowering serum urate levels in patients with mild to moderate renal impairment [270, 271].

1.10.3.1.3 Anti-inflammatory prophylaxis when initiating urate-lowering therapy

As episodes of acute gouty arthritis are frequent during the initiation of urate lowering therapy due to rapid changes in serum urate levels, prophylaxis therapy with, or just prior to, urate lowering therapy is recommended [228]. The ACR guidelines endorse low dose colchicine (0.5 mg to 0.6 mg once or twice daily) [249] or low dose NSAIDs (i.e. 250 mg naproxen twice daily) [272] as first line options. In patients intolerant to colchicine or NSAIDs, low dose prednisone or prednisolone (< 10 mg/day) is recommended [228, 273]. Prophylaxis therapy should be continued if signs or symptoms of gout continue, including episodes of acute arthritis, tophus, or chronic synovitis, or if the serum urate target is not achieved [228].

1.10.3.2 Patient and practitioner education

Patient and practitioner education is central to the success of long-term management [274-277]. The lack of knowledge about gout expressed by patients [278] highlights the importance of patient education. Information provided in currently used written resources includes education on symptoms, diagnosis, causes and risk factors and the importance of urate lowering therapy and lifestyle changes [279]. However, the success of such resources is dependent on the literacy of the patient and the complexity of the information provided. People with gout have reported difficulty in understating existing gout education resources [280]. Furthermore, a review of existing education tools found that 60% did not include important information relating to serum urate targets or the prophylaxis of acute arthritis during initiation of urate lowering therapy [279].

1.10.3.3 Diet and lifestyle changes

Although there is a lack of evidence supporting lifestyle interventions in the management of gout, lifestyle modifications are recommended for ideal health, including reduction in body weight, regular exercise, smoking cessation, adequate hydration and dietary adjustments [228]. Lifestyle measures are important not only in promoting and maintaining general wellbeing, but also in preventing and managing associated comorbidities [228]. However, without pharmacological therapy, lifestyle changes alone are unlikely to achieve serum urate targets. A recent review found that clinical trials on diet and fitness reported a 10% to 18% decrease in serum urate levels [281].

Due to the lack of blinded randomised-controlled trials, the ACR recommendations for dietary and lifestyle changes in people with gout are based on dietary factors identified in epidemiological studies as increasing the risk of incident gout [228]. The ACR guidelines recommend limiting the consumption of foods rich in purines including meat, seafood and alcohol [61, 70] as well as sugar-sweetened beverages [281]. The guidelines also encourage intake of low fat or non-fat dairy products and vegetables [281, 282].

1.11 Conclusion

Gout has been identified since ancient history as a condition affecting the foot, and in particular the 1MTP. Today, the prevalence and incidence of gout and hyperuricaemia is increasing worldwide and is particularly prevalent in New Zealand due to the high percentage of Māori and Pacific inhabitants who are genetically predisposed to hyperuricaemia. Although the development of gout requires the presence of hyperuricaemia, not all individuals with high urate levels develop symptoms. As a result, the urate lowering pharmacological therapy advocated for people with gout is not currently recommended for individuals with asymptomatic hyperuricaemia.

Chapter two: Gout in the foot and ankle

2.1 Introduction

Gout most commonly affects musculoskeletal structures of the foot and ankle. This chapter reviews the joints and tendons most frequently subject to acute gouty arthritis and monosodium urate (MSU) deposition. Patient-reported pain, disability and impairment, as well as structural and functional changes at the foot and ankle in people with gout are also reviewed. The chapter concludes with a review of current evidence supporting non-pharmacological management strategies specific to the foot in people with gout. This review was published in 2016 in *Gout and Hyperuricaemia* [283] and is included in **Appendix 1** with permission from the publishers (**Appendix 2**) .

2.2 Joint and tendon involvement

The foot and ankle region is well recognised as the most commonly affected during episodes of acute gouty arthritis [284-286]. The 1MTP is the most frequently involved joint in acute gout (62% to 76%), followed by the midfoot (20% to 57%) and ankle joints (15% to 64%) [153, 284, 287]. This pattern of joint involvement is reflected in the distribution of MSU crystal deposits in which the feet have the highest volume of MSU deposition compared with other regions of the body [288-290]. Between 37% and 68% of people with gout have MSU crystal deposits within structures of the foot and ankle [289, 290]. The 1MTP demonstrates the highest occurrence of MSU deposits (up to 57%), followed by the midfoot and ankle joints (up to 21% and 26%, respectively) [288, 290-292]. The local deposition of MSU crystals at the 1MTP and ankle have been strongly associated with acute gouty arthritis in these areas [293].

The presence of MSU crystal deposition is strongly associated with structural joint damage [194]. Whilst examining foot and ankle bones using computed tomography, Dalbeth et al. [294] reported bone erosions exhibited a similar pattern of involvement as MSU deposition and symptoms of acute arthritis, with the 1MTP demonstrating the highest prevalence for bone erosion. The 1MTP is also the most frequent site for other osseous changes including sclerosis, osteophytes, spur formation, joint space narrowing and periosteal formation [194].

While other foot joints are less frequently involved by symptoms and signs of gouty arthritis, several case studies have reported intraosseous tophi within the talus [295, 296]; os trigonum

[297]; phalangeal bones [298], lesser metatarsals [296, 299] and sesamoid bones [300-302] with several cases also reporting fractures at sites of MSU deposition within the foot [299, 303-305].

MSU crystals also deposit within certain tendon sites within the foot. The body and enthesis of the Achilles tendon are major sites for MSU crystal deposition, with a prevalence ranging from 28% in newly diagnosed gout, to 52% in patients with chronic tophaceous gout [288, 290, 292]. The peroneal tendons are the second most commonly affected by MSU deposits (15% to 29%) [290, 292]. Tibialis posterior and anterior tendons, and the flexor and extensor tendons of the hallux and lesser digits have also been reported as sites of MSU deposition [292]. Several case studies have reported longitudinal tears [306, 307] and ruptures [308-311] associated with tophus infiltration in foot and ankle tendons.

MSU deposition within the foot has also been observed using ultrasound imaging in people with asymptomatic hyperuricaemia. Crystal deposition along the articular cartilage of the 1MTP ranges from 20% to 29% [125, 312-315], while 8% of people with hyperuricaemia demonstrate cartilage deposition in the ankle joint [312].

2.3 Foot-related pain, disability and impairment

During episodes of acute arthritis involving the foot and/or ankle, people with gout report high levels of foot pain [316]. Although foot pain has been shown to reduce by 73% once acute gout resolves, pain scores do not completely normalise [316]. This persistent nature of foot pain in people with gout is reflected in other studies that report moderate to high levels of foot pain during asymptomatic periods [317-320]. In a large primary care-based study of 1,184 participants with gout, 22% reported foot pain in the past month with over two-thirds of these classified as having disabling foot pain [321, 322]. While foot pain in the previous month was associated with gout disease characteristics (including current acute arthritis and oligo- and poly-articular involvement) and comorbidities, disabling foot pain was associated only with comorbidities [321, 322]. The 1MTP was the most frequent site for foot pain in the past month (72%), followed by the lesser toes (67%), midfoot (62%), hallux (59%), ankle (54%), posterior heel (35%) and plantar heel (21%) [321, 322].

Rome et al. [316] found that participants with gout also reported high levels of foot-related impairment and disability during episodes of acute arthritis involving the foot and ankle. The participants with gout also indicated severe restrictions with lower-limb-related daily living and recreational activities [316]. Qualitative studies have shown that the most common functional limitation during acute arthritis is walking-related disability with 91% to 97% of participants with

gout reporting difficulty with walking [153, 211]. Furthermore, the influence of pain on walking ability during acute gouty arthritis is recognised as a discriminatory feature of the disease by people with gout [170]. Climbing stairs and standing are also among the main concerns people with gout have with daily activity limitations [207, 211].

These functional limitations remain persistent during intercritical periods once the symptoms resolve with 54% still experiencing high levels of foot-related impairment and 35% to 60% reporting severe foot-related disability [316, 318]. Not surprisingly, people with ulcerated tophaceous gout of the foot also report moderate to high levels of foot-related disability and impairment [323].

Although foot pain and foot-related impairment and disability are present in asymptomatic gout, it is unknown whether people with asymptomatic hyperuricaemia also experience similar impairments given the substantial degree of subclinical features including MSU deposition and systemic inflammation that have been observed in these individuals [324-326].

2.4 Functional and structural characteristics

The patient-reported lower limb-related functional limitations are reflected in laboratory-based gait studies which reveal that participants with gout exhibit alterations in several gait parameters despite the absence of acute gouty arthritis [318, 320]. Compared to age- and gender-matched controls, participants with gout walk slower with reduced cadence, step length and stride length and increased step and stance times while walking at comfortable self-selected speeds in their own footwear [318] and barefoot [320]. These gait patterns, primarily the shorter step and stride lengths and prolonged stance times, are reflective of not only the reduced walking velocity, but also an inability to transfer body weight forward during walking [327, 328]. Stewart et al. [320] also found that patient-reported measures of foot-related pain and disability were strongly associated with reduced step length, stride length and velocity, supporting previous postulations that gait strategies adopted by people with gout may be attributed to pain-avoidance mechanisms [318].

Biomechanical research has shown that participants with gout walk with significantly reduced peak plantar pressure and pressure time integrals beneath the hallux and increased pressure time integrals beneath the midfoot compared to controls [318]. Although increased midfoot pressure time integrals may be reflective of increased stance time, they may also be a result of the pes planus foot type observed in the gout population with 54% demonstrating a flat foot

profile [316, 318]. The authors proposed the reduced hallux pressure was an attempt to offload pressure at the commonly affected 1MTP due to pain [318]. This is further emphasised in qualitative research in which participants with gout report attempting to walk more cautiously with an adjusted foot position in an attempt to relieve the big toe [211]. Inefficient 1MTP function during the toe off phase of gait may further contribute to the propulsive strategies seen in people with gout [327, 328].

Patient-reported foot pain and disability has also been associated with reduced foot and ankle muscle strength in people with gout [319]. The authors reported that participants with gout demonstrated reduced muscle strength for plantarflexion, inversion and eversion of the foot compared to matched controls and found strong correlations between these strength reductions and increased foot pain and disability [319]. Considering the frequency of MSU crystal deposition in the Achilles, peroneal and tibialis posterior muscle tendons in people with gout [288, 290, 292], it is possible that musculotendinous tophus infiltration may reduce the tensile capacity of these tissues. It has also been proposed that the pain-avoidance gait strategies employed by people with gout may also contribute to reduced muscle activity and consequent disuse-related muscle atrophy [318].

2.5 Non-pharmacological management of the foot in gout

2.5.1 Footwear

Many people with tophaceous gout of the foot report difficulty in wearing shoes [329-331] and not being able to wear shoes is rated highly as an important concern by people with gout [332]. The challenges people with gout have with wearing appropriate footwear is also highlighted in qualitative research [174, 207]. People with gout report an inability to wear the correct shoes required for social and work situations, hence they avoid participating in certain activities and even take days off work [174, 207].

The inability to find and wear shoes that fit properly and are appropriate to their level of pain and disability has been demonstrated in a study which characterised features of footwear worn by people with gout [333]. Forty-four percent of participants with gout were found to wear shoes classed as poor, including sandals, slippers and jandals. Over half wore shoes that were too narrow, lacked cushioning and motion control properties and were older than 12 months. Fifty-four percent of participants also wore shoes with flexion points before the level of the metatarsal heads which can limit gait efficiency by inhibiting normal 1MTP function during

propulsion [334] and hence may exacerbate the problems of efficient toe-off observed in people with gout [318]. Furthermore participants who wore poor footwear reported higher levels of foot-related impairment and disability [333].

A prospective intervention study, which trialled the effect of a variety of footwear on patient-reported outcomes related to the foot and lower limb, found that footwear with good characteristics significantly reduced foot pain, general pain and activity limitation over an eight week period [317]. Contrastingly, improvements in patient-reported outcomes were not seen in participants with gout who wore footwear with poor characteristics over the study period. The authors proposed this may have resulted from certain properties of the good shoes, including excellent motion control, gel cushioning and an in-built rocker system designed to encourage heel-to-toe transition and efficient propulsion [317]. This was confirmed in a subsequent gait analysis study in which participants with gout wearing the good footwear demonstrated decreased heel and lateral forefoot pressure and increased midfoot pressure compared to walking in their own shoes. These patterns are reflective of a more efficient heel to toe gait pattern [335].

2.5.2 Podiatric palliative care

In a recent survey in the United Kingdom, 43% of people with gout reported consulting with their general practitioners in the past year about foot problems and 24% reported seeing a podiatrist [322]. A study of 56 New Zealand podiatrists found that 95% managed patients with gout in their practice with 59% feeling somewhat confident in providing podiatric care to these patients [336]. Podiatric interventions have been shown to reduce pain by 18% and foot disability by 23% after a single podiatry visit in a group of patients with rheumatic conditions including gout [337]. Treatments provided included callus reduction, ulcer debridement, treatment of nail conditions, clinical padding, foot orthoses, footwear advice, foot-health education and exercise prescription.

2.6 Conclusion

The pattern of crystal deposition in individuals with gout demonstrates a clear preference for structures of the foot and ankle, in particular the 1MTP and Achilles tendon. The high frequency of foot involvement in gout is reflected in lower-limb-related functional and structural limitations observed by clinicians and reported by people with gout. Emerging research suggests

that foot-specific interventions including footwear and podiatric care may play a role in the management of patients with gout who experience foot-related pain and disability.

Chapter three: The first metatarsophalangeal joint in gout: A systematic review and meta-analysis

3.1 Introduction

Despite the well-recognised susceptibility of the first metatarsophalangeal joint (1MTP) to acute arthritis in gout, evident by its inclusion in several gout classification criteria [104, 144, 152, 338], a formal synthesis of the prevalence of acute 1MTP arthritis in gout has yet to be undertaken. Furthermore, the burden of 1MTP involvement on patient-reported outcomes in gout is unclear. Despite the significant role of the 1MTP during normal gait, particularly the forward transfer of body weight during propulsion [339, 340], it is also unclear to what extent the structure and function of the joint is compromised in people with gout. This chapter reviews the anatomy and function of the 1MTP and describes existing theories addressing the propensity for 1MTP involvement in gout. A systematic review follows, which summarises studies which have investigated characteristics of the 1MTP in gout. A meta-analysis is also undertaken to provide a pooled estimate for the true average prevalence of acute gouty arthritis at the 1MTP. The systematic review and meta-analysis were published in 2016 in BMC Musculoskeletal Disorders [341] (**Appendix 3**).

3.1.1 First metatarsophalangeal joint anatomy

The first metatarsophalangeal joint is a synovial condyloid joint comprised of an articulation between the head of the first metatarsal and the base of the proximal phalanx [342]. The plantar surface of the first metatarsal also articulates with two sesamoid bones which provide a fulcrum point to assist with motion of the joint [343]. The capsuloligamentous complex, which stabilises the joint, includes a fibrocartilaginous plantar plate and an extensor hood which blend with surrounding ligaments to reinforce the joint capsule [344]. Dynamic control is maintained by a total of six muscles which cross the 1MTP [345] (**Figure 3.1**). The flexor hallucis longus and brevis muscles, which cross the joint plantarly, provide sagittal plane motion along with the extensor hallucis longus and brevis muscles which cross the joint dorsally. The abductor hallucis and adductor hallucis muscles cross the joint medially and laterally, respectively, to provide transverse plane stability. The tibialis anterior and peroneus longus also assist with functioning of the 1MTP [346].

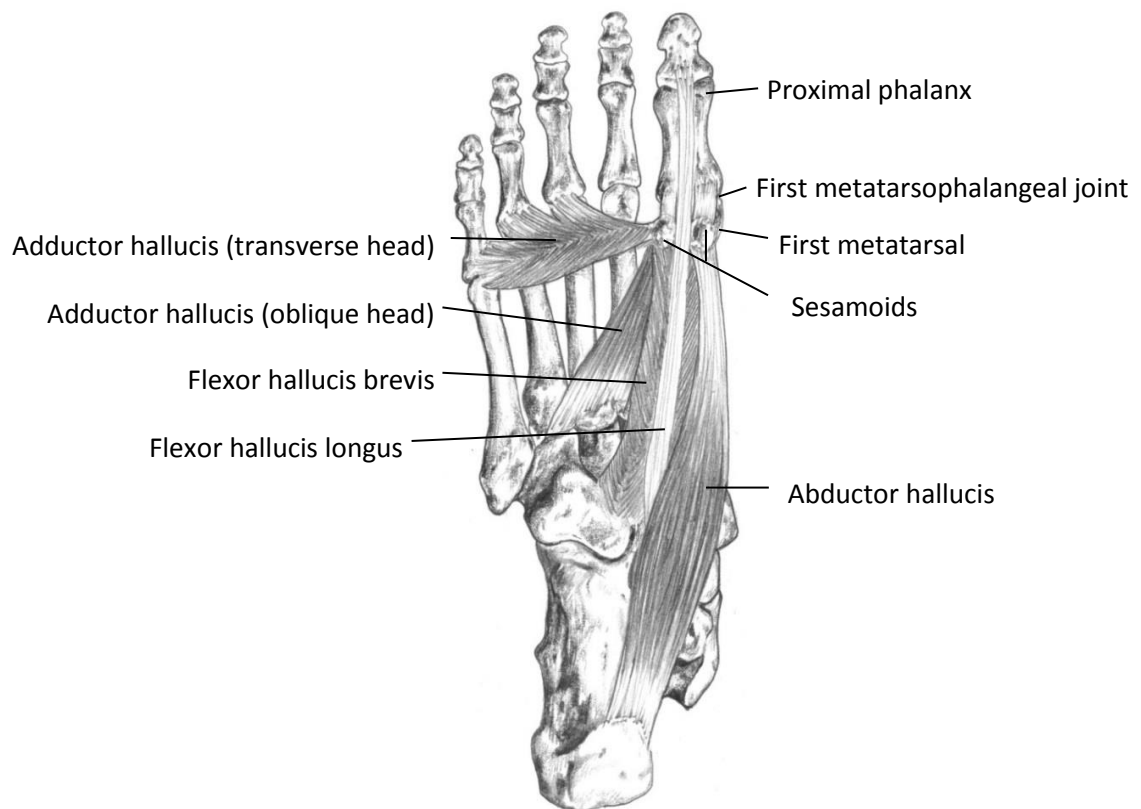


Figure 3.1 First metatarsophalangeal joint anatomy - plantar view (original image)

3.1.2 The role of the first metatarsophalangeal joint during gait

Motion at the 1MTP is predominantly sagittal with normal non-weight-bearing motion approximately 30° plantarflexion and 90° dorsiflexion [347]. During weight-bearing this full range of motion is not utilised as normal walking requires only 65° to 75° of 1MTP dorsiflexion for efficient forward transfer of body weight [340, 348]. The achievement of adequate 1MTP dorsiflexion during the terminal and pre-swing phases of gait requires first metatarsal plantarflexion. This allows the proximal phalanx to dorsally rotate on the first metatarsal head, which in turn also enables the midtarsal joint to lock, the rearfoot to supinate and the tibia to externally rotate [349, 350]. This ensures the foot is converted from a mobile adaptor to a rigid lever enabling the 1MTP to efficiently propel body weight forward. During propulsion the first metatarsal head is subject to considerable plantar pressure as the proximal phalanx passes over it [351]. As the first metatarsal must carry this significant amount of weight, it is the shortest and broadest of all the metatarsals [339, 346].

3.1.3 Why does gout target the first metatarsophalangeal joint?

Despite a similar level of urate concentration throughout the body, MSU crystal deposition and gout-related features have a certain propensity for the 1MTP. Several theories have been proposed in attempt to explain this phenomenon, which are explored in more detail below; however, the high frequency of gouty involvement in this joint is likely to result from a complex interplay between several factors.

3.1.3.1 Temperature

Low temperatures substantially reduce the solubility of urate and enhance the nucleation of MSU crystals [98, 352]. It has been proposed that this may contribute to the precipitation of crystals in the cooler peripheral joints of the foot, and the relative sparing of axial joints [353]. In the peripheral joints of the foot, temperature has been recorded at 35°C with a lower urate solubility measured at 0.33 mmol/l [98]. Additionally, the high rate of cardiovascular disease in people with gout [72] and the association between peripheral arterial disease and hyperuricaemia [354] places people with gout at an increased risk of peripheral blood flow disturbance, and thus may further encourage MSU crystal nucleation in peripheral joints. However, it has been acknowledged that this temperature mechanism cannot explain why gout targets the 1MTP while the lesser metatarsophalangeal joints and more distal interphalangeal joints are rarely involved [355, 356].

3.1.3.2 Physical trauma

The susceptibility of the 1MTP to physical trauma through daily activities such as walking has also been identified as an important factor contributing to the high frequency of 1MTP involvement in gout. Mechanical agitation of solutions supersaturated with urate has been shown to enhance crystal nucleation [99]. The authors hypothesised that physical trauma lowers synovial pH and increases calcium ion activity which in turn creates an environment that favours MSU crystal nucleation [99]. The susceptibility of the 1MTP to physical trauma may be further enhanced in people with marked tophaceous deformity, which prevents the wearing of properly fitting protective footwear [174, 329-333].

3.1.3.3 Biomechanical loading

It has also been hypothesised that the sites in the foot frequently affected by MSU crystal deposition and structural joint damage in gout, including the 1MTP, are at particular risk due to greater biomechanical loading during gait [114, 294]. Repetitive loading, particularly in mal-aligned or poorly functioning joints, may lead to intra-articular debris that can provide a nucleus for crystal formation [357]. Biomechanical stress may also disrupt pre-existing deposits within the joint, which may trigger the release of microcrystals and a resulting inflammatory response [114]. Conversely, Dalbeth et al. [358] recently found no association between areas of increased tissue stress in the feet of healthy individuals, which were highest at the third metatarsal head, and areas of crystal deposition in people with gout, which were highest at the first metatarsal head. However, other factors present in individuals with gout, including pre-existing osteoarthritis and other comorbid conditions may influence loading during gait and contribute to the susceptibility for urate formation and deposition at preferential sites in the foot.

3.1.3.4 Osteoarthritis

Osteoarthritis is a degenerative condition involving progressive destruction of articular cartilage at areas of abnormal biomechanical friction or stress [359]. Osteoarthritis shares gout's pattern of joint involvement in the foot with the most common joint affected being the 1MTP [360]. As such, it has been proposed that osteoarthritis may be associated with the frequency of local formation and deposition of MSU crystals in this joint [353, 356]. In fact, strong associations have been observed between gout and conventional radiographically-proven [361] and clinically-diagnosed [362] osteoarthritis of the 1MTP. Furthermore, a recent dual energy computed tomography study also found associations between the presence of MSU crystals at the 1MTP and coexisting conventional radiographic features of osteoarthritis, including joint space narrowing and osteophytosis [194].

Although it is difficult to infer causality due to the cross-sectional nature of current research, previous studies support the theory that degenerative cartilage predisposes to the local formation and deposition of MSU crystals [353, 361, 362]. It has been postulated that the preference for MSU crystals to deposit on cartilage surfaces is due to the facilitated nucleation and crystallisation of urate by components of normal cartilage (chondroitin sulfate and phosphatidylcholine) [363]. Furthermore, the altered composition of proteoglycans in degenerative cartilage has been hypothesised to interfere with urate crystallisation [364]. Roddy

et al. [362] noted that the strength of the association between gout and osteoarthritis did not increase as the disease duration of gout increased, which would be expected if joint damage was initiated and progressed by MSU crystals [362]. Conversely, Muehleman et al. [365] favoured a bidirectional association whereby degraded cartilage provides small openings for the nucleation of MSU crystals, which then further perpetuates joint damage.

In contrast, although Dalbeth et al. [194] found associations between conventional radiographic features of osteoarthritis and MSU crystals, stronger relationships were found between more gout-specific radiographic features and crystal presence, which supports the notion that MSU crystals may influence structural damage in gout [194]. This is supported by current research that suggests that chondrocytes directly interact with MSU crystals resulting in cartilage damage through increased production of degrading enzymes and pro-inflammatory mediators [366-368].

3.2 Aims

This systematic review aimed to qualitatively synthesise studies that have investigated characteristics of the 1MTP in gout and to undertake a meta-analysis to provide a pooled estimate for the average prevalence of acute 1MTP arthritis in gout across studies.

3.3 Methods

3.3.1 Search strategy

A comprehensive electronic search was completed in March 2015 using the following databases: Scopus (1960 to March 2015), Medline (1966 to March 2015), CINAHL (1937 to March 2015), SportsDiscus (1985 to March 2015), the Cochrane Library. Additionally, conference abstracts available at the time were also searched, including ACR abstracts (2009 to 2013) and EULAR abstracts (2002 to 2012). The search terms used are presented in **Table 3.1**. This search was supplemented with hand-searching of reference lists of all potentially eligible full-text articles and selected review articles.

Table 3.1 Search terms	
#1	gout* OR uric OR urate OR hyperuric* OR toph*
#2	"first metatarsophalangeal" OR "first metatarsal phalangeal" OR hallux OR "big toe" OR "first toe" OR digit OR podagra OR "1MTP*" OR 1mtp* OR foot OR feet
#3	imaging OR sonograph* OR ultraso* OR "Doppler" OR radiograph* OR xray OR "magnetic resonance" OR mri OR "computed tomograph*" OR ct OR "dect" OR "dual energy"
#4	histol* OR microscop*
#5	function* OR gait OR walk* OR "plantar pressure" OR motion
Final search term: #1 AND #2 AND (#3 OR #4 OR #5)	

3.3.2 Selection criteria

All potentially eligible articles were screened by a single author (SS) at title, abstract, and full-text stages. The review was conducted with reference to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA) statement [369]. Studies considered for this review were published in peer-reviewed journals and limited to randomised controlled trials, cohort studies, case-control studies and cross-sectional studies. Peer-reviewed conference proceedings and abstracts were also considered for inclusion. Case reports, case series with < 5 cases and review articles were excluded.

The inclusion criteria included studies published in English, adults over 18 years old and that involved participants who had a diagnosis of gout. Included studies presented original findings relating to the following outcome measures: incidence or prevalence of acute inflammatory arthritis at the 1MTP; clinical features of acute gouty arthritis, intercritical gout and chronic gouty arthropathy (including tophaceous gout) at the 1MTP; structural and functional characteristics of the 1MTP; microscopy of the 1MTP; and imaging features of the 1MTP including MSU crystals, bone disease and synovial disease. Studies that assessed the 1MTP amongst other joints, but did not report outcome measures specifically relating to the 1MTP, were also excluded.

3.3.3 Data extraction

The following data were extracted from all included papers: the first author's last name, publication year, country where the study was conducted, the study design and aim(s), the outcome measure(s) reported, the results of the outcome measure(s) and the characteristics of the participants with gout including: sample size, gender, mean age (years), mean disease duration (years) and the method of diagnosis.

3.3.4 Statistical analysis

A meta-analysis was conducted to obtain an estimate of the prevalence of acute arthritis at the 1MTP in people with gout at any point during the course of their disease. Due to the expected high prevalence of acute 1MTP arthritis, a double arcsine transformation was adopted to address variance instability. This transformation method is the preferred transformation option as it avoids an undue large weight for studies [370]. The meta-analysis was carried out using the inverse of the variance of the transformed proportion as study weight. The pooled transformed prevalence and its upper and lower 95% confidence intervals were transformed back for the final presentation of the data. A random-effects model was used and the degree of heterogeneity was evaluated using the Higgins I^2 statistic which was interpreted as follows: I^2 of 25% = low heterogeneity, I^2 of 50% = medium heterogeneity, I^2 of 75% = high heterogeneity [371]. Statistical analysis was undertaken in MetaXL version 2.0 (EpiGear International Pty Ltd, Brisbane, Australia).

3.4 Results

3.4.1 Description of studies

Figure 3.2 shows a flow chart of the literature search. The initial search identified 576 papers through database searching and 12 papers from conference abstracts. Following the removal of 160 duplicates, 428 papers were screened, of which 240 papers were considered for further examination based upon the title and abstract. Forty-five studies met the criteria and were included in the review (including four conference abstracts published in peer-reviewed journals [321, 372-374] and two English abstracts from non-English papers [361, 375]). Of the 45 studies,

8 were longitudinal cohort studies, 20 cross-sectional studies, 10 case-control studies, 5 retrospective studies, and two randomised clinical trials. Details of the 45 included studies are displayed in **Table 3.2**.

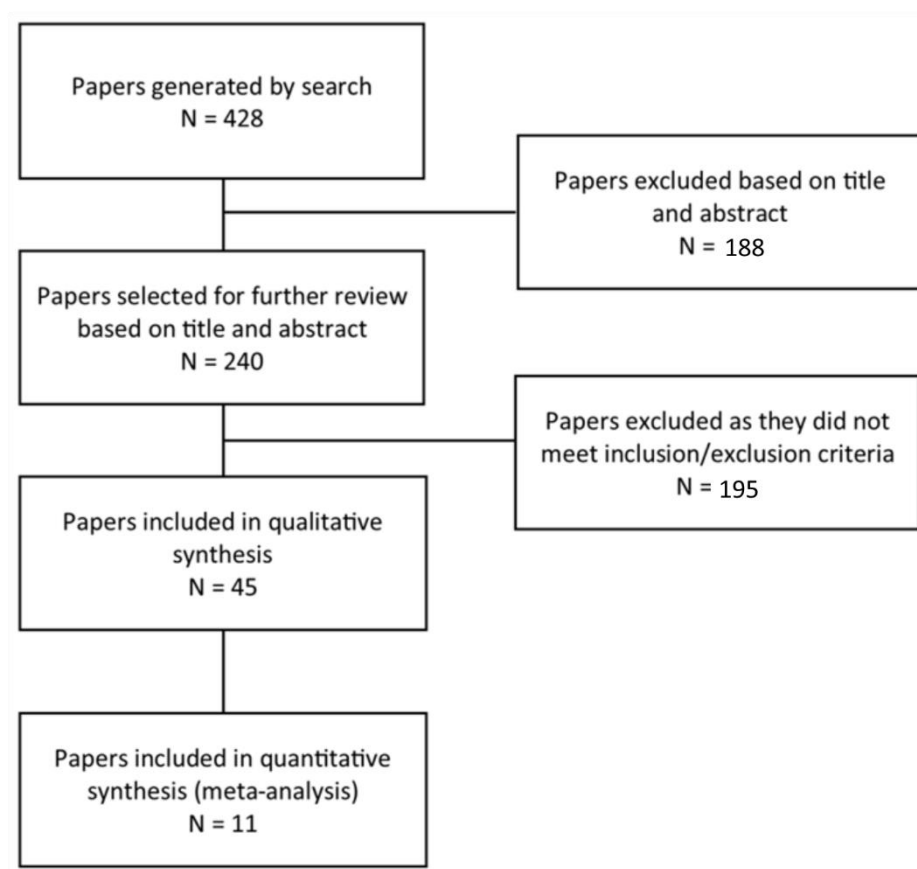


Figure 3.2 PRISMA flow chart of included studies

The 45 included studies involved 44 different groups of participants with gout (2 studies used the same participants [362, 376]) totalling a pooled sample size of 5,478 participants. Thirty-eight studies involving 5,067 participants reported gender, of which 4,348 (86%) were male. Thirty-six studies reported mean participant age which ranged from 28 years to 69 years. Twenty-nine studies reported disease duration, which ranged from newly diagnosed gout to 22 years.

Five studies did not report how participants with gout were diagnosed [290, 361, 372, 373, 377]. Fifteen studies, totalling 1,773 participants, included only participants with gout who were diagnosed via microscopic identification of MSU crystals in synovial fluid/tophus aspirates. Fifteen studies, totalling 1,116 participants, diagnosed gout via the 1977 ACR criteria [144] in which participants either had MSU-proven gout or met 6 of the 12 clinical criteria. Of these studies, nine reported the number of crystal-proven participants (300/656 (46%)). Two studies

knowingly included participants with gout who did not meet the ACR criteria (n = 36). The remaining seven studies included in the review diagnosed participants with gout using other methods detailed in **Table 3.2** [31, 172, 284, 288, 321, 374, 378].

Table 3.2 Details of studies included in review					
Author	Location	Study design	Aim	Characteristics of participants with gout	Outcome measures relevant to review
Bellamy [172]	Canada	Longitudinal cohort	Natural progression of 1MTP acute flares	N = 11 Male 100% Mean age 55 years Mean disease duration 4 years Diagnosis: “patients presenting with classical features of acute podagra, had experienced prior attacks of gouty arthritis and were known to be or have been hyperuricaemic”.	Clinical characteristics of 1MTP gout
Carter [379]	USA	Cross-sectional	The presence of synovial inflammation during intercritical gout	N = 72 Male 90% Mean age 56 years Mean disease duration 10 years Diagnosis: ACR criteria (incl. 42% crystal proven)	Epidemiology of 1MTP gout
Dalbeth [294]	New Zealand	Cross-sectional	Scoring bone erosion in gout using CT imaging	N = 25 Male 75% Median age 60 years Median disease duration 21 years Diagnosis: ACR criteria (incl. 44% crystal proven)	Imaging features of the 1MTP in gout
Dalbeth [194]	New Zealand	Cross-sectional	Relationship between radiographic joint damage and MSU crystal deposition using DECT imaging	N = 92 Male 93% Mean age 58 years Mean disease duration 22 years Diagnosis: ACR criteria (incl. 48% crystal proven)	Imaging features of the 1MTP in gout

Dalbeth [382]	New Zealand	Cross-sectional	Comparison of DECT MSU deposition in participants with gout and participants with asymptomatic hyperuricaemia	N = 33 Male = 85% Mean age 61 years Mean disease duration 11 years Diagnosis: MSU crystal proven	Imaging features of the 1MTP in gout
Deesomchok [380]*	Thailand	Cross-sectional	Clinical pattern of gout in females and males	N = 194 Male 89% Mean age 59 (F) 52 (M) years Mean disease duration 3 (F) 10 (M) years Diagnosis: ACR criteria (incl. 81% crystal proven)	Epidemiology of 1MTP gout
DeSouza [186]	Brazil	Cross-sectional	Clinical and laboratory features of gout in men and women	N = 58 Male 53% Mean age 64 (F) 61 (M) years Mean disease duration 9 (F) 14 (M) years Diagnosis: ACR criteria (% crystal proven not reported)	Epidemiology of 1MTP gout
Grahame [284]*	UK	Retrospective	Characteristics of people with gout	N = 354 Male 90% Mean age NR Mean disease duration NR Diagnosis: people with “recurrent acute episodes of arthritis in the presence of hyperuricaemia”	Epidemiology of 1MTP gout
Hall [31]*	USA	Longitudinal cohort	Epidemiology of gout and hyperuricaemia	N = 86 Male 87% Mean age 58 years Mean disease duration 9 years Diagnosis: people who met two of the following: a typical attack of arthritis characterised by acute pain, usually accompanied by swelling and heat, lasting from a few day sot two weeks, and	Epidemiology of 1MTP gout

				followed by complete remission of symptoms; an attack of arthritis exhibiting a striking and prompt response to therapeutic colchicine; the presence of hyperuricaemia.	
Howard [315]	USA	Cross-sectional	Reliability of ultrasound for tophi and double contour sign	N = 50 Male 100% Mean age 69 years Mean disease duration NR Diagnosis: ACR criteria (% crystal proven not reported)	Imaging features of the 1MTP in gout
Huppertz [288]*	Germany	Case-control	Diagnostic accuracy of DECT and ultrasound for detecting MSU crystal deposition	N = 39 Male NR Mean age NR Disease duration newly diagnosed Diagnosis: Janssens score [104] of > 8 or MSU crystal proven (46%)	Imaging features of the 1MTP in gout
Janssens [104]*	Netherlands	Cross-sectional	Validation of a diagnostic model to predict gout	N = 209 Male 89.5% Mean age 59 years Mean disease duration NR Diagnosis: MSU crystal proven	Epidemiology of 1MTP gout
Kawenoki-Minc [361]	Poland	Cross-sectional	Incidence of radiographic evidence of degenerative articular changes in people with gout	N = 262 Male NR Mean age NR Mean disease duration NR Diagnosis: not reported	Imaging features of the 1MTP in gout
Kennedy [378]	London	Cross-sectional	MSU crystal presence in aspirated 1MTP joint fluid	N = 31 Male 100% Mean age 61 years Mean disease duration 10 years	Microscopy in 1MTP gout

				Diagnosis: people who had “previously had podagra” including 52% who were MSU crystal proven	
Kienhorst [171]	Netherlands	Longitudinal cohort	Validation of clinical diagnosis of 1MTP gout	N = 123 Male 85% Mean age 59 years Mean disease duration NR Diagnosis: MSU crystal proven	Clinical characteristics of 1MTP gout
Kim [289]	Korea	Cross-sectional	DECT presence of MSU deposition	N = 101 Male 95% Mean age NR Mean disease duration NR Diagnosis: ACR criteria (% crystal proven not reported)	Imaging features of the 1MTP in gout
Kim [291]	Korea	Longitudinal cohort	Comparison of clinical outcomes of arthrodesis and tophi excision & evaluate MRI features of tophaceous gout	N = 15 Male 67% Mean age 57 years Mean disease duration NR Diagnosis: MSU crystal proven	Clinical characteristics of 1MTP gout; Functional characteristics of 1MTP gout; Imaging features of the 1MTP in gout
Lally [37]*	USA	Retrospective	Comparison of gouty arthritis in men and women	N = 98 Male 77% Mean age 63 (F) 63 (M) years Mean disease duration 5 (F) 14 (M) years Diagnosis: MSU crystal proven	Epidemiology of 1MTP gout
Mallinson [290]	Canada	Retrospective	Distribution of MSU crystal deposition in gout using DECT imaging	N = 148 Male 82% Mean age 61 years Mean disease duration NR Diagnosis: not reported	Microscopy in 1MTP gout
Mijiyawa [287]*	Togo	Retrospective	Characteristics of people with gout	N = 106 Male 99% Mean age 53 years	Epidemiology of 1MTP gout

				Mean disease duration 8 years Diagnosis: ACR criteria (incl. 17% crystal proven)	
Kang [381]	Korea	Longitudinal cohort	Ultrasound characteristics of gout & efficacy of intra-articular steroid injection for acute 1MTP flares	N = 21 Male 86% Mean age 64 years Mean disease duration NR Diagnosis: ACR criteria (% crystal proven not reported)	Clinical characteristics of 1MTP gout; Imaging features of the 1MTP in gout
Naredo [383]	Spain	Case-control	Diagnostic value of ultrasound for gout	N = 91 Male 100% Mean age 56 years Mean disease duration 7 years Diagnosis: MSU crystal proven	Imaging features of the 1MTP in gout
Ordenez [372]	Spain	Cross-sectional	Reliability of ultrasound in detection of lesion at 1MTP in gout	N = 15 Male NR Mean age NR Mean disease duration NR Diagnosis: not reported	Imaging features of the 1MTP in gout
Ottaviani [384]	France	Longitudinal cohort	Ultrasonography showing disappearance of MSU crystals following urate lowering therapy	N = 16 Male 100% Mean age 61 years Mean disease duration 7 years Diagnosis: MSU crystal proven	Imaging features of the 1MTP in gout
Pascual [112]	Spain	Cross-sectional	MSU crystal presence in aspirated 1MTP joint fluid	N = 101 Male 98% Mean age 56 years Mean disease duration 5 years Diagnosis: ACR criteria (incl. 77% crystal proven)	Microscopy in 1MTP gout

Pascual [385]	Spain	Longitudinal cohort	Disappearance of MSU crystals following urate lowering therapy	N = 18 Male 100% Mean age 56 years Mean disease duration 10 years Diagnosis: MSU crystal proven	Microscopy in 1MTP gout
Pelaez-Ballestas [338]*	Mexico	Cross-sectional	Identifying criteria for diagnosis of chronic gout	N = 549 Male 96% Mean age 50 years Mean disease duration 12 years Diagnosis: MSU crystal proven	Epidemiology of 1MTP gout
Radak-Perovic [375]	Serbia	Case-control	Comparison of ultrasound and x-ray for detection of 1MTP erosions	N = 30 Male NR Mean age NR Mean disease duration NR Diagnosis: ACR criteria (% crystal proven not reported)	Imaging features of the 1MTP in gout
Roddy [362]	UK	Case-control	Concomitant gout and osteoarthritis	N = 164 Male 81% Mean age 63 years Mean disease duration 10 years Diagnosis: 91% met ACR criteria (% crystal proven not reported)	Epidemiology of 1MTP gout; Functional characteristics of 1MTP gout
Roddy [386]	UK	Cross-sectional	Ultrasound characteristics of gout	N = 40 Male 78% Mean age 65 years Mean disease duration 13 years Diagnosis: ACR criteria (incl. 53% crystal proven)	Imaging features of the 1MTP in gout
Roddy [321]	UK	Cross-sectional	Prevalence of hallux valgus, foot pain and disability in gout	N = 1184 Male 78% Mean age 66 years Mean disease duration 12 years	Clinical characteristics of 1MTP gout; Structural characteristics of 1MTP gout

				Diagnosis: "Patients who had consulted their GP about gout or been prescribed allopurinol or colchicine within the preceding two years"	
Roddy [376]	UK	Case-Control	Nodal osteoarthritis and the risk of developing gout	N = 164 Male 81% Mean age 63 years Mean disease duration 10 years Diagnosis: 91% met ACR criteria (% crystal proven not reported)	Clinical characteristics of 1MTP gout; Structural characteristics of 1MTP gout
Rome [318]	New Zealand	Case-control	Functional and biomechanical characteristics of gait in participants with gout	N = 25 Male 75% Mean age 61 years Mean disease duration 22 years Diagnosis: ACR criteria (incl. 44% crystal proven)	Functional characteristics of 1MTP gout
Rouault [126]*	USA	Case-control	1MTP aspiration as a diagnostic tool for gout	N = 23 Male NR Mean age NR Mean disease duration NR Diagnosis: MSU crystal proven	Epidemiology of 1MTP gout; Microscopy in 1MTP gout
Schlesinger [173]	USA	Randomised controlled trial	Effect of ice therapy in acute gouty arthritis	N = 5 Male NR Mean age NR Mean disease duration NR Diagnosis: MSU crystal proven	Clinical characteristics of 1MTP gout
Sivera [387]	Spain	Cross-sectional	Feasibility of 1MTP aspiration for gout diagnosis	N = 22 Male 82% Mean age 61 years Mean disease duration NR Diagnosis: MSU crystal proven	Microscopy in 1MTP gout

Sun [293]	China	Cross-sectional	DECT imaging features of gout	N = 80 Male 94 % Mean age 52 years Mean disease duration 5 years Diagnosis: ACR criteria (% crystal proven not reported)	Imaging features of the 1MTP in gout
Taylor [153]*	Multinational, multicentre	Cross-sectional	Clinical, laboratory, imaging findings in gout	N = 509 Male 86% Mean age 60 years Median disease duration 6 years Diagnosis: MSU crystal proven	Epidemiology of 1MTP gout; Clinical characteristics of 1MTP gout
Thiele [114]	USA	Case-control	Sonographic features of gout	N = 16 Male 81% Mean age 64 years Mean disease duration NR Diagnosis: MSU crystal proven	Imaging features of the 1MTP in gout
Thiele [388]	USA	Retrospective	Detection of erosions with ultrasound and conventional radiography in chronic gout	N = 42 Male NR Mean age NR Mean disease duration NR Diagnosis: MSU crystal proven	Imaging features of the 1MTP in gout
Vreju [373]	Romania	Longitudinal cohort	Importance of ultrasound in gout diagnosis	N = 23 Male 53% Mean age 53 years Disease duration < 1 year Diagnosis: not reported	Imaging features of the 1MTP in gout
Wang [377]	Taiwan	Randomised controlled trial	Comparison of arthroscopic removal of 1MTP MSU crystals with medical treatment alone	N = 28 Male 100% Mean age 28 years Mean disease duration 2 years Diagnosis: not reported	Clinical characteristics of 1MTP gout; Functional characteristics of 1MTP gout

Wallace [144]*	USA	Cross-sectional	Development of a criteria for the classification of arthritis due to primary gout	N = 178 Male 86 % Mean age 56 years Mean disease duration 10 years Diagnosis: 88% met ACR criteria (incl. 43% crystal proven)	Epidemiology of 1MTP gout
Weinberger [122]	USA	Case-control	MSU crystals in aspirated 1MTP joint fluid	N = 9 Male 100% Mean age 54 years Mean disease duration 2 years Diagnosis: MSU crystal proven	Microscopy in 1MTP gout
Wright [389]	Ireland	Case-control	Comparison of ultrasound and x-ray for detection of erosions in gout	N = 39 Male 100% Mean age 52 years Mean disease duration 12 years Diagnosis: ACR criteria (incl. 28% crystal proven)	Imaging features of the 1MTP in gout
Zleik [374]	USA	Longitudinal cohort	Risk & predictors additional flares in newly diagnosed gout	N = 158 Male 73% Mean age 59 years Mean disease duration Newly diagnosed Diagnosis: via the New York, Rome or ACR criteria (% crystal proven not reported)	Epidemiology of 1MTP gout
*Papers included in meta-analysis; NR = Not reported					

The 45 studies reported on one or more of the following outcome measures relating to 1MTP gout: epidemiology (n=14, including n=11 articles reporting on the prevalence of acute 1MTP arthritis at any point during the course of the disease which were included in the meta-analysis), clinical characteristics (n=8), structural characteristics (n=2), functional characteristics (n=4), microscopy (n=7); and imaging features (n=19).

3.4.2 Epidemiology

Acute 1MTP arthritis presenting as the manifestation of gout at disease onset, ranged from 43% to 76% [37, 153, 374, 379, 380]. The frequency of acute 1MTP arthritis as the initial manifestation of gout was not significantly different between genders [37, 186, 380]. However, acute 1MTP arthritis at any point during the disease was significantly more frequent in men (68.6%) compared to women (31.8%) [186, 380]. Two studies reported 54% and 72% of participants with gout only experienced acute arthritis isolated to the 1MTP [153, 171].

Eleven studies reported the prevalence of acute 1MTP arthritis at any point during the course of the disease and were included in the meta-analysis [31, 37, 104, 126, 144, 153, 284, 287, 288, 338, 380]. The studies provided a pooled sample size of 2,464 participants. In total, 87% were male with a mean age ranging between 50 to 63 years old. Mean or median disease duration was reported by eight studies and ranged from newly diagnosed to 14 years [31, 37, 144, 153, 287, 288, 338, 380]. Fifty-six percent of 2,110 participants from 10 studies demonstrated aspirate proven gout [31, 37, 104, 126, 144, 153, 287, 288, 338, 380]. The reported prevalence of acute arthritis at any point during the course of the disease ranged from 48% to 97%. The pooled prevalence of acute 1MTP arthritis across studies was 73% (95% CI 65%, 80%). The heterogeneity was high with an I^2 of 93% (95% CI 90%, 96%). **Figure 3.3** presents the forest plot showing the pooled prevalence of acute 1MTP arthritis in gout.

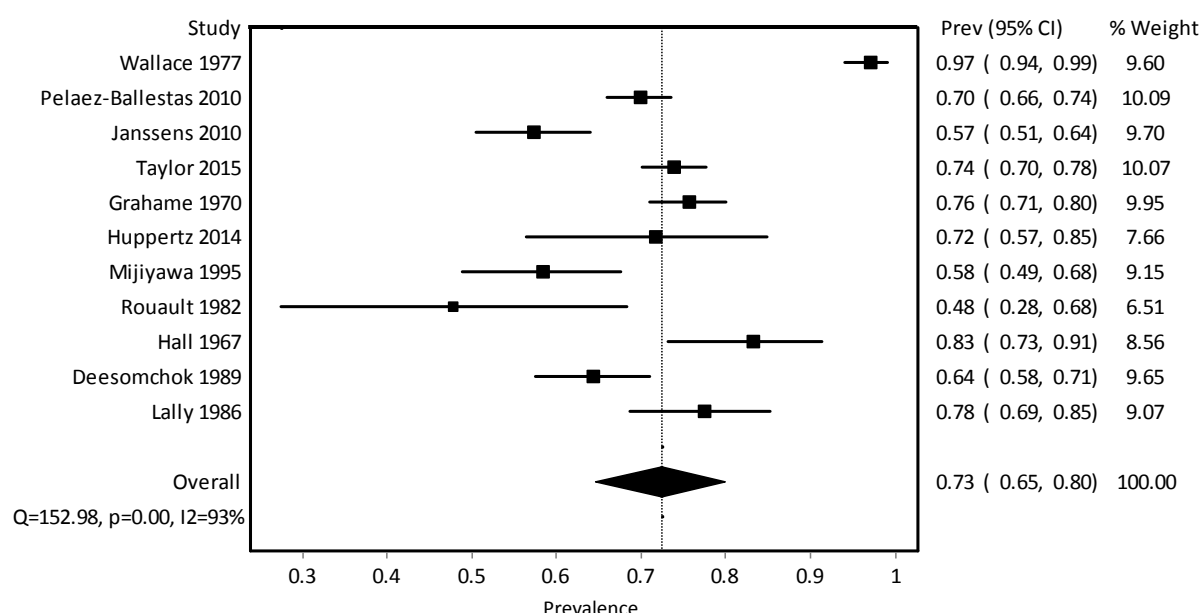


Figure 3.3 Forest plot of pooled prevalence of acute 1MTP arthritis in gout

3.4.3 Clinical characteristics

Four studies reported the characteristics of acute 1MTP arthritis, which included rapid onset of extremely severe pain and tenderness with moderate swelling, erythema and inflammation [153, 171-173]. Seventy-nine percent of participants reported onset within one day [171]. Erythema was observed in 95% of participants with acute 1MTP arthritis [171]. In a study following the natural progression of acute 1MTP arthritis for 7 days in 11 participants, improvements in erythema and juxta-articular skin temperature were observed by day 4, while 1MTP pain and swelling improved in most by day 5 [172]. Two studies reported pain during acute 1MTP arthritis using 100 mm Visual Analog Scales (VAS) [171, 381]. Mean patient-reported pain ranged from 54.3 to 71.1 mm [171, 381].

During intercritical periods, in the absence of acute symptoms, a significantly greater number of people with gout reported current 1MTP pain compared to healthy matched controls (16% versus 6%, respectively) [376]. In one study, 72% of participants with long-standing gout, with a mean of 12 years disease duration, reported 1MTP pain in the previous month [321]. During clinical examination of 78 1MTPs from 39 participants with currently asymptomatic gout, 35% of joints demonstrated mild tenderness, 9% demonstrated moderate tenderness and 6% demonstrated marked tenderness [389].

High levels of 1MTP pain were reported in participants with chronic tophaceous gout affecting the 1MTP [291, 377], with participants scoring a mean of 7.6 cm to 7.8 cm on a 10 cm pain VAS [291].

3.4.4 Structural characteristics

Structure of the 1MTP has also been assessed in people with gout through the presence of self-reported hallux valgus, a structural forefoot deformity involving lateral deviation of the hallux at the 1MTP [321, 376]. A case-control study involving 164 participants with gout found that self-reported hallux valgus was significantly more common in participants with gout [376]. However, a larger cohort study involving 1,184 participants with gout revealed 36% of participants had self-reported hallux valgus, which the authors reported was similar to the general population and not related to gout-specific factors [321].

3.4.5 Functional characteristics

Moderate to high levels of general disability and walking disability were reported using a 100 mm VAS in participants with current acute 1MTP arthritis (mean 60.0 mm to 64.1 mm) [381]. Similarly, when using the Hallux Metatarsophalangeal-Interphalangeal section of the American Orthopaedic Foot and Ankle Society (AOFAS) scale [390], which provides a total score out of 100 based on pain, range of motion, joint instability and alignment, and activity- and footwear-related limitations, participants with 1MTP tophi scored very highly (65 to 61) [291].

A study on 164 participants with gout found a significant association between acute 1MTP arthritis and the presence of 1MTP osteoarthritis, defined as restricted motion, bony swelling and/or crepitus [362]. In a further study of participants with severe tophaceous gout, the mean total range of motion at the 1MTP was 19°, which reduced to 14° in joints that also demonstrated severe cartilage loss [291].

A study assessing foot function in 25 participants with long-standing chronic gouty arthropathy using in-shoe plantar pressure analysis found peak plantar pressure beneath the first metatarsal was greater in the gout group, although not significantly [318]. However, peak plantar pressure and pressure-time integrals beneath the hallux were significantly reduced in the gout group when compared to the controls, which the authors proposed reflected an attempt to offload pain at the 1MTP [318].

3.4.6 Microscopy

The success of joint fluid acquisition for the purposes of microscopic identification of MSU crystals from the 1MTP ranged from 81% to 91% [112, 378, 387]. The presence of MSU crystals in 1MTP fluid ranged from 83% to 89% of currently asymptomatic 1MTPs in participants with gout with a history of acute 1MTP arthritis [112, 126]. In participants with gout with no history of acute 1MTP arthritis, 52% to 67% of aspirated 1MTPs were positive for crystals [122, 126, 378]. In participants experiencing current acute 1MTP arthritis the presence of MSU crystals ranged from 85% to 93% [387, 391].

The occurrence of acute 1MTP arthritis as a diagnostic feature has been compared with the presence of MSU crystals in aspirated 1MTP fluid [104, 171]. Based on clinical characteristics of acute 1MTP arthritis in 159 participants, general practitioners diagnosed 98% of participants as having gout [171]. When validated against the presence of MSU crystals, a sensitivity of 0.99 and a specificity of 0.08 was demonstrated [171]. In a study of 328 participants with monoarthritis, Janssens [104] reported that the 1MTP as the location of the monoarthritis was an independent predictor of MSU crystal presence [104].

3.4.7 Imaging Features

3.4.7.1 Urate crystal deposition

Ultrasonography allows the visualisation of MSU crystal deposition along the surface of articular cartilage, referred to as the 'double contour sign', the presence of which ranged from 22% to 87.5% at the 1MTP [381, 383, 384, 386, 389]. Naredo et al. [383] noted the double contour sign was more frequent at the dorsal aspect of the 1MTP (62%) compared to the plantar aspect (23%).

Dual-energy computed tomography (DECT) may be less sensitive than ultrasound due to the lower spatial resolution [288]. In a study of 39 participants (79% with newly diagnosed gout) DECT detected urate crystals in 26% of 1MTPs, and ultrasound in 74% of the same joints [288]. The presence of MSU deposition using DECT increased from 26% of joints in newly diagnosed gout [290], to 36% after 5 years disease duration [293], and 54% in participants with 11 years mean duration [382]. In participants with tophaceous gout and a mean disease duration of 22 years, MSU crystals were present in 38% of 184 1MTPs [194].

In a DECT study assessing feet with current flares, the authors reported crystal deposition in 41% of 1MTPs in participants with 1MTP flares, compared to 27% of 1MTPs in participants with current ankle flare [293]. The presence of DECT MSU crystal deposition was found to be a risk factor for acute 1MTP arthritis (Odds Ratio = 3.38) [293].

3.4.7.2 Tophi

In sonographic studies, the presence of tophi in 1MTPs of participants with gout ranged from 50% to 100% [114, 381, 383, 384, 388, 389]. Thiele and Schlesinger [114] noted tophi were more often seen medial and dorsal to the joint with a distinct pattern in which unformed micro-particles were seen in the dorsal proximal recess and central area, while formed tophi were more frequent in the medial compartment and impinging on the dorsal proximal phalanx [114]. Using MRI, a study of 15 participants with 1MTP tophaceous gout, reported that the medial sesamoid was the most common location for tophaceous infiltration (seen in 47% of participants), followed by the first metatarsal shaft (40%) and lateral sesamoid (33%) [291]. In the majority of participants (57%) tophi were observed both extra-articularly and intra-articularly at the 1MTP.

3.4.7.3 Bone disease

In participants with long-standing tophaceous gout, erosions on conventional radiography were noted in 79% of 1MTPs [194]. Other conventional radiographic features of bone damage have been observed frequently in the 1MTP joints in people with gout including spur formation (40% of joints), joint space narrowing (39%), osteophytes (44%), sclerosis (73%) and periosteal new bone formation (13%) [194]. A study of 262 participants with gout reported conventional radiographic proven osteoarthritis (defined as destruction of the articular surfaces) in 44% of 1MTPs and found a significant correlation between osteoarthritis and acute arthritis at this joint [361].

Sonographic evidence of bone erosion in 1MTPs ranged from 40% to 67% in participants with gout [114, 375, 381, 388, 389]. Wright [389] reported 92% of detected erosions were present on the medial aspect of the metatarsal head, with 7% on the dorsal metatarsal head, and the remaining 2% on the medial aspect of the proximal phalangeal base. Erosions at the 1MTP can

be multifocal or unifocal and generally measure at least 2 mm in diameter [381, 389]. Thiele and Schlesinger [114] noted all erosions at the 1MTP were adjacent to tophaceous material.

Using MRI, Kim [291] reported erosions and intraosseous involvement present in the first metatarsal shaft of 40% of participants with symptomatic 1MTP tophaceous gout. Using conventional CT, Dalbeth [294] reported 78% of 1MTPs had erosions present at the first metatarsal head, and 34% had erosions at the proximal phalanx. The proportion of eroded bone was also greater at the metatarsal head compared to the proximal phalanx and was higher in those with clinically-evident tophi.

3.4.7.4 Synovial disease

Synovial disease, in the form of joint effusion, synovial hypertrophy, and synovitis has been assessed using both grey-scale and power Doppler ultrasound [114, 381, 386, 389]. Joint effusion, which has been observed in 29% to 74% of 1MTPs in people with gout [114, 381, 386, 389], is less specific for gout and has been seen at a similar rate in other rheumatic conditions (64% to 73%) [114, 389]. Similarly, synovial hypertrophy is seen at a similar rate in gouty 1MTPs (53% to 87%) [381, 386, 389], and other rheumatic conditions (64%) [389]. Synovitis, which can be assessed using power Doppler ultrasound has been shown to be more sensitive than clinical assessment (18% versus 5%, respectively) [386]. Synovitis has been reported to occur at the 1MTP with a mild Doppler signal in 15%, moderate signal in 18% and marked signal in 10% [389]. Synovitis occurs at a significantly greater frequency in 1MTPs in those joints with acute arthritis, with Kang [381] reporting 95% of 1MTPs with acute arthritis demonstrated mild to moderate power Doppler signals. However, synovitis is not specific to gout and is seen in 18% to 50% of other inflammatory joint diseases [114, 389].

3.5 Discussion

The historical observation of gout as a condition specifically affecting the 1MTP is reflected in modern epidemiological literature, and is evident by the pooled 73% prevalence estimate of 1MTP acute arthritis reported in the meta-analysis of 11 studies. The clinical diversity between these studies, which is generally considered inevitable in meta-analyses [392], may explain the wide range of estimated prevalence values and account for the high heterogeneity observed.

The included studies represented participants with gout from a wide range of countries, resulting in different participant demographics, genetic factors and lifestyle factors. Additionally, disease duration of participants with gout varied considerably and is likely to impact the calculated prevalence estimate, as longer disease duration would increase the likelihood of experiencing an episode of acute 1MTP arthritis. Furthermore, only 42% of participants included in the meta-analysis were diagnosed with gout using the gold standard MSU crystal identification [31, 37, 104, 126, 144, 287, 288, 338, 380]. The differences in study designs adopted by the included studies (e.g. cohort, cross-sectional, case-control, retrospective and randomised controlled trial) may also have contributed to the increased heterogeneity. Nevertheless, this prevalence estimate provides useful quantitative data that corroborates the traditional notion that gout is a condition with frequent manifestations at the 1MTP.

Pain experienced during acute 1MTP arthritis is considerable [171, 172, 381], and remains present following the resolution of acute symptoms [321, 389]. Outcome measurement methods used for measuring 1MTP pain varied from 5-point Likert scales [172], visual analog scales [171, 381], simply recording whether 1MTP pain was present or absent [376], to measuring tenderness with palpation [389]. However, it appears that 1MTP pain is a chronic foot problem in people with gout, which is further reflected by the sub-clinical joint inflammation observed during intercritical periods [386, 389]. In participants with 1MTP tophaceous gout, high levels of pain are coupled with reduced joint function [291, 377]. Although it is unclear whether these clinical symptoms are a consequence of pain-avoidance, joint damage, synovial inflammation, mechanical obstruction by tophi, or a combination of these factors, the clinical implications of symptomatic 1MTP gout on the ability to undertake everyday weight-bearing activities, such as walking, are recognised as important features of the disease [381]. People with gout walk significantly slower and demonstrate gait patterns consistent with 1MTP pain-avoidance strategies [318]. Abnormal 1MTP loading at toe-off in people with gout may be further exacerbated by biomechanical strain as a result of MSU deposition within the 1MTP flexor and extensor tendons [292, 293].

As the initiation of acute gouty arthritis is not possible in the absence of MSU crystals, the susceptibility of the 1MTP to gout over other joints must be related to certain factors which predispose to the precipitation and deposition of crystals at this site. It has been hypothesised that the predilection for MSU deposition and patient symptoms in the foot and ankle may be attributed to the biomechanical loading or physical stress during the normal gait cycle [114, 194, 292, 294]. This is further emphasised in the distinct pattern of crystal deposition at the 1MTP observed in imaging studies where MSU deposits have been reported to occur more often on the medial and dorsal aspects of the joint compared to the plantar aspect [114, 383, 393]. It has

been proposed that this distinct pattern of crystal deposition at the 1MTP may result from the shifting of tophaceous deposits with dorsiflexion during walking and their eventual clustering at pressure points within the joint [114].

Osteoarthritis observed at the 1MTP has also been implicated in the co-occurrence of gout at this joint [361, 362]. However, the distinction between joint damage caused by chronic gouty arthritis and osteoarthritic joint damage is unclear, particularly due to the high prevalence of 1MTP osteoarthritis in the general population [394].

This review has a number of limitations. Firstly, the literature search and screening was conducted by a single reviewer. Secondly, the methodology adopted may have created a selection bias through the exclusion of non-English language studies, which may have resulted in an incomplete and potentially biased set of evidence. In regard to the methodologies used in included studies, most were cross-sectional descriptive studies, which provide lower-level evidence and limit investigation in to the cause-effect relationship between 1MTP characteristics and gout. Many of the studies also involved small sample sizes. Furthermore, gout disease characteristics of participants in the included studies varied and the majority of participants were diagnosed based on clinical criteria. Although this reflects diagnostic methods employed in clinical practice, there are several limitations to current classification criteria [153] and the demonstration of MSU crystals in synovial/tophus aspirates remains the only method to permit a definitive diagnosis of gout [120]. Lastly, there is an absence of a recommended outcome measure to assess patient-reported outcomes relating specifically to the 1MTP in gout research which makes comparisons between studies challenging.

This review highlights the need for future research that adopts standardised assessment approaches when investigating patient-reported outcomes specifically relating to the 1MTP in gout. Advanced imaging may be implemented to determine the structural characteristics of the joint in relation to clinical features, particularly how 1MTP involvement affects patient-reported outcomes and the ability to carry out daily activities, including walking. This may direct further research that investigates the biomechanical role of the 1MTP in the frequent occurrence of gout at this joint. By recognising the local factors that contribute to the 1MTPs susceptibility to crystal deposition and inflammation, further studies may assess non-pharmacological interventions that are specifically aimed at the 1MTP including footwear, foot orthoses and foot-related health education, which have previously been shown to be effective with general-foot pain and disability in people with gout [317, 335, 337].

3.6 Conclusion

This review aimed to evaluate and summarise the findings from existing literature that assessed the 1MTP in people with gout. This review confirms the long-standing notion that acute 1MTP arthritis is highly prevalent in people with gout and has a substantial impact on patient-reported outcomes related to pain and disability. Current research also suggests that the structure and function of the 1MTP is impaired in people with gout. This review highlights the importance of clinical, laboratory and imaging findings related to the 1MTP in the diagnosis of gout in clinical practice and underlines the need for interventions that specifically target improvements in structure, function and patient-reported outcomes related to the 1MTP in people with gout.

Chapter four: Imaging in gout and asymptomatic hyperuricaemia

4.1 Introduction

Medical imaging techniques used for gout have developed and advanced considerably in recent research. Conventional radiography has been surpassed by the use of more advanced imaging techniques, including conventional computed tomography (CT), dual-energy computed tomography (DECT), magnetic resonance imaging (MRI), and musculoskeletal ultrasound. These advanced techniques have allowed improved accuracy in establishing early diagnosis of gout, particularly when monosodium urate (MSU) crystals are unable to be identified through microscopy. The application of imaging in gout research has also facilitated a better understanding of the pathogenesis of gout and has proven useful in monitoring disease activity and treatment response. Advanced methods of imaging, particularly DECT and ultrasound, have also provided a better understanding of the impact of subclinical MSU deposition in people with asymptomatic hyperuricaemia. This chapter will review current literature that has used conventional radiography, CT, DECT, MRI and musculoskeletal ultrasound to assess musculoskeletal structures in people with gout. The chapter will conclude with a particular focus on the sonographic features of gout as well as the monitoring and diagnostic value of ultrasonography in people with gout.

4.2 Conventional radiography

Conventional radiography is the traditional and most widely available imaging modality, which utilises radiation energy to produce a two-dimensional projected image of internal body structures. The resulting image is dependent on the density and composition of the object being imaged, which informs the amount of x-ray beams absorbed or reflected. It allows visualisation of multiple areas at a relatively low cost with limited exposure to ionising radiation. As such, conventional radiographic appearances of gout are well-established and appear in several classification criteria [120, 144, 152]. However, as the conventional radiographic appearance of acute gouty arthritis is non-specific and often normal, apart from soft-tissue swelling [395], the diagnostic role of conventional radiography is limited to the detection of advanced features of gout, which often take up to 10 years to develop after disease onset [396, 397]. Furthermore, although conventional radiography has demonstrated high specificity (0.93) when compared

against the clinical gold standard in people with advanced gout, the diagnostic sensitivity is low (0.31) [398]. This suggests that radiography has a strong ability to correctly identify those without gout (specificity), but a weak ability to correctly identify those with gout (sensitivity).

Although conventional radiography cannot detect MSU crystal deposition or inflammatory changes in synovial and osseous tissue, it is able to visualise features seen in more advanced gouty arthropathy including tophi, erosions and new bone formation. Subcutaneous tophi appear as non-specific soft tissue opacities with or without calcification [399]. Erosions in gout may be located intra- or peri-articularly, as well as intra-osseously and have a characteristic punched-out appearance, often with an overhanging margin. Joint space in gout is usually preserved until advanced disease. New bone formation is frequent in gout and appears as sclerosis, osteophyte formation and bone spurs [194, 400]. Although peri-articular osteopenia is absent in gout [401], subchondral cystic changes and collapse may occur [396]. Conventional radiographic features of chronic gouty arthropathy are well-correlated with clinically-evident tophi [254, 402] and DECT-evident MSU crystal deposition [194]. Conventional radiographic changes in gout are most commonly seen at the first metatarsophalangeal joint (1MTP), followed by the fifth metatarsophalangeal joint, midfoot and hand [403].

Conventional radiography has limited capability for the diagnosis of gout but may provide a useful means of monitoring disease. A conventional radiographic bone erosion scoring system for chronic gouty arthropathy was developed based on the Sharp/van der Heijde system [196] and has demonstrated high correlation with musculoskeletal disability [193] and markers of bone resorption [119] in gout. Furthermore, the use of urate lowering therapy has been shown to reduce this conventional radiographic score alongside decreased soft tissue masses and increased sclerosis over a 12 month period [404], suggesting conventional radiographic scoring of bone erosion may be a sensitive tool to monitor changes in bone damage over time.

4.3 Conventional computed tomography

Conventional CT is considered the gold standard for bone erosion in inflammatory joint disease [405] due to its three-dimensional multi-planar scanning technique. CT scanning utilises multiple x-ray beams directed at the body from several angles, which produces a cross-sectional image. However, compared to conventional radiography, the cost and exposure to ionising radiation is higher. As with conventional radiography, CT cannot detect MSU crystal deposition or inflamed soft tissue so has limited diagnostic sensitivity in early gout.

Tophi can be differentiated from bone and soft tissue on CT and appear as discrete dense masses of approximately 170 Hounsfield units [406]. Tophi can be well visualised both intra- and extra-articularly, as well as within tendons and subcutaneous tissue [407, 408]. CT has also allowed the demonstration of the relationship between tophi and bone erosions [294, 409], with 82% of joints with CT-evident erosions also demonstrating tophi [409]. This supports tophus infiltration as a dominant mechanism behind the development of bone erosion in gout [119, 410]. CT can also visualise several forms of new bone formation in gout including sclerosis, osteophytes and periosteal new bone formation [400].

Despite the limited diagnostic value of CT in gout, it may prove useful in assessment of bone damage and tophus burden [294, 406]. A semi-quantitative CT bone erosion scoring system has been developed for use in gout research, which involves the assessment of seven bones in the midfoot and ankle that are areas frequently affected by gout, but poorly visualised by conventional radiography [294]. This scoring system demonstrated excellent inter-rater reliability [294]. CT has also shown excellent inter-rater reliability for the measurement of tophus volume [406]. A strong correlation was also found between physical and CT measurements of tophus dimensions [406]. However, further use and validation of CT in monitoring gout progression is yet to be undertaken.

4.4 Dual-energy computed tomography

Unlike other imaging techniques, DECT is able to directly identify and differentiate MSU crystals from surrounding material in joints, tendons, ligaments and soft tissue structures [411]. DECT involves the use of two x-ray sources running simultaneously at 80 kV and 140 kV, which provides two data sets with different attenuation. This enables colour coding of the chemical composition of the materials scanned [411]. DECT-evident MSU deposition has been verified against the gold standard synovial fluid analysis [292, 412] and has recently been included as a criterion in the 2015 ACR/EULAR Classification Criteria for gout [152]. DECT has also been shown to demonstrate high inter-rater reliability for the detection of MSU crystal deposition [412]. However, compared with other imaging modalities, DECT has limited availability, is expensive and exposes the patient to ionising radiation.

The sensitivity and specificity of DECT-detected MSU deposits varies and ranges from 0.75 to 1.0 and 0.84 to 1.0, respectively [293, 382, 412-416]. Although DECT has detected MSU deposits in participants with no clinical evidence of tophi [414, 417], the diagnostic sensitivity of DECT is

reduced in the absence of tophaceous disease [417, 418]. A DECT study of participants with acute gouty arthritis and no prior history of gout found that 20% of participants did not demonstrate MSU deposition on DECT [417]. This may be a result of an inability to detect smaller MSU deposits [419] and may explain the association between detectable MSU deposits and disease duration, urate lowering therapy and serum urate levels [289, 416, 419, 420]. The diagnostic usefulness of DECT may therefore be limited in early gout.

The sensitivity of DECT in gout is also dependent on the anatomical site being imaged [417] with the 1MTP, knee joint and ankle being the most common sites for MSU deposition, whereas DECT-detectable MSU deposits are less frequent in the upper limb joints [414]. Furthermore, the specificity and sensitivity of DECT is also influenced by the imaging software settings; in particular the parameter ratios [411, 421]. A standardised diagnostic protocol for DECT has yet to be developed. Previous research protocols vary from scanning only the most symptomatic joint [412], or the most frequently affected site (i.e. feet/ankles) [422], or including all peripheral joints (i.e. feet/ankles, knees, wrists/hands, elbows) [413, 414]. Due to the high cost of DECT and the exposure to ionising radiation, fewer sites would be preferred in the development of a diagnostic protocol.

DECT may also be useful in monitoring the change in MSU burden in response to treatment due to its ability to measure tophus volume [423, 424]. The reproducibility of DECT tophus volume measurements is very high with excellent inter- and intra-rater reliability [412, 413, 425]. DECT has also been shown to be more reproducible than physical methods of assessing tophus size [422]. However, the measurable MSU volume has been shown to be below the smallest detectable change in people with gout undergoing urate lowering therapy, which may limit the potential of DECT in monitoring the response to treatment [420].

To date, three studies have utilised DECT to assess urate deposition in participants with asymptomatic hyperuricaemia, with contrasting results [293, 382, 426]. Kimura-Hayama et al. [426] assessed the prevalence of urate deposition in 27 renal transplant participants with asymptomatic hyperuricaemia. They reported only one MSU deposit in a quadriceps tendon resulting in a low prevalence of 0.03%. However, this may be explained by the definition of hyperuricaemia as ≥ 0.38 mmol/l. In contrast, a two-arm cross-sectional study observed MSU deposits in the feet of 86% of 22 asymptomatic participants with moderate hyperuricaemia (mean urate 0.49 mmol/l) compared to 98% of participants with gout [293]. The areas of urate distribution were similar in both groups with the distal first toe being the most common, followed by the 1MTP and distal fifth toe [293]. Dalbeth et al. [382] also assessed the distribution of MSU deposition in the feet, including joints and tendons. However, they observed MSU

deposition in only 24% of 25 asymptomatic participants with severe hyperuricaemia (defined as ≥ 0.54 mmol/l), compared to 84% of 33 participants with gout. Although DECT urate deposition was observed in both joints and tendons in participants with asymptomatic hyperuricaemia, the tophus volume was much lower compared to the gout group, suggesting that volume may influence the progression to symptomatic gout [382]. These three studies provide a rationale for further longitudinal research that attempts to determine factors relating to urate presence and volume contributing to the progression of symptomatic gout in individuals with hyperuricaemia.

4.5 Magnetic resonance imaging

MRI utilises a powerful oscillating magnetic field and radio waves to provide excellent contrast and resolution of both soft tissue and osseous structures without exposure to ionising radiation. However, its high cost, restricted availability and limited patient acceptability, particularly in those with aneurysm clips and pacemakers, reduce its role in the routine assessment of gout.

Similar to DECT, MRI cannot detect small MSU deposits on cartilage surfaces [427], however MRI demonstrates high specificity (0.98) and moderate sensitivity (0.63) when compared to DECT for the detection of tophi [428]. Tophi appear as discrete masses with low signal intensity on T1-weighted images and with variable signal intensity on T2-weighted images [403]. MRI has demonstrated greater sensitivity for the detection of soft tissue and osseous tophi when compared to conventional radiography and physical examination [429]. Both inter- and intra-rater reliability for the detection of tophi on MRI is high [379, 421].

MRI also has the potential to reliably visualise less specific features of gout, including synovitis, effusions, erosions, cartilage damage and bone marrow oedema [379, 421, 429-432]. MRI has demonstrated the presence of synovial inflammation in 87.5% of asymptomatic participants with gout emphasising the persistence of subclinical inflammation despite the absence of acute gouty arthritis [379, 433]. Erosions are also commonly seen on MRI in participants with gout [432], which demonstrates greater sensitivity than conventional radiography and ultrasound for this feature [433]. Prevalence of bone marrow oedema is highly variable in participants with uncomplicated gout (ranging from 1% to 56%) [311, 379, 427, 428], although appears to be a characteristic feature in gout complicated by osteomyelitis [311]. An MRI cartilage damage scoring system (GOMRICS) has also demonstrated good correlation with the conventional radiographic Sharp van der Heijde score for joint space narrowing in participants with gout [431]. The authors reported that cartilage damage was closely associated with erosions, synovitis, and

tophus size suggesting the influence of MSU crystal deposition may contribute to the focal lesions observed in cartilage and bone.

The use of MRI in monitoring treatment response has not yet been established, however MRI has demonstrated good intra- and inter-rater reliability for measuring tophus volume with absolute percentage differences reported as 17.2% and 14.2%, respectively [432]. However, unlike DECT, tophus volume measurement using MRI involves a time-consuming manual outlining procedure which would likely limit its practicality in clinical and research settings [432].

4.6 Ultrasonography

Musculoskeletal ultrasound involves the transmission of high frequency sound waves which are reflected back from internal tissue interfaces to produce a two-dimensional image. Through this mechanism, ultrasound is able to create high resolution images of both soft tissue and osseous pathology. Ultrasound has several advantages over other advanced imaging modalities due to its dynamic, real-time capabilities, which allow the assessment of moving joints and give the examiner complete control to fully investigate the areas of interest [435]. Furthermore, ultrasound produces no radiation, is relatively low cost compared to other imaging techniques and is portable and time efficient [436, 437]. However, the reliability of ultrasound is highly dependent on the skill of the examiner and requires a degree of experience in both acquisition and interpretation of the images [435]. Although the penetration depth of ultrasound is limited compared to other imaging, it provides excellent resolution of small peripheral joints [436], such as those affected in gout.

4.6.1 Image acquisition and interpretation

The high frequency sound waves typically used in ultrasound imaging range from 3 to 15 MHz [438]. These sound waves are produced by the ultrasound probe that converts electrical energy to mechanical energy known as the piezoelectric effect. The higher the frequency, the better the resolution, but the less penetration of sound waves to deeper structures. A proportion of the ultrasound waves transmitted from the probe into the body tissues are reflected back and converted into a two-dimensional grey scale image. The appearance of the ultrasound image is dependent on the reflectivity of the acoustic interfaces that the sound waves encounter as they travel through the body's structures. Echogenicity refers to the ability of these structures to

reflect ultrasound waves back to the transducer [439, 440]. Hyperechoic structures are highly reflective so appear whiter, while hypoechoic structures are not as reflective and appear grey. Anechoic structures completely lack reflection so appear black.

Sound waves cannot penetrate bone, which appears anechoic on ultrasound with a hyperechoic rim and an acoustic shadow beyond it [439]. Cartilage and muscle, which are more penetrable by ultrasound than bone, appear hypoechoic. Ligaments, tendons, fascia, and other connective tissues appear hyperechoic due to their greater reflectivity, while fat and fluid appear anechoic on grey scale images. Musculoskeletal ultrasonography also has Power Doppler capabilities, which can detect flow-rate within blood vessels [441]. Flow towards the probe appears red, while flow away from the probe appears blue [439]. The echogenicity of structures is highly dependent on the angle of incidence at which the sound waves encounter the surface of the structure. When the probe is perpendicular, more ultrasound waves will be reflected back to the transducer resulting in a higher resolution image. Anisotropy, which is a deceptive hypoechoic appearance, occurs when the angle of incidence is not perpendicular, and can greatly influence interpretation of the resulting image [438].

4.6.2 Sonographic features in gout

4.6.2.1 Synovial inflammation

Sonographic examination in gout will demonstrate a wide spectrum of findings indicative of synovial inflammation. Synovial inflammation is identifiable by joint effusion, synovial hypertrophy and the Power Doppler signal [442]. These features have been identified in gout even in the absence of clinical evidence of acute arthritis [389, 443]. This persistent nature of subclinical inflammation in gout was evident in a longitudinal study (n = 30) in which the number of clinically active joints decreased once acute arthritis resolved, but sonographic features of synovitis did not disappear [442].

Synovial effusion appears as a compressible anechoic or hypoechoic joint cavity widening [443]. The reported prevalence of synovial effusion is variable and has been observed in 26% to 90% of people with gout [114, 381, 386, 389, 393, 443-445]. The sonographic presence of joint effusion is considerably higher than clinical evidence of effusion [393, 443]. Despite this high sensitivity, joint effusion has also been observed in 64% to 73% of disease controls and 13% of healthy controls [114, 389]. The 1MTP and knee joints, which are routinely imaged in sonographic studies [114, 386, 389, 393, 398, 443, 445], are susceptible to joint effusions

through hydrostatic pressure and active joint motion, which may account for the high prevalence of effusion regardless of whether gouty arthritis is present or not.

Synovial hypertrophy, which appears as a hypoechoic thickening of the synovial membrane, also has a variable prevalence in gout ranging from 8% to 97% [381, 386, 389, 393, 445]. As with synovial effusion, synovial hypertrophy has also been observed in 15% to 64% of other inflammatory diseases and 6% of controls [389, 398, 445].

Evidence of the power Doppler signal, which represents increased vascularisation, has been observed in 8% to 100% of people with gout during both episodes of acute arthritis and asymptomatic periods [114, 182, 381, 386, 389, 398, 443, 445, 446]. However, this highly sensitive feature lacks specificity as it is present in 50% of other arthropathies [389]. Inter-rater reliability for measuring power Doppler signal in gout is excellent ($k = 0.96$) [182].

The presence of intra-articular hyperechoic spots within synovial fluid, also referred to as “bright stippled foci” has been documented commonly in gout, with a prevalence ranging from 12% to 93% of joints examined [182, 381, 389, 398, 447]. These spots are thought to represent MSU crystals in the synovial fluid producing small bright echoes [448]. With gentle pressure from the ultrasound transducer, these small mobile aggregates appear to float within the joint space, creating a “snowstorm appearance” [448]. However, intra-articular hyperechoic spots have been reported in 14% to 35% of other types of arthritis [389, 447] and in up to one quarter of controls [383, 389, 398]. These reflective spots may also represent joint debris or bubbles from joint movement which often cannot be differentiated from MSU crystal aggregates [448, 449]. The presence of hyperechoic spots is therefore not considered a specific sonographic feature for gout [450]. However, studies have demonstrated high inter-rater agreement and excellent intra-rater agreement for both bright stippled foci ($k = 0.73$, and 0.88 , respectively) and the snowstorm appearance ($k = 0.71$ and 0.81 , respectively) [447]. In contrast, a recent study reported the inter-rater reliability for aggregates was poor ($k = 0.21$) [451].

The prevalence of synovial inflammation in individuals with asymptomatic hyperuricaemia has been investigated by four studies. Synovial hypertrophy was reported in 52% [313], effusion in 15% [444], and the Power Doppler signal in 23% [314] of participants with asymptomatic hyperuricaemia. The prevalence of either of these features of soft tissue inflammation was reported by a further study to occur in 42% of participants with asymptomatic hyperuricaemia [312].

4.6.3.2 Articular cartilage

The normal appearance of articular cartilage presents sonographically as two well-defined hyperechoic margins demarcating an anechoic and homogenous layer [448]. With MSU deposition on the cartilage surface, the superficial margin is enhanced and appears as thick as subchondral bone [398]. This hyperechoic, irregular band over the anechoic hyaline cartilage is described as the double contour sign [114]. The reflectivity of the margin is independent of the angle of incidence so can be confirmed by dynamic assessment and differentiated from the cartilage interface sign, which is seen at a 90 degree insonation angle [114, 448]. The double contour sign is best visualised on the dorsal aspect of the 1MTP and the femoral condyles [383, 445], whereas joints with thin cartilage or osteoarthritis limit the visibility of the sign [452].

The reported prevalence of the double contour sign is highly variable in the gout population, ranging from 10% to 92% of participants imaged [114, 182, 315, 381, 383, 386, 389, 393, 444, 445, 447, 452-455]. The prevalence appears to be dependent on the joint being assessed with the prevalence ranging from 2% to 44% in knee joints [383, 452-454] and 22% to 92% of 1MTPs [114, 383, 386, 389, 452, 454]. The higher 92% prevalence was observed in joints with current acute gouty arthritis [114], whereas the lower 22% was observed in asymptomatic 1MTPs [389]. Although a higher frequency of the double contour sign has been observed in joints with a history of acute gout versus clinically unaffected joints [315], the sign has also been observed in 25% to 48% of individuals with asymptomatic hyperuricaemia [125, 312, 313, 315, 444].

Against the gold standard presence of MSU crystals under microscopy, the sensitivity of the double contour sign ranges from 44% to 77% in individuals with gout [453, 456]. The specificity of the double contour sign appears to be greater than the sensitivity with numerous studies reporting the absence of the double contour sign in both healthy controls [313, 389, 444] and individuals with other rheumatic diseases [114, 389, 448]. Contrastingly, Naredo et al. [383] observed the double contour sign in 17% of control participants, 64% of whom had other rheumatic diseases. Ottaviani et al. [452] also reported the double contour sign in 21% of knees in their disease controls, however no double contour sign was observed in metatarso- or metacarpo-phalangeal joints in the controls. A recent retrospective study (n = 225 joints) found that although the double contour sign was able to predict a crystal-related joint disease, it could not distinguish between them, with a specificity of just 64% for gout [457].

Reliability analyses have reported inconsistent results regarding both the inter- and intra-rater agreement for the double contour sign, raising doubts about the usefulness of the traditionally regarded high diagnostic value of this sonographic feature. Inter-rater reliability for measuring the double contour sign ranges from moderate ($k = 0.47$) to excellent ($k = 0.96$) [125, 182, 447, 451-453]. Intra-rater reliability also ranges from moderate to excellent ($k = 0.53$ to 1.00) [315, 447, 451, 454].

4.6.3.3 Tophi

Tophi can be visualised on ultrasound in various locations, including intra-articularly, within bursa, tendons and ligaments as well as other soft tissues [314, 448, 458]. Tophi demonstrate a varying degree of echogenicity depending on the density of the MSU crystal compaction [448]. The majority of tophi (69% to 80%) appear as irregularly-shaped heterogenic masses [458-460]. Generally tophi visualised on ultrasound appear hyperechoic (75% to 96% of imaged tophi) [458, 460]. Tophi that are sonolucent are termed “soft” tophi, while more hyperechoic material represents long-standing “hard” tophi [448]. The majority of tophi observed on ultrasound are either soft or mixed, with very few being hard [381, 389]. Eighty three to 89% of tophi also have poorly defined margins [315, 458] and 56% demonstrate a peripheral anechoic halo representing inflammatory cells [315, 459]. Very few (15%) show posterior acoustic shadowing [460]. Formed tophi can be distinguished from urate deposition along cartilage surfaces as they do not move with cartilage or bone upon motion of the joint [114]. The sonographic definition of tophi has varied considerably between studies. This has led to the recent development of a standardised definition by Outcome Measures in Rheumatology (OMERACT) as a circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (which may or may not generate posterior acoustic shadow), which may be surrounded by a small anechoic rim [450].

The sensitivity of ultrasound-detected intra-articular tophi in people with gout ranges from 19% to 100% [114, 182, 312, 315, 381, 383, 389, 393, 447, 452, 454, 456], while the sensitivity of tendon or ligament tophi is 64% in people with gout [383]. The prevalence appears to be dependent on the gout disease duration [454], serum urate level [315], and the anatomical site being imaged [383]. The most common joint sites for ultrasound-detected tophi are the 1MTP, radiocarpal joint, midcarpal joint and knees, while the most common tendon sites are at the patellar, triceps, quadriceps and Achilles tendons [383]. Tophi have been reported to be present equally in joints with current acute arthritis and in asymptomatic joints in participants with gout [315]. Furthermore, intra-articular and tendinous tophi have also been identified in individuals with asymptomatic hyperuricaemia with a prevalence ranging from 16% to 45% [125, 312-314].

The specificity of ultrasound-detected tophi is also variable. Reuss-Borst [312] reported a 19% prevalence of tophi in healthy control participants, while the prevalence of tophi in individuals with arthropathies other than gout ranges from 7% to 35% [383, 389, 447, 452, 456]. Three studies identified no tophi in control participants [114, 313, 389]. The sensitivity and specificity of ultrasound in diagnosing gout and asymptomatic hyperuricaemia increases with the identification of either tophi or the double contour sign with a sensitivity of 100% and specificity of 76% to 88% [125, 288].

When compared to the gold standard microscopic identification of MSU crystals, the criterion validity of sonographically-detected tophi is high (83% to 93%) [456, 461]. Ultrasound also shows high construct validity when compared against MRI for detecting tophi, with 90% of tophi on MRI being detectable by ultrasound [461]. The inter-rater reliability for sonographic evidence of tophi ranges from $k = 0.63$ to 1.0 [125, 182, 315, 433, 451, 452, 454, 459].

4.6.3.4 Bone

The sonographic appearance of bone erosion is described as irregularity or discontinuity of the hyperechoic bone surface, evident in two perpendicular planes [450]. The prevalence of ultrasound-detected erosions ranges from 24% to 66% in participants with gout [114, 312, 381, 389, 398, 460] and 12% to 23% in participants with asymptomatic hyperuricaemia [312, 313]. Erosions appear to be more common in clinically involved joints in participants with gout [433] and a strong association has been observed between the frequency of acute arthritis and erosion presence [389]. However, erosions have also been identified in joints that have never been subject to acute arthritis and in the absence of any clinical tenderness [389]. Erosion presence has been correlated with disease duration, but not with serum urate [389, 443].

The specificity of ultrasound-detected erosions for gout is low, as the prevalence of erosions has been reported in up to 43% of joints imaged in other inflammatory conditions [114, 389, 398, 460]. Similarly, erosions are present in 6% to 19% of healthy controls in the absence of any arthritic disease [312, 313, 389]. The specificity of ultrasound-detected erosions in diagnosing gout may be increased through the observation of adjacent tophi or synovial inflammation [114, 389, 460]. A strong correlation has been observed between bone erosions and the presence of ultrasound-detected tophi [389], while 37% of erosions have also been shown to demonstrate the power Doppler signal [389].

Compared to MRI, ultrasound underestimates the extent and number of erosions [433]. However, several studies have shown that ultrasound can detect erosions with a greater sensitivity than conventional radiography [114, 389, 398, 433]. Wright et al. [389] reported ultrasound detected significantly ($P < 0.05$) more 1MTP erosions in participants with gout (66%) compared to conventional radiography (28%). Ultrasound is particularly useful for the detection of small erosions < 2 mm, which are not seen radiographically [443].

The inter-rater reliability for the identification of erosions in gout is high, ranging from $k = 0.74$ to 1.0 [182, 389, 433, 447, 451], while the intra-observer reliability has been reported to be excellent [447].

4.6.5 Diagnostic value

Studies assessing the diagnostic performance of ultrasound are limited [171, 456]. Most ultrasound studies assess participants with long-standing gout where a diagnosis has already been established. Pascal et al. [455] recently assessed the diagnostic performance of ultrasound in participants with current acute arthritis, many of whom were experiencing their first symptoms. Tophi or the double contour sign were assessed in symptomatic joints and other joints (knee, ankle, 1MTP). When assessing symptomatic joints with current flares, sensitivity for gout was 60% and specificity 92%. When other joints were taken into account, sensitivity rose to 84%. However, the specificity dropped to 78%. The reduced sensitivity may have been because of the shorter gout disease duration of the participants, as MSU crystals are known to accumulate over time [455]. This is illustrated in a recent multi-centre study reported by Ogdie et al. [462] who assessed the diagnostic value of ultrasound in early and long-standing disease using MSU crystal identification as the gold standard. The authors reported a greater sensitivity in those with long-standing disease duration (> 2 years) compared to early disease for the presence of the double contour sign (63% vs. 51%) and tophus (51% vs. 34%). Specificity remained consistently high across disease duration, ranging from 91% to 95%.

There is currently no consensus on the sonographic features and anatomic sites to be scanned for the diagnosis of gout. Few sonographic assessment protocols have been proposed for the diagnosis of gout [182, 383, 456, 457]. Using MSU crystal identification as the gold standard, Peiteado et al. [182] established the accuracy of a four-joint ultrasound test for the diagnosis of gout. They found that a simple six minute ultrasound examination of bilateral knees and 1MTPs

allowed detection of either tophi or the double contour sign in 97% of participants with crystal-proven gout. Similarly, Naredo et al. [383] assessed the diagnostic value of a 12-site ultrasound assessment (including bilateral assessment of one joint, three articular cartilages and two tendons) for MSU aggregates and the double contour sign. They reported acceptable sensitivity (85%) and specificity (83%) for the diagnosis of gout. However, it should be noted that participants in these studies had long-standing disease, were asymptomatic at the time of assessment and already had a known diagnosis of gout.

Contrastingly, Lamers-Karnebeek [456] proposed a six-joint assessment in people with initial presentations of current acute arthritis. The detection of the double contour sign, tophi or the snowstorm appearance generated a sensitivity of 96% when compared with the gold standard identification of MSU under microscopy [456]. Also assessing participants presenting with acutely affected joints was a study by Loffler et al. [457] who investigated the accuracy of ultrasound in differentiating gout from other crystal deposition diseases (namely calcium phosphate deposition disease) by imaging only the affected joint. When assessing for the double contour sign, the specificity for gout was similar to that of CPPD (64% vs 52%). However, when using the double contour sign in combination with the power Doppler signal and elevated serum urate, the specificity for gout increased to 92%, although the sensitivity reduced to just 42%. It is clear from these studies that further use and validation of currently proposed diagnostic protocols are required to ascertain the ability of ultrasound to diagnose gout and differentiate it from other inflammatory conditions.

4.6.6 Monitoring value

The value of ultrasound in evaluating treatment response in people with gout has been assessed by a number of studies [384, 388, 446, 461]. Thiele et al. [388] and Ottaviani et al. [384] observed a strong correlation ($k = 0.81$ to 1.00) between decline or disappearance of the double contour sign and serum urate concentrations following seven to 18 months of urate lowering therapy. The double contour sign improved or resolved in 100% of knee joints and in 90% of 1MTPs in people achieving a serum urate target of < 0.36 mmol/l [384].

Ottaviani et al. [384] also observed a disappearance or decrease in tophi in all knee and 1MTP joints in participants achieving this urate target. Similarly, Perez-Ruiz [461] noted a reduction in the maximum diameter and volume of sonographic tophi in 53% of participants following 12 months of urate lowering therapy, while a complete resolution of tophi was observed in 24%. The authors reported high inter-rater reliability for tophus diameter and volume measurements

(ICC 0.71 to 0.83, and 0.95 to 0.98, respectively) and concluded that ultrasonography successfully fulfilled the OMERACT filter for an outcome measure [461].

The power Doppler signal also appears to be sensitive to urate lowering therapy, although less so than sonographically-detected urate deposition (double contour sign and tophi). Peiteado et al. [446] detected the power Doppler signal in 96% of participants at baseline, which reduced significantly at the 24 month follow up to 73%. Although this demonstrates responsiveness to change, the persistence of the Doppler signal raises questions regarding the use of this ultrasound finding as an outcome measure in gout, as well as the efficacy of current pharmacological management.

4.6.7 Ultrasonography: A summary

In summary, ultrasonography has clear advantages over other imaging modalities, yet its operator-dependent nature and high level of skill required in acquiring and interpreting images limits its use in clinical practice. However, the application of ultrasound in research settings has allowed the identification of several features of gout and asymptomatic hyperuricaemia, including generic signs of inflammation and damage seen in synovial inflammation and erosions, as well as more specific features of gout, including MSU deposition on cartilage surfaces and in the form of tophi. Ultrasonography also appears to be useful as a diagnostic tool and has been shown to be sensitive to change with urate lowering therapy. However, the continually improving quality of equipment and progressive understanding of sonographic interpretation in gout and asymptomatic hyperuricaemia will likely advance current knowledge in the usefulness of ultrasound during different disease stages and varying levels of clinical severity as well as at different anatomic sites.

4.7 Conclusion

Several imaging modalities have been employed in gout to aid in diagnosis, evaluate the burden of disease and monitor response to treatment. Conventional radiography, although the most widely available, is less sensitive to early changes, so has limited diagnostic capability. CT and DECT allow improved resolution images at the expense of increased radiation exposure and limited availability. DECT has the ability to directly detect MSU deposits, although is limited by its expense. MRI and ultrasonography both allow visualisation of synovial, cartilage, bone and soft tissue involvement without exposure to radiation, yet the latter is more widely available

and currently the preferred imaging modality in gout. Advanced imaging methods have also provided new insights into the pathophysiology of gout, including the role of tophi in bone erosions, the pattern of MSU deposition in anatomic areas, and the presence of subclinical inflammation and damage in individuals with asymptomatic hyperuricaemia – the significance of which is yet to be determined.

Chapter five: Aims and hypotheses

5.1 Aims

- I. To identify clinical characteristics of the 1MTP in participants with gout and participants with asymptomatic hyperuricaemia.
- II. To identify sonographic features of the first metatarsophalangeal joint (1MTP) in participants with gout and participants with asymptomatic hyperuricaemia.
- III. To determine the association between clinical characteristics and sonographic features of the 1MTP while accounting for the diagnostic group.

5.2 Hypotheses

- I. There will be significant differences in clinically assessed characteristics between participants with gout and normouricaemic controls, and between participants with asymptomatic hyperuricaemia and normouricaemic controls.
 - *Primary clinical outcome measures:* 1MTP pain and 1MTP dorsiflexion range of motion.
 - *Secondary clinical outcome measures:* foot pain and disability and gait velocity.
 - *Exploratory clinical outcome measures:* general body pain, patient global assessment, activity limitation, lower limb function, 1MTP plantarflexion and dorsiflexion muscle force, hallux valgus severity, foot type, 1MTP temperature, vibration perception threshold, protective sensation, spatial and temporal gait parameters and plantar pressure parameters.
- II. There will be a significantly higher proportion of sonographic features at the 1MTP in participants with gout compared to normouricaemic controls, and in participants with asymptomatic hyperuricaemia compared to normouricaemic controls.
 - *Primary sonographic outcome measure:* double contour sign.
 - *Secondary sonographic outcome measures:* tophus, erosion, synovial hypertrophy, effusion, synovitis, snowstorm appearance and cartilage thickness.
- III. There will be a significant association between the clinically assessed characteristics and sonographic features of the 1MTP while accounting for the diagnostic group.

- Clinical outcome measures assessed will include all the primary and secondary clinical outcome measures and selected exploratory clinical outcome measures based on the results from Aim I.
- Sonographic outcomes measures assessed will include the primary sonographic outcome measure and selected secondary sonographic outcome measures based on the results from Aim II.

Chapter six: Methods

6.1 Introduction

The three research aims explored in this thesis were addressed in a single cross-sectional study. This chapter outlines the methodology used, including the study design, participant recruitment and the collection of clinical and sonographic variables. The chapter concludes with the statistical approaches used to analyse the data.

6.2 Study design

This thesis was founded in the philosophy of positivistic observational research. This encapsulates the use of quantifiable observed phenomena using scientific methods of enquiry that lend themselves to statistical analyses. A single cross-sectional design was employed to address all research aims. This methodology provided a snapshot of the populations of interest during a pre-specified time point in which participants were asymptomatic. This allowed for an investigation of clinical and sonographic characteristics which can be considered to manifest sub-clinically (i.e. in the absence of clinical symptoms).

6.3 Participants

6.3.1 Sample size calculation

The sample size calculation was based on adjusted pooling of data derived from studies available at the time, which had reported the prevalence of the double contour sign at the first metatarsophalangeal joint (1MTP) in participants with gout, asymptomatic hyperuricaemia and/or normouricaemic controls [313, 315, 383, 389, 454]. From these studies the expected prevalence rates of the double contour sign were calculated as 20.6% in gout, 15.4% in asymptomatic hyperuricaemia and 0% in normouricaemic controls. As both 1MTPs in each participant were to be scanned, the required sample size was divided by two and increased by a design effect factor of 1.1 (corresponding to a small intra-class correlation coefficient of approximately 0.1) to account for association in the probability of the double contour sign within a participant. Sample sizes were Familywise Error Rate-adjusted for multiplicity using a

Bonferroni correction. The calculated sample sizes were 21 with gout, 29 with asymptomatic hyperuricaemia and 34 normouricaemic controls. These sizes provide approximately 80% power to detect a difference between asymptomatic hyperuricaemia and controls and 87% power to detect a difference between gout and normouricaemic controls at a Bonferroni-corrected significance level of 5% against two-sided alternatives.

6.3.2 Diagnostic group definitions

The following diagnostic group definitions were used to stratify participants into one of three diagnostic groups:

- i. Gout: participants with gout were to meet the American College of Rheumatology (ACR) Preliminary Criteria for the Classification of Acute Arthritis of Primary Gout [144] (**Table 1.1**).
- ii. Asymptomatic hyperuricaemia: participants with asymptomatic hyperuricaemia were to have no history of acute gouty arthritis, did not meet the ACR criteria [144], but had a serum urate of ≥ 0.41 mmol/l assessed on the day of the study visit.
- iii. Normouricaemic control: participants in the normouricaemic control group were to have no history of acute gouty arthritis, did not meet the ACR criteria [144], and had a serum urate of < 0.41 mmol/l assessed on the day of the study visit.

6.3.3 Inclusion and exclusion criteria

Participants were included if they met one of the diagnostic group definitions and were ≥ 20 years of age (which excludes legal minors as defined by the Auckland University of Technology Ethics Committee [AUTEC]).

Participants were excluded if they:

- i. had a history of other inflammatory arthritis;
- ii. were experiencing an episode of acute gouty arthritis at the time of the clinical visit;
- iii. had foot and/or ankle surgery in the previous 3 months;
- iv. had a history of 1MTP surgery;

- v. had lower limb amputation; or
- vi. were unable to walk 10 metres unaided.

6.3.4 Ethical considerations

Ethical approval for the study was obtained from AUTECH (13/100) (**Appendix 4**) and Locality Assessment was obtained from the Auckland District Health Board (ADHB) Research Office (A+5891). Māori consultation was sought from an ADHB Māori Research Advisor (07/2013). Potential participants were provided with an Information Sheet (**Appendix 5**) detailing the purpose of the study, the requirements of participation, and the potential risks involved. Participants were given the opportunity to ask questions or express any concerns to the researcher and/or their whanau/family prior to giving consent (**Appendix 6**). All participants were provided with travel reimbursement to cover the cost of travelling to and from Auckland University of Technology (AUT) for the study.

6.3.5 Recruitment

Participants with gout were recruited initially, followed by the participants with asymptomatic hyperuricaemia and control participants to ensure diagnostic groups were age-, sex-, and ethnicity-matched. Recruitment endeavoured to reflect the prevalence of Māori in the New Zealand gout population [27]. Participants meeting the gout diagnostic definition were recruited from the AUT Podiatry Clinic's existing rheumatology research databases, which included patients from the ADHB Rheumatology Department who had previously participated or showed interest in podiatric research. Participants not meeting the gout diagnostic group definition were recruited from AUT staff, AUT Podiatry Clinic patients, and through advertisements around the local community. Participants without gout underwent a serum urate test during the clinical visit and were then stratified into either the group with asymptomatic hyperuricaemia or control group based on their serum urate level. When the control group size was met, purposeful sampling was used to directly recruit participants with known asymptomatic hyperuricaemia from ADHB research databases.

6.4 Procedure

All data collection took place between February 2014 and January 2015 at AUT. All data were collected during a single study visit of between 80 and 90 minutes.

6.4.1 Serum urate testing

All participants who did not meet the gout group diagnostic definition underwent a serum urate test during the study visit. The Reflotron® Plus, an in-vitro diagnostic device designed for the quantitative determination of clinical chemistry parameters, was used for serum urate testing. This device uses methods similar to those used in accredited chemical pathology laboratories using a uricase assay, a method which has high reliability and precision [592]. Furthermore, to ensure quality and performance, all testing was undertaken by the researcher who was adequately trained to ensure competency and adherence to health and safety procedures. System calibration and quality control was undertaken regularly in accordance with the New Zealand Best Practice Guidelines for Point-of-Care testing [593].

The Reflotron® Plus works on the principle of reflectance photometry utilising a 32 µl blood sample applied to a Reflotron® Uric Acid Test reagent strip. Blood samples were collected in accordance with the Reflotron® Plus User Guidelines. The serum urate test result was used to determine whether the participant was put in the group with asymptomatic hyperuricaemia (serum urate ≥ 0.41 mmol/l) or the normouricaemic control group (serum urate < 0.41 mmol/l).

6.4.2 Demographic and medical history

Demographic data was collected from all participants during the study visit including gender (male/female), age (years) and ethnicity (European/Māori/Pacific/Asian). Weight (kg) and height (m), were used for the calculation of Body Mass Index (BMI) (kg/m^2), and were collected using standardised weight and height measurement devices. Current use of the following medications was recorded for all participants: diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and prednisone, and for gout only: allopurinol, colchicine, probenecid, benzbromarone and febuxostat. Current medical conditions, including hypertension, cardiovascular disease and diabetes were also recorded as present or absent for all participants.

Gout disease characteristics were documented for participants in the gout group using clinical records and self-reported data. This involved recording: the ACR criteria through which they were classified (i.e. aspirate proven, or classified based on clinical features), their disease duration (years), the age of their first episode of acute arthritis (years), their latest serum urate level (mmol/l), the highest serum urate level reported in medical records since diagnosis, the number and location of gout flares experienced in the preceding three months, and the presence of 1MTP acute arthritis at any time during the history of their disease for right and left feet. Each participant with gout was also examined to record the presence or absence of subcutaneous tophi, the total number of body tophi, the total number of foot tophi, and the presence of tophi at the right and left 1MTPs.

All participants were assessed for tender and swollen joints using the 66/68 Tender Swollen Joint Count [463]. This joint count includes assessment of 66 joints for swelling and 68 joints for tenderness including: the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of the hands; the metatarsophalangeal, and distal interphalangeal joints of the feet, and the shoulder, elbow, wrist, hip (tenderness only), knee, ankle, tarsus, and temporomandibular, sternoclavicular, and acromioclavicular joints. Assessment was carried out according to Sokka and Pincus [464] with the participant seated. Swollen joints were assessed by observing and palpating for evidence of soft tissue swelling along the joint margins. Tender joints were assessed by observing the participants' reaction whilst the researcher palpated the joints with their thumb and index finger to exert pressure that was sufficient to cause whitening of the nail bed. Scores out of 66 for swollen joints, and 68 for tender joints were recorded for each participant.

6.4.3 Clinical assessment

6.4.3.1 Equipment and procedure

All clinical assessments were performed in the AUT Podiatry Clinic by a single researcher. Ambient room temperature was thermostatically maintained at a consistent temperature of 22 °C \pm 2 °C throughout the data collection period. All data collected during the clinical assessment were recorded on a clinical report form (**Appendix 7**).

6.4.3.2 Outcome measures

Clinical assessments were performed in four areas: (i) patient-reported outcomes, (ii) functional and structural assessments, (iii) neurovascular assessments, and (iv) dynamic gait assessments. 1MTP pain was a primary clinical outcome measure as patient-reported pain is considered a mandatory outcome domain in gout [223]. 1MTP dorsiflexion range of motion was also a primary clinical outcome due to its previous use as a clinical measure of osteoarthritis at the joint [362] and the importance of 1MTP motion in efficient gait and foot function [340, 348]. Patient-reported foot pain and disability were included as a secondary clinical outcome, as people with gout have previously reported that being unable to carry out everyday tasks related to lower limb function are important features of the disease [170]. Gait velocity was also a secondary clinical outcome as reduced walking speed is recognised as a functional consequence of foot pain [469] and is considered an important disability in people with gout [170, 318]. All remaining clinical outcome measures were exploratory.

6.4.3.2.1 Patient-reported outcome measures

6.4.3.2.1.1 First metatarsophalangeal joint pain

The severity of right and left 1MTP pain were assessed using two 100 mm Visual Analog Scales (VAS) (one for each foot). For each VAS, participants were asked to indicate how much pain they had experienced in their big toe joint in the past week by placing a cross through the line which was anchored on the left with “No pain” (0 mm) and on the right with “Extreme pain” (100 mm). The 100 mm VAS has been shown to be reliable in assessing pain in lower limb pathology [470] and has also been used specifically to assess 1MTP pain in previous studies [471, 472].

6.4.3.2.1.2 Foot pain and disability

Foot pain and disability were assessed using the Manchester Foot Pain and Disability Index (MFPDI) [473]. This 19-item index measures foot-related items associated with functional limitations, pain, and physical appearance. Statements relating to each item were answered ‘none of the time’ (scored as 0), ‘on some days’ (scored as 1) and ‘on most/everyday(s)’ (scored as 2) in the past month. A total score of 38 was calculated for each participant. In addition, it

was noted whether each participant had the presence of disabling foot pain, defined as at least one item scored as 1 or 2 [473]. As the MFPDI was developed through interviewing podiatric patients, its construct validity can be considered good [473]. The index has also been validated against the commonly used Short Form 36 [474]. Good internal consistency has been established [473-476] and test-retest reliability has been reported as moderate for all three subscales [476]. The MFPDI has been used previously as an outcome measure in gout research [319, 320, 477].

6.4.3.2.1.3 General body pain

A 100 mm VAS was used to measure general body pain. Participants were asked to indicate how much body pain they had experienced in the past week by placing a cross through the line which was anchored on the left with “No pain” (0 mm) and on the right with “Extreme pain” (100 mm). This tool has been endorsed by OMERACT and considered to have face and content validity, internal consistency, and feasibility in measuring pain in people with gout [223].

6.4.3.2.1.4 Patient global assessment

Patient global assessment was also measured using a 100 mm VAS. Participants were asked to indicate their overall level of wellbeing in the past week by placing a cross through the line which was anchored on the left with “Completely well” (0 mm) and on the right with “Extremely unwell” (100 mm). This tool has also been endorsed by OMERACT and is also considered to meet the OMERACT filters of truth, discrimination and feasibility for outcome measures in gout [223].

6.4.3.2.1.5 Activity limitation

The Health Assessment Questionnaire Disability Index (HAQ-DI) [478] was used to measure activity limitation. The HAQ-DI comprises of 10 tasks for which participants are asked to rate their ability to perform them in the past week (without difficulty = 0, some difficulty = 1, much difficulty = 2, or unable = 3). The scores are summated and divided by the total number of questions answered to give an overall value between 0 (minimal loss of function) and 3 (completely disabled). The HAQ-DI also meets the OMERACT filters and is recommended as an outcome measure for activity limitation in people with gout [223].

6.4.3.2.1.6 Lower limb function

The Lower Limb Task Questionnaire (LLTQ) [479] was used as a measure of lower limb function. The LLTQ consists of two sections, one related to activities of daily living and the other to recreational activities. Each section includes 10 activities for which participants are asked to rate the difficulty they have had with each in the past 24 hours (unable = 0, severe difficulty = 1, moderate difficulty = 2, mild difficulty = 3, and no difficulty = 4). The sum of each section was calculated and given a total score out of 40.

6.4.3.2.2 Structural and functional outcome measures

6.4.3.2.2.1 1MTP dorsiflexion range of motion

Passive, non-weight-bearing dorsiflexion range of motion of the 1MTP was measured using a plastic hand-held goniometer (Whitehall Manufacturing Ltd., California, USA) with 16 cm lever arms. The scale on the goniometer was marked in one degree increments. Motion was measured in accordance with the procedure outlined by Hopson and McPoil [480]. Participants were positioned seated with knees extended and the ankle held at zero degrees of dorsiflexion, plantarflexion, inversion and eversion. The shafts of the first metatarsal and proximal phalanx were palpated and bisected in the sagittal plane. Lines were drawn on the medial aspect of the foot and the joint centre was marked. The goniometer was aligned with the centre of the joint with the fixed arm held parallel to the first metatarsal bisection and the moving arm parallel to the bisection of proximal phalanx (**Figure 6.2**). The examiner applied a passive dorsiflexion force to the hallux until the hallux could no longer be passively moved into further extension. The angle in degrees between the two bisection lines was measured from the goniometer. This measurement technique has been shown to be highly reliable in people with and without 1MTP pain (ICC = 0.95) [480, 481]. Three repetitions for each foot were performed.

6.4.3.2.2.1.1 Intra-rater between-session reliability

To determine intra-rater reliability for measuring 1MTP dorsiflexion range of motion in participants with gout, the above procedure was repeated during a second testing session

approximately one to two hours after the first session. A randomly selected 10 participants belonging to the gout group participated in the second session.

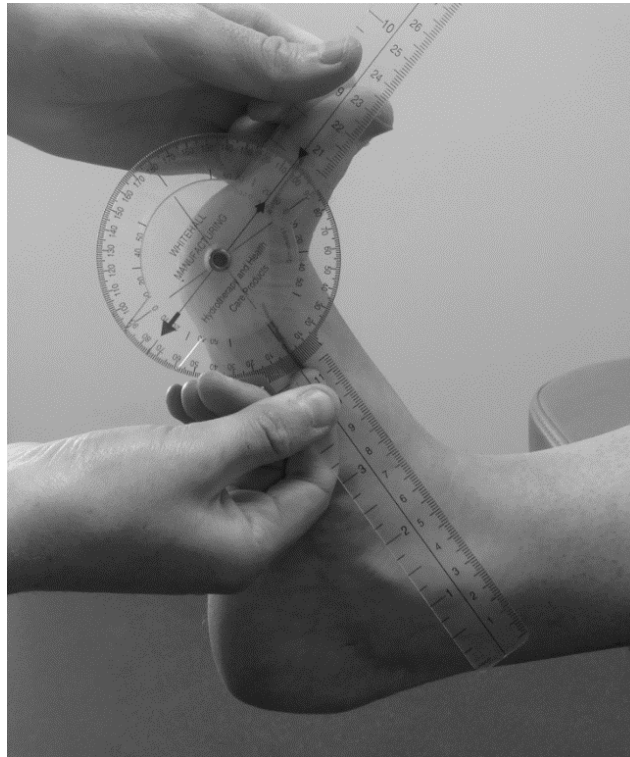


Figure 6.2 *Goniometer measurement of 1MTP dorsiflexion*

6.4.3.2.2.2 1MTP plantarflexion and dorsiflexion muscle force

Isometric muscle force for plantarflexion and dorsiflexion of the hallux was measured using a CITEC hand-held dynamometer (CIT Technics, Haren, Netherlands). The device is calibrated to a sensitivity of 0.1% and a range of 0-500 N. Participants were positioned seated during testing with knees extended. The lower leg and foot were stabilised in a custom-made device comprised of two wooden boards angled at 90 degrees. The plantar aspect of the foot was positioned against the vertical board with the ankle in a neutral position. Velcro straps were applied across the dorsum of the foot and the lower leg to ensure the limb was held stationary and so the 1MTP could be isolated during testing. Strength of the muscles responsible for plantarflexion and dorsiflexion of the hallux were assessed using the 'make' technique in which the examiner held the dynamometer stationary while the participant exerted maximal external force against it [482]. The dynamometer was positioned against the plantar aspect of the interphalangeal joint of the hallux during plantarflexion testing (**Figure 6.3a**) and on the dorsal aspect of the hallux

during dorsiflexion (**Figure 6.3b**) [483]. Participants were instructed to keep the plantar and posterior aspects of their foot in contact with the board at all times. Three consecutive contractions of three to five seconds were recorded for each muscle group. Verbal encouragement was given during each contraction. This method has shown to have excellent intra-rater reliability (ICC 0.81 to 0.94) and inter-rater reliability (ICC 0.87 to 0.88) for measuring hallux plantarflexion force [483].

6.4.3.2.2.1 Test-retest reliability

To determine test-retest reliability for measuring the plantarflexion and dorsiflexion muscle force in participants with gout, the above procedure was repeated during a second testing session approximately one to two hours after the first session. A randomly selected 10 participants belonging to the gout group participated in the second session.

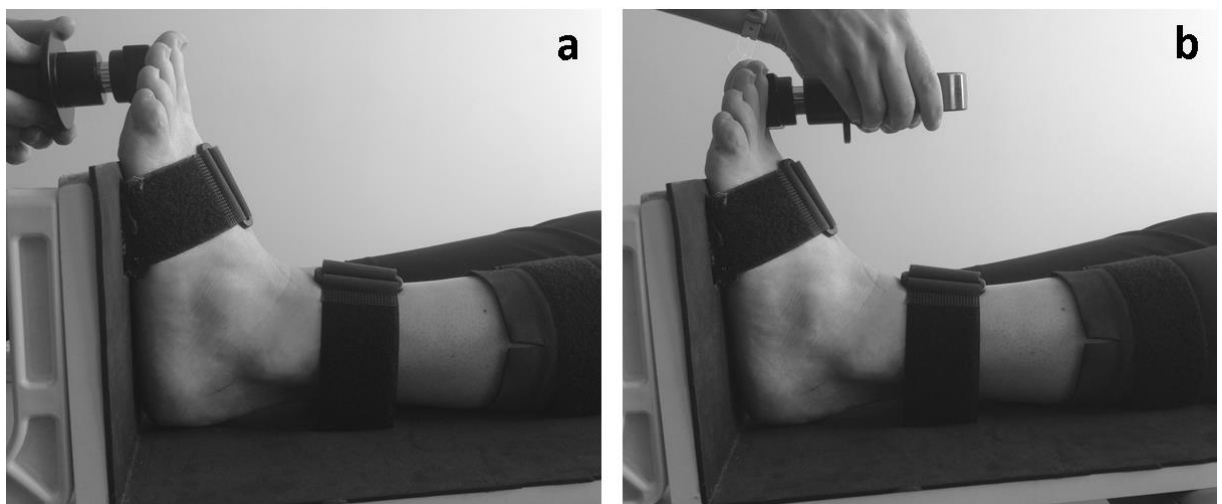


Figure 6.3 Muscle force testing for plantarflexion strength (a) and dorsiflexion strength (b)

6.4.3.2.2.3 Hallux valgus severity

Hallux valgus severity was assessed using the Manchester Scale [484]. The scale comprises of four photographs graded as 0 being 'no deformity', 1 being 'mild deformity', 2 being 'moderate deformity' and 3 being 'severe deformity' (**Figure 6.4**). The participant was asked to stand in a relaxed weight-bearing position while the examiner used the photographs to grade the deformity on each foot. This tool has been shown to have excellent reliability [484] and validity [485, 486].



Figure 6.4 Manchester Scale for hallux valgus grading. Image from Garrow et al 2001 [484].

6.3.4.2.2.4 Foot type

Foot type was assessed using the Foot Posture Index (FPI) [487]. During assessment the participant was instructed to stand in a relaxed weight-bearing position while the examiner assessed each foot for the following six FPI criteria: talar head position, supralateral and inferolateral malleolar curvature, calcaneal frontal plane position, prominence in the region of the talonavicular joint, medial arch height and abduction and adduction of the forefoot on the rearfoot. Each FPI criterion was scored on a five-point scale (range, -2 to +2). The scores for the six criteria were then summated to give an overall score of foot posture for each foot. The summated score ranged from -12 (highly supinated) to +12 (highly pronated). The FPI is a valid and reliable assessment tool [487, 488].

6.3.4.2.3 Neurovascular outcome measures

6.4.3.2.3.1 1MTP temperature

Temperature of the 1MTP was measured using a DermaTemp 1001 (Exergen Corporation, Massachusetts), which is a hand-held infrared thermographic scanner with an in-built sensor. According to the manual, the DermaTemp is accurate to within 0.1 °C. Along with the thermostatically controlled room temperature (22 °C \pm 2 °C), participants were protected from drafts and exposure to cold surfaces. Furthermore, it was ensured that participants were given adequate equilibration time in the room and had been seated with legs extended (to minimise vascular pooling) for at least 15 minutes prior to testing [489]. Temperatures were recorded

from three sites around the 1MTP: medial, dorsal, and plantar (**Figure 6.5**). The device was held within 5 mm, perpendicular to the skin surface, during measurement to ensure maximum accuracy. Temperatures were recorded from the digital analog display on the top of the device. Three readings for each site were repeated for both right and left feet.

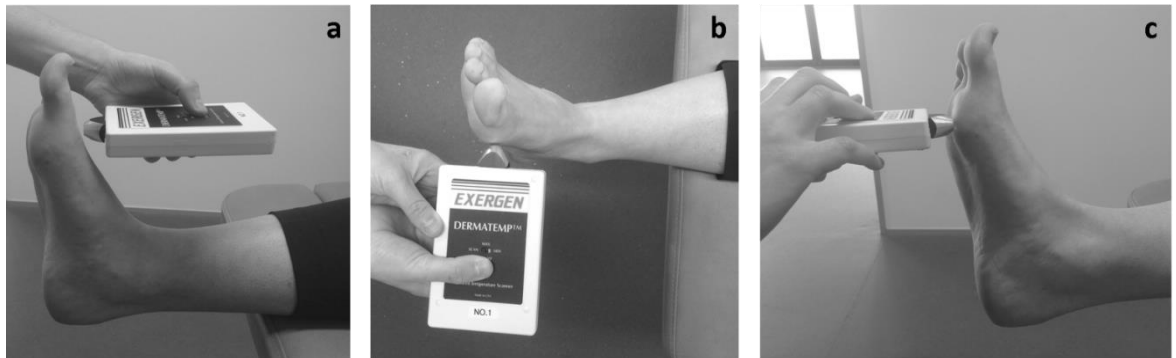


Figure 6.5 Temperature measurements of dorsal (**a**), medial (**b**), and plantar (**c**) aspects of the first metatarsophalangeal joint

6.4.3.2.3.2 Vibration perception threshold

A biothesiometer (Bio-Medical Instrument Company, Ohio, USA) was used to determine the threshold at which the participant was able to perceive vibration. The biothesiometer has a 12 mm rubber probe with a contact area of 10 mm² which vibrates at a fixed frequency of 100 Hz at an amplitude that can be controlled between 0 and 50 volts. Prior to assessment, participants were familiarised with the vibratory sensation by demonstrating the test on the dorsum of their hand. Testing was carried out with the participant seated with knees extended. The probe was held firmly and applied with minimal pressure, perpendicular to the medial aspect of the 1MTP (**Figure 6.6**). The amplitude was gradually increased from zero until the participant indicated that vibration was felt. This vibration perception threshold was recorded and the procedure repeated three times for each foot. The biothesiometer is considered an accurate and reliable test of peripheral nerve function [490-493].

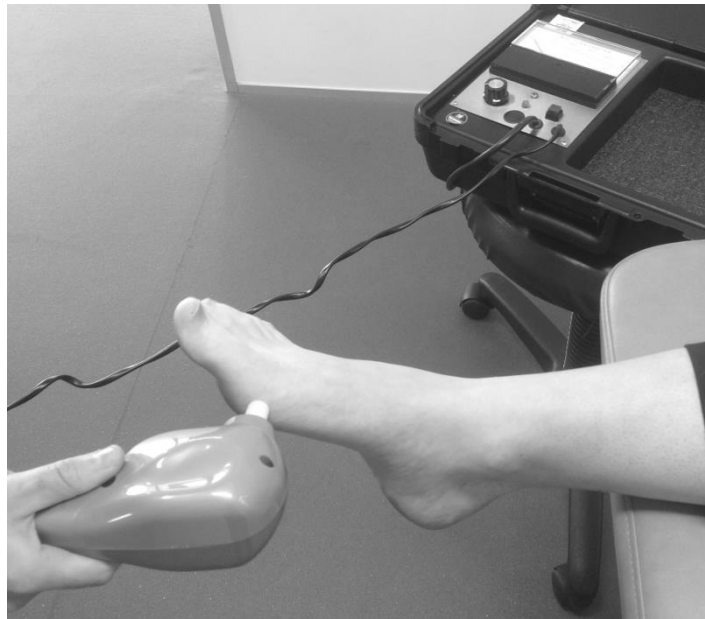


Figure 6.6 Biothesiometer probe placement

6.4.3.2.3.3 Protective sensation

Tactile sensitivity under the plantar aspect of each foot was assessed by measuring the perception threshold to light touch with a 10 g Semmes-Weinstein retractable monofilament (Bailey Instruments Ltd, Salford, Lancashire, UK). Prior to assessment the examiner demonstrated the test on the dorsum of the participant's hand. During assessment the participant was seated with knees extended and instructed to keep their eyes closed. Three sites were tested on the plantar foot: the hallux, first metatarsal head, and fifth metatarsal head [494]. The monofilament was applied perpendicular to the skin surface until it buckled to ensure 10 g of pressure was being applied (**Figure 6.7**). The monofilament was held in this position for 2 seconds. The participant was instructed to indicate by saying "yes" when they felt the pressure. Application of the monofilament to the three sites was carried out in a random order with a total of two applications at each site as well as a 'mock' application in which no filament was applied. Protective sensation was considered present at each site if the participant correctly answered two of the three applications. Overall, a loss of protective sensation for each foot was considered present if protective sensation was absent in at least two of the three sites tested [495].



Figure 6.7 Application of 10g Semmes-Weinstein monofilament

6.4.3.2.4 Dynamic gait outcome measures

6.4.3.2.4.1 Spatial and temporal gait parameters

Spatial and temporal parameters of gait during level barefoot walking were collected using the GAITRite walkway system (CIR Systems, Inc., New Jersey, US). The GAITRite is an electronic walkway containing a total of 18,432 sensors which are embedded in a 610 mm wide and 4,880 mm long walkway. As participants walk across the walkway, the sensors close under pressure. Data is sampled from the walkway at a frequency of 80 Hz allowing a temporal resolution of 11 milliseconds. Prior to calculation of the gait parameters, the data were reviewed on the monitor screen to ensure that right and left footfalls had been correctly identified, and again any footfall not completely on the walkway at either end was removed. The spatial and temporal characteristics of gait were processed and stored by an IBM compatible computer using GAITRite® gold, Version 3.2b software. The GAITRite system has strong concurrent validity and test retest reliability in both young and older people [496, 497].

Prior to data acquisition participants were encouraged to walk along the walkway to familiarise themselves with the protocol. Participants were instructed to start and finish walking at 1.5 m either end of the walkway to ensure that when they reached the walkway they were walking at a normal speed and momentum. Participants were instructed to walk at their own normal comfortable walking speed [498] (**Figure 6.8**). Data collection was triggered by the first pressure contact on the walkway. Each participant undertook three trials of barefoot walking.



Figure 6.8 *GAITRite walkway system*

The GAITRite software was used to compute the following temporal and spatial parameters for both right and left feet for each trial: velocity, cadence, step length, stride length, support base, step time, swing time, stance time, and single and double support time. These 10 variables were defined as displayed in **Table 6.1**.

Table 6.1: Definitions of temporal and spatial gait parameters	
Temporal parameters	
Step Time (s)	The time elapsed from the first contact of one foot to the first contact of the opposite foot
Stance time (s)	The time elapsed between the first contact and the last contact of two consecutive footfalls on the same foot
Swing time (s)	The time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot (equal to the single support time of the opposite foot)
Single support time (s)	The time elapsed between the last contact of the current footfall to the first contact of the next footfall of the same foot (equal to the swing time of the opposite foot)
Double support time (s)	The time elapsed between first contact of the current footfall and the last contact of the previous footfall, added to the time elapsed between the last contact of the current footfall and the first contact of the next footfall
Velocity (m/s)	Obtained after dividing the distance by the ambulation time (the time elapsed between the first contacts of the first and last footfalls)
Cadence (steps/min)	The number of footfalls
Spatial Parameters	
Step length (m)	The distance measured on the horizontal axis of the walkway from the heel point of the current footfall to the heel point of the previous footfall on the opposite foot
Stride length (m)	The distance measured on the line of progression between the heel points of two consecutive footfalls of the same foot (left to left, right to right)
Support base (m)	The perpendicular distance from heel point of one footfall to the line of progression of the opposite foot

6.4.3.2.4.1.3 Test-retest reliability

To determine test-retest reliability for measuring the temporal and spatial gait parameters, the above procedure was repeated during a second testing session approximately 1 to 2 hours after the first session. Twenty participants with gout and 20 participants without gout participated in the second session.

6.4.3.2.4.2 Plantar pressure measurements

Dynamic plantar pressure measurements were captured during level barefoot walking using the TekScan MatScan® system (Boston, MA, USA) (**Figure 6.9a**). The system consists of a 5 mm thick platform (432 x 368 mm), comprising of 2,288 resistive sensors (1.4 sensors/cm²) that sample data at a frequency of 40 Hz. Data were collected using the two-step gait initiation protocol as it requires fewer trials and has similar retest reliability to the mid-gait protocol [499]. The two-step protocol requires the participant to step on the platform on their second step. This ensured that a constant velocity and momentum had been reached and pressure data reflected their normal gait. Prior to data acquisition, participants were instructed to familiarise themselves with the protocol and align themselves with the platform to ensure their second step landed in the sensing area. Participants were instructed to walk at their own natural comfortable walking speed and to continue walking past the platform for at least two more steps. Three trials were recorded for each foot.

Plantar pressure data were calculated for seven regions of the plantar foot: the heel, midfoot, first metatarsal, second metatarsal, metatarsals three to five, the hallux and the lesser toes. The Research Foot® Version 6.61 was used to mask the regions (**Figure 6.9b**). This masking method has demonstrated excellent reliability for each of the seven masked regions (ICCs 0.96 to 0.99) [500]. Peak plantar pressure (kPa) and pressure time integrals (kPa*s) were computed from the software for each region for both right and left feet.

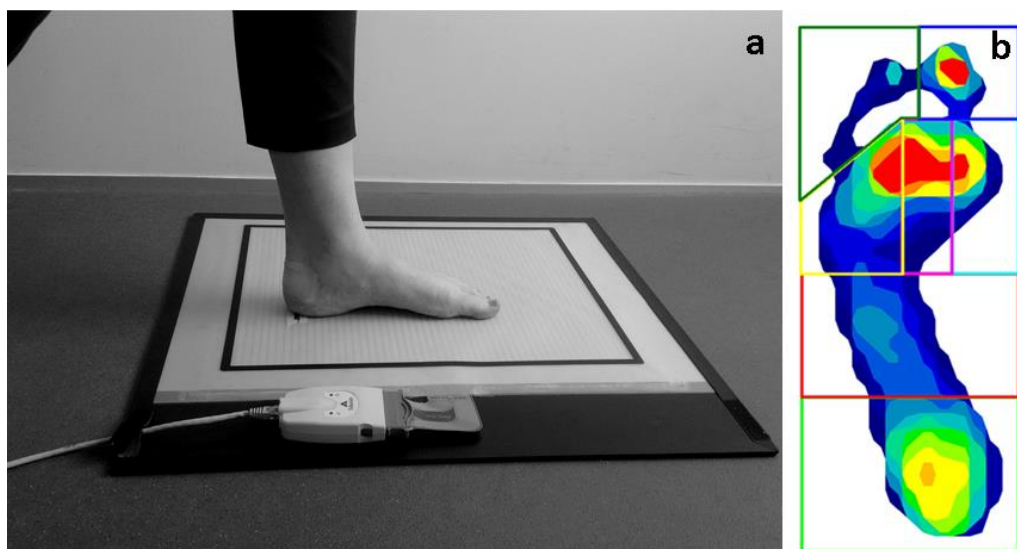


Figure 6.9 TekScan MatScan® platform (**a**), and masking of the seven plantar regions (**b**)

6.4.4 Sonographic assessment

6.4.4.1 Equipment and procedure

Sonographic examination of the 1MTPs was performed at the AUT Horizon Scanning Clinic by a single experienced musculoskeletal radiologist (Dr Bruce Allen) who was blinded to the diagnostic group the participant belonged to. A Phillips iU22 diagnostic ultrasound machine (Universal Diagnostic Solutions Inc., California, USA) with a 10 MHz, 55 mm linear array transducer was used for all scanning. The sonographic assessment of bilateral 1MTPs was performed in accordance with the EULAR guidelines for musculoskeletal ultrasound in rheumatology [436]. Participants were positioned supine with legs extended. A water-based gel was applied to the skin to optimise transducer-skin contact and to provide an acoustic interface. The dorsal, medial, and plantar aspects of each joint were scanned using a multi-planar technique in which transverse and longitudinal planes were imaged (**Figure 6.1**). Each joint was maximally dorsiflexed and plantarflexed by the radiologist during scanning to ensure direct visualisation of the articular surfaces. Each joint was scanned in B-mode grey scale and then using power Doppler to detect abnormal blood flow (inflammation). Power Doppler involved the use of a standardised pulse frequency of 400 to 500 Hz and low wall filters with the gain adjusted to a level just below the disappearance of the colour signs under the bony cortex. All ultrasound scans for each participant were saved and stored on a compact disc.

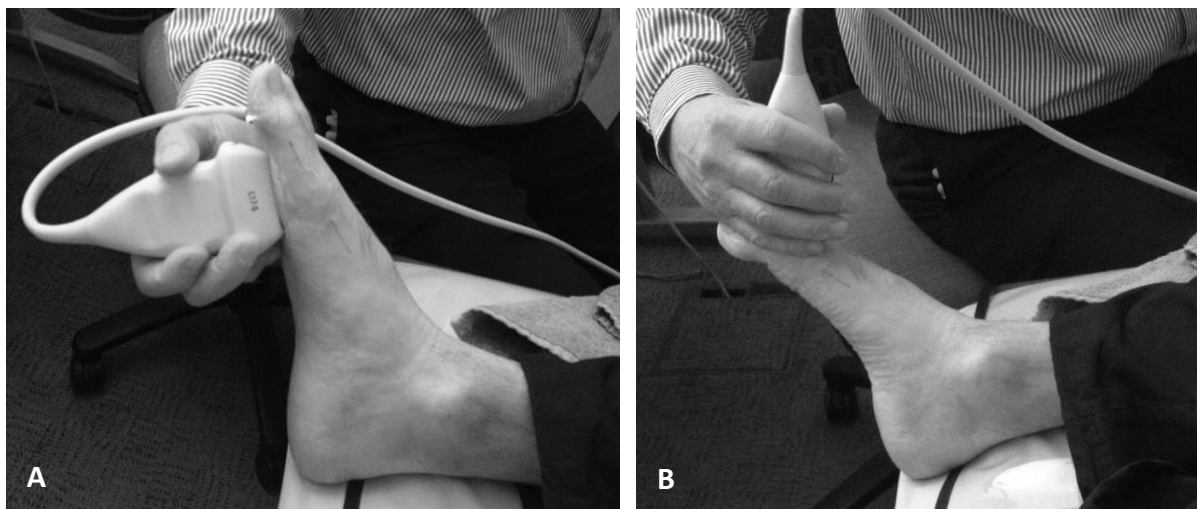


Figure 6.1 Sonographic assessment of **A)** the plantar aspect, and **B)** the dorsal aspect of the 1MTP in the longitudinal plane.

6.4.4.1.1 Sonographic image interpretation

At completion of data collection, two musculoskeletal radiologists (Dr Bruce Allen and Dr Rhian Miranda) blinded to the diagnostic group the images belonged to and to each other's scores, independently reviewed the static images on each compact disc for the presence and/or grading of seven outcome measures which were recorded on an Ultrasound Assessment Form (**Appendix 8**). For the final analysis, features recorded as present by both readers were considered present, while features disagreed on were considered absent.

6.4.4.1.2 Inter-rater reliability

The inter-rater reliability between the two radiologists was determined for the presence, grading and size measurements related to each of the seven outcome measures.

6.4.4.2 Outcome measures

6.4.4.2.1 Double contour sign

Presence of the double contour sign was chosen as the primary outcome measure as it was recognised by physicians as the most discriminatory ultrasound feature at the time of study conception [170]. The double contour sign was defined in accordance with the 2015 Outcome Measures in Rheumatology (OMERACT) International Consensus for ultrasound lesions in gout [450]: abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation and which may be either irregular or regular, continuous or intermittent and can be distinguished from the cartilage interface sign. The presence of the double contour sign on articular cartilage was recorded as present or absent at the dorsal aspect of the first metatarsal head.

6.4.4.2.2 Intra-articular tophi

Tophus presence was a secondary outcome measure and defined using the OMERACT definition as a circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (that may or

may not generate a posterior acoustic shadow), which may be surrounded by a small anechoic rim [450]. The presence of intra-articular 1MTP tophi was recorded as present or absent for the proximal and distal aspects in each of the dorsal, medial, and plantar joint spaces. In addition, the diameter of the largest tophi was recorded in millimetres using the digital callipers on the ultrasound machine.

6.4.4.2.3 Erosions

The presence of bone erosion was defined using the OMERACT definition of intra-articular discontinuity of the bone surface, visible in two perpendicular planes [450]. The presence of erosions was recorded for the dorsal, medial, and plantar areas of the first metatarsal head and proximal phalangeal base and graded on a four-grade semi-quantitative scale [465]. Grade 0 was considered a regular bone surface; Grade 1 was irregularity of the bone surface without formation of a defect seen in two planes; Grade 2 was formation of a defect in the surface of the bone seen in two planes; and Grade 3 was a bone defect creating extensive bone destruction [465]. Erosions were considered absent if graded as 0 or 1, and considered present if graded 2 or 3. This scoring system has demonstrated high inter-rater agreement for assessment of metatarsophalangeal joints in rheumatology [465]. In addition to grading erosions in each area, the diameter of the largest erosion was measured in millimetres using the digital callipers on the ultrasound machine.

6.4.4.2.4 Joint effusion

The presence of joint effusion, a secondary outcome measure, was defined as an abnormal hypoechoic or anechoic intra-articular material (relative to subdermal fat) that was displaceable and compressible [466]. The presence of joint effusion was recorded for the medial, dorsal, and plantar joint spaces. The presence of joint effusion was graded on a four-grade semi-quantitative scale with Grade 0 representing no fluid; Grade 1 representing minimal fluid; Grade 2 representing moderate fluid without distension of the joint capsule; and Grade 3 representing extensive fluid with distension of the joint capsule [465]. Joint effusion was considered absent when graded 0 or 1, and present when graded 2 or 3. This grading system has shown good inter-rater reliability for the detection of joint effusion in metatarsophalangeal joints in rheumatology [465].

6.4.4.2.5 Snowstorm appearance

The snowstorm appearance, another secondary outcome measure, represents monosodium urate crystal aggregates within the joint space. The snowstorm appearance was defined as bright stippled foci floating within the joint space when pressure was applied by the radiologist [398]. The presence of the snowstorm appearance was assessed for the dorsal, plantar and medial synovial compartments.

6.4.4.2.6 Synovial hypertrophy

The presence of synovial hypertrophy was a secondary outcome measure defined as abnormal hypoechoic intra-articular tissue (relative to subdermal fat) that was non-displaceable and poorly compressible [466]. Synovial hypertrophy was noted at dorsal, plantar and medial joint membranes and graded according to a four grade semi-quantitative scale in which Grade 0 was no synovial thickening; Grade 1 was minimal synovial thickening filling the angle between the periarticular bones without bulging over the line linking the tops of the bones; Grade 2 was synovial thickening bulging over the line linking the tops of the periarticular bones but without extension along the bone diaphysis; and Grade 3 was synovial thickening bulging over the line linking the tops of the periarticular bones and with extension to at least one of the bone diaphyses [465]. Synovial hypertrophy was considered absent if graded as 0 or 1, or present if graded 2 or 3. This grading system has shown very high inter-rater reliability for the detection of synovial hypertrophy in metatarsophalangeal joints in rheumatology [465].

6.4.4.2.7 Synovitis

Synovitis, representing increased blood flow within the joint space, was a secondary outcome measure assessed using the power Doppler mode. Power Doppler allows the assessment of inflammation in the absence of clinical evidence of acute gout [389, 443]. Synovitis was defined as the presence of the power Doppler signal within the joint space and was graded using a four grade semi-quantitative scale in which Grade 0 was no flow in the synovium; Grade 1 was single vessels signals; Grade 2 was confluent vessel signals in less than half of the area of the synovium, and Grade 3 was vessel signals in more than half of the area of the synovium [465]. Grade 0 was considered normal, while Grades 1 to 3 were considered to represent the presence of synovitis

[467]. This grading system has demonstrated high inter-rater reliability for measuring synovitis in the metatarsophalangeal joints in rheumatology [465].

6.4.4.2.8 Cartilage degeneration

Cartilage degeneration was the final secondary outcome and was considered a measure of osteoarthritic changes to the articular surface. Cartilage degeneration was assessed by measuring the longest diameter of the hypoechoic layer of articular cartilage at the point perpendicular to the bone surface between the subchondral margin and the leading interface (appearing as a white band on the superficial margin of the cartilage) using digital callipers. Cartilage thickness in millimetres was recorded for the dorsal aspect of the metatarsal head. Sonographic measurement of cartilage thickness has demonstrated excellent validity when compared to thickness of cadaveric cartilage, as well as demonstrating good correlation with conventional radiographic joint space narrowing [468]. Furthermore, ultrasound has excellent intra-rater and inter-rater reliability for measuring the metacarpophalangeal joint articular cartilage thickness in rheumatology [468].

6.5 Data analysis

6.5.1 Descriptive statistics

All raw data including participant characteristics, sonographic outcome measures and clinically assessed outcome measures were described separately for each diagnostic group as number (percentage) for categorical data and mean (standard deviation (SD)) for continuous data. For clinically assessed outcome measures that were assessed over three repeated trials, the mean was calculated for each participant, and the mean of the means reported.

6.5.2 Reliability analyses

6.5.2.1 Intra-rater reliability

Intraclass correlation coefficients ($ICC_{2,1}$) were used to determine test-retest reliability for the following clinically assessed outcome measures in participants with gout: 1MTP dorsiflexion

range of motion, plantarflexion and dorsiflexion muscle force, and temporal and spatial gait parameters. ICCs assess the consistency of measurements over repeated trials by a single rater. ICCs were reported along with their 95% confidence intervals and interpreted using the following benchmarks: < 0.40 poor reliability; $0.40 - 0.75$ fair to good reliability; and ≥ 0.75 excellent reliability [502].

6.5.2.2 Inter-rater reliability

To determine the agreement between the two radiologists in assessing the presence of the double contour sign, tophus, erosion, synovial hypertrophy, joint effusion, synovitis, and the snowstorm appearance at each joint, Cohen's kappa (k) was used. Cohen's kappa assesses the extent of reproducibility of dichotomous outcome measures and is useful in determining inter-rater agreement that occurs over and above chance. k values of 0 to 0.2 were considered poor; 0.2 to 0.4 fair; 0.4 to 0.6 moderate; 0.6 to 0.8 good; and 0.8 to 1.0 excellent [501]. Associated 95% confidence intervals and P values were also reported.

To determine the inter-rater agreement in assessing cartilage thickness and tophus and erosion diameters and the severity grading for erosions, synovial hypertrophy, joint effusion and synovitis two-way mixed consistency intra-class correlation coefficients ($ICC_{3,1}$) were used. ICCs were reported along with their 95% confidence intervals and interpreted using the following benchmarks: < 0.40 poor reliability; $0.40 - 0.75$ fair to good reliability; and ≥ 0.75 excellent reliability [502].

6.5.3 Inferential statistics

6.5.3.1 Participant characteristics

To determine whether participant characteristics relating to demographic, medical, laboratory and clinical characteristics were significantly different between diagnostic groups, appropriate regression models were used with the diagnostic group as the independent variable and the participant characteristics as the dependent variables.

6.5.3.2 Data normality

All continuous outcomes were reviewed for normality using the residuals from a linear model which included relevant demographic covariates and the diagnostic group as the independent variables. Visual inspections of residual histograms, residual normal Q-Q plots, and scatterplots of fitted values against residuals were carried out. Formal tests, including Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to test for significant departure from normality, with the power of the tests addressing mainly skewness and kurtosis, respectively.

6.5.3.3 Model selection

Appropriate regression models were identified for Aim I and II based on the nature of the dependent variable. The default regression models for all continuous dependent variables was linear regression, or in the case of non-normal data, generalised linear regression. For the ordinal outcome measures, the default regression model was multinomial logistic with cumulative logit link. For dichotomous dependent variables binary logistic regression models were used. The control group was always categorised as the reference group in order to consider the two contrasts of interest: Gout versus controls, and asymptomatic hyperuricaemia versus controls.

Linear regression models were used to address Aim III, which aimed to determine the association between the dichotomous sonographic features (i.e. presence versus absence) and the selected clinically assessed characteristics of the 1MTP. Data from all diagnostic groups were used in the analyses and the overall models included the sonographic feature as a fixed effect as well as the interaction effect between the sonographic feature and diagnostic group.

6.5.3.4 Aim I: Clinically assessed characteristics

To determine between-group differences in the clinically assessed outcome measures, the outcomes were fitted as the dependent variables in appropriate regression models, which were related to the diagnostic group as the independent variable.

As in the Aim I analyses, the models accounted for any repeated measures taken from right and left feet of each participant through adopting a mixed modelling approach in which a participant-specific random effect and participant-nested random effect for foot-side were included. Additionally, in situations where measurements were taken across three repeated trials, they were not averaged, but instead included as separate observations in the analysis. In these cases, the regression model employed a scaled identity repeated covariance structure which assumes equal variances for each of the three trials.

For outcomes measures that formed a natural vector of related variables (for example, temperature, which was measured at three sites of the 1MTP, or plantar pressure which was measured at seven sites of the plantar foot), a heterogeneous compound symmetry covariance structure was employed, which allowed for separate variances for each site as well as different covariances (but equal correlations) between each pair of sites.

As for Aim I analyses, adjustments for gender, age group and ethnicity were considered and a single adjusted model was sought for each category of clinically assessed outcome measures (i.e. patient-reported outcomes, structural and functional outcomes, neurovascular outcomes and dynamic/gait outcomes).

6.5.3.5 Aim II: Sonographic features

To determine between-group differences in sonographic outcome measures, the sonographic outcomes were fitted as the dependent variables in appropriate regression models, which were related to the diagnostic group as the independent variable.

Dichotomous sonographic variables (the double contour sign, snowstorm appearance and tophus) were considered present if recorded as present by both readers at the dorsal aspect of the 1MTP for the double contour sign or at the dorsal, plantar and/or medial aspect of the 1MTP for the remaining variables. For ordinal variables (grading of erosions, synovial hypertrophy, joint effusion and synovitis), the mean grade of the two readers for each of the dorsal, medial and plantar sites was calculated and rounded to zero decimal places.

For sonographic features that were assessed at multiple sites of the 1MTP (i.e. dorsal, medial and plantar sites), the maximum grade was used in the final analyses. If this grade was ≥ 2 for effusion, erosion and synovial hypertrophy then the feature was considered present. If the grade was ≥ 1 for power Doppler then the feature was considered present. For continuous variables (tophus and erosion diameters and cartilage thickness), the maximum value from the dorsal,

medial and/or plantar sites was used in the final analyses. When no tophi or erosions were present, size values were entered as zero.

The models accounted for repeated measures taken from right and left feet of each participant through adopting a mixed modelling approach in which a participant-specific random effect and participant-nested random effect for foot-side were included. This analysis produces results identical to an analysis of measures averaged for each foot-side that would allow for a between-foot-side correlation, and also allows for any reweighting required due to missing values.

Adjustments for gender, age group, BMI and ethnicity were considered. These covariates were not expected to behave as confounders due to the frequency matching, but had the potential to decrease residual variance as possible independent variables. For the purpose of covariate testing, age, a continuous variable, was transformed into a categorical variable by grouping data into three bins using two cut points placed at 40 years and 70 years. Adjustments for the three covariates, which were entered into each linear model simultaneously, were considered only if their level of observed significance achieved at least 10% on an F-test (or equivalent deviance test (i.e. Wald test) for generalised linear models). Potential covariates were also explored by reviewing box plots of random effects by covariate group. A single-adjusted model was sought for all sonographic outcome measures.

6.5.3.6 Aim III: Associations between sonographic features and clinically assessed characteristics

To determine the association between the clinically assessed and sonographic outcome measures, regression models were used in which the clinically assessed characteristics were considered the dependent variables and the sonographic features were considered the independent variables.

For the purpose of Aim III, the dichotomous sonographic data (i.e. presence versus absence) from Aim II were used. Clinically assessed variables from Aim I were used. In situations where measurements were taken across three repeated trials, these were averaged, and the mean value used for the inferential analyses.

The dependent variables (clinically assessed characteristics) selected for Aim III included the primary and secondary clinically assessed outcome measures and selected exploratory outcome measures which were chosen based on clinical importance and significant between-group differences identified in the Aim I analyses. The independent variables (sonographic features)

selected for Aim III included the primary sonographic outcome measure and selected secondary dichotomous outcome measures which were chosen based on outcomes which achieved significance in the inferential analyses in Aim II.

As described in Aims I and II, the models accounted for repeated measures taken from right and left feet of each participant through adopting a mixed models approach in which a participant-specific random effect and participant-nested random effect for foot-side were included.

6.5.3.7 Rationale for mixed-models analysis approach

The mixed models approach was adopted to analyse data for all research aims. In situations when data are collected from multiple feet and sites, statistical approaches need to take into account the within-subject dependence between feet as a result of common subject factors which often render data from right and left limbs to be highly correlated. This approaches adopted in this thesis, correctly account for the association between feet, sites and trials and utilise all information available from repeated trials. As a result, this approach addresses the assumption that each data point is an independent observation, and therefore meets the assumptions of independence. When comparing the mixed models approach used in this thesis to more commonly used approaches (such as analysing data from a randomly selected right or left foot, analysing data from each foot separately, or averaging data across right and left feet), the results produce similar mean estimates, yet produce narrower confidence intervals for these estimates and therefore demonstrate greater efficiency (data not yet published). This approach also retains information that would have been lost in traditional models in which data are averaged across feet and/or trials. Additionally, the approach used was able to derive efficiency and power from the information present in the covariance between the areas of the feet by using the covariance structures which appropriately account for correlations between each site within a foot.

6.5.3.8 Missing data

Missing data were resolved by multiple imputation in the case of missing covariates and record deletion in the case of missing outcomes. Multiple imputation involves filling in multiple values for each missing value in order to accurately reflect the uncertainty due to missingness. The repeated measures approach used for the inferential analyses accommodated outcome missingness without further adjustment.

6.5.3.9 Significance levels

All hypothesis tests (excluding covariate testing) for Aim I and Aim II were carried out at a 5% level of significance against two-sided alternatives. No adjustment for multiplicity was used, but all test-statistics, their null distributions and their observed significance levels were reported.

For Aim III, hypothesis tests were carried out at a Bonferroni-adjusted significance level, which was based on the number of dependent (clinically assessed) variables included in the analyses.

6.5.3.10 Software

Data were analysed using IBM SPSS Statistics version 22, R version 3.2.3 and SAS version 9.3.

Chapter seven: Aim I results: Clinically assessed characteristics of the 1MTP in participants with gout and asymptomatic hyperuricaemia

7.1 Introduction

This chapter presents the results from Aim I which sought to identify clinically assessed features of the 1MTP in participants with gout and asymptomatic hyperuricaemia. This chapter begins with a description of the participants, followed by the intra-rater reliability results, descriptive statistics and finally, the inferential statistics.

7.2 Participants

7.2.1 Diagnostic groups

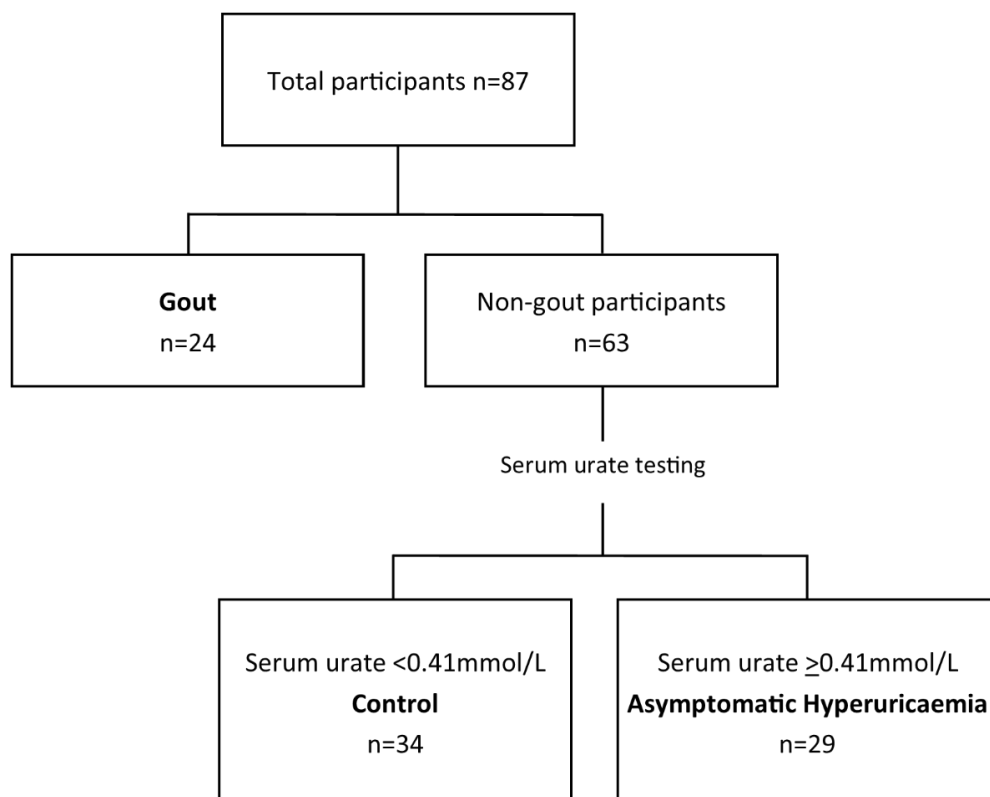


Figure 7.1 Flow chart of participants

A total of 87 people participated in the study (**Figure 7.1**). Twenty-four participants met the gout diagnostic group definition. Sixty-three participants who did not meet this definition underwent serum urate testing. Of these, 34 were included in the normouricaemic control group and the remaining 29 in the group with asymptomatic hyperuricaemia. One participant in the gout group did not undertake the ultrasound assessment due to family bereavement. All other participants (n = 86) undertook both the ultrasound assessment and clinical assessment.

7.2.2 Participant characteristics

Participant demographic characteristics are displayed in **Table 7.1**. All participants were male with a mean age of 58 years and predominantly of European ethnicity. The control group had a significantly reduced body mass index compared to the participants with gout ($P < 0.001$) and participants with asymptomatic hyperuricaemia ($P < 0.001$).

Table 7.1. Demographic characteristics[†]			
Variable	Control	Gout	Asymptomatic hyperuricaemia
n	34	24	29
Gender, male, n (%)	34 (100%)	24 (100%)	29 (100%)
Age, years	58 (14)	58 (13)	58 (19)
Ethnicity, n (%)	European 30 (88%) Māori 1 (3%) Pacific 0 (0%) Asian 3 (9%)	European 14 (58%) Māori 1 (4%) Pacific 5 (21%) Asian 4 (17%)	European 24 (83%) Māori 0 (0%) Pacific 3 (10%) Asian 2 (7%)
BMI, kg/m ²	25.0 (2.9)	30.2 (4.0) [‡]	29.3 (5.9) [‡]
[†] Values are the mean (SD) unless otherwise indicated. [‡] Significantly different from control group ($P < 0.05$). BMI = Body Mass Index.			

Medical, laboratory and clinical characteristics are presented in **Table 7.2**. Compared to controls, participants with gout had a significantly higher frequency of NSAID use ($P = 0.004$). The control group had a significantly lower prevalence of hypertension compared to the participants with gout ($P = 0.001$) and with asymptomatic hyperuricaemia ($P = 0.023$) and a significantly lower prevalence of cardiovascular disease compared to the gout group ($P = 0.019$). Participants with gout also had significantly higher tender and swollen joints counts compared to the control participants ($P = 0.032$ and $P < 0.001$, respectively). **Table 7.3** displays the disease characteristics for the gout group.

Table 7.2. Medical, laboratory and clinical characteristics [†]				
Variable		Control	Gout	Asymptomatic hyperuricaemia
Diuretic use, n (%)		4 (12%)	3 (12%)	7 (24%)
NSAID use, n (%)		7 (21%)	14 (58%) [‡]	11 (38%)
Prednisone use, n (%)		0 (0%)	5 (21%)	0 (0%)
Hypertension, n (%)		9 (26%)	17 (70%) [‡]	16 (55%) [‡]
Cardiovascular disease, n (%)		1 (3%)	7 (29%) [‡]	5 (17%)
Diabetes, n (%)		2 (6%)	4 (17%)	1 (3%)
Urate, mmol/l	mean (SD)	0.32 (0.06)	0.35 (0.10)	0.46 (0.05) [‡]
	range	0.20 - 0.40	0.24 - 0.63	0.41 - 0.63
	highest ever	-	0.60 (0.13)	-
1MTP tenderness, n (%) [§]		1 (1%)	7 (15%)	1 (2%)
1MTP swelling, n (%) [§]		0 (0%)	1 (2%)	0 (0%)
66/68 joint count	Tender	0.6 (1.2)	2.7 (6.1) [‡]	1.5 (1.9)
	Swollen	0.0 (0.0)	1.0 (1.7) [‡]	0.2 (0.7)
[†] Values are the mean (SD) unless otherwise indicated. [‡] Significantly different from control group ($P < 0.05$). NSAID = Non-Steroidal Anti-Inflammatory Drugs. [§] 1MTP tenderness and swelling values are based on joints (control, n = 68; gout, n = 48; asymptomatic hyperuricaemia, n = 58).				

Table 7.3. Gout disease characteristics [†]	
Classification criteria, n (%)	Aspirate proven 6 (25%) Clinical criteria 18 (75%)
Disease duration, years	17 (11)
Age of onset, years	41 (18)
Acute flares in preceding 3 months	1.3 (1.4)
1MTP flares in preceding 3 months, n (%)	6 (25%)
History of 1MTP flares, n (%)	21 (88%)
Presence of subcutaneous tophi, n (%)	17 (71%)
Presence of 1MTP tophi, n (%)	6 (25%)
Number of tophi in feet	1.9 (3.5)
Total number of tophi	6.1 (8.7)
Colchicine use, n (%)	13 (54%)
Urate lowering therapy [‡] , n (%)	23 (96%)
Allopurinol use, n (%)	19 (79%)
Probenecid use, n (%)	3 (12%)
Benzbromarone use, n (%)	2 (8%)
Febuxostat use, n (%)	2 (8%)
[†] Values are the mean (SD) unless otherwise indicated. [‡] 3 participants were taking > 1 urate lowering agent	

7.3 Clinically assessed characteristics

7.3.1 Intra-rater reliability

Table 7.4 presents the mean (SD) values from session one and session two for 1MTP dorsiflexion range of motion, plantarflexion force and dorsiflexion force. Excellent ICCs were demonstrated for all variables (all ICC \geq 0.98).

Table 7.4. Intra-rater reliability for rom and muscle force in participants with gout (n = 10) [†]				
Variable	Session One	Session Two	ICC_(2,1)	95% CI for ICC
Dorsiflexion ROM, °	62.2 (16.1)	61.9 (16.3)	0.99	0.97, 1.00
Plantarflexion force, N	70.5 (30.3)	69.6 (32.1)	0.98	0.94, 0.99
Dorsiflexion force, N	63.4 (35.1)	64.6 (34.4)	0.99	0.97, 0.99
[†] Values are the mean (SD) unless indicated otherwise. ROM = range of motion. CI = Confidence Interval.				

Table 7.5 presents the mean (SD) values from session one and session two for the spatial and temporal gait parameters in participants with gout. Excellent reliability was demonstrated for stride length, support base, step time, double support time and velocity. Good reliability was observed for step length, swing time, single support time, and cadence.

Table 7.5. Intra-rater reliability for gait parameters in participants with gout (n = 20) [†]					
Variable	Session One	Session Two	Change	ICC_{2,1}	95% CI for ICC
Step time, s	0.59 (0.04)	0.59 (0.04)	0.00	0.69	0.52, 0.87
Step length, cm	66.2 (9.1)	66.7 (9.1)	-0.46	0.88	0.80, 0.96
Stride length, cm	132.7 (18.3)	133.7 (18.3)	-1.01	0.90	0.82, 0.97
Support base, cm	12.1 (3.8)	12.1 (3.8)	-0.02	0.81	0.70, 0.92
Swing time, s	0.44 (0.04)	0.44 (0.04)	-0.00	0.61	0.43, 0.79
Stance time, s	0.73 (0.07)	0.73 (0.07)	0.00	0.70	0.53, 0.88
Single support time, s	0.44 (0.04)	0.44 (0.04)	-0.00	0.61	0.43, 0.79
Double support time, s	0.29 (0.05)	0.29 (0.05)	0.00	0.80	0.67, 0.93
Velocity, m/s	114.4 (20.2)	115.0 (20.2)	-0.63	0.84	0.73, 0.95
Cadence, steps/min	103.3 (8.3)	103.1 (8.3)	0.23	0.73	0.56, 0.90
[†] Values are the mean (SD) unless indicated otherwise. CI = Confidence Interval.					

7.3.2 Descriptive statistics

Descriptive statistics for patient-reported outcomes are presented in **Table 7.6**, structural and functional outcomes in **Table 7.7**, neurovascular outcomes in **Table 7.8** and dynamic/gait outcomes in **Tables 7.9 to 7.11**.

Table 7.6. Descriptive statistics for patient-reported outcomes [†]			
Variable	Control n = 34	Gout n = 24	Asymptomatic Hyperuricaemia n = 29
1MTP pain VAS, mm	1.6 (4.0)	8.3 (15.4)	7.0 (15.1)
Pain VAS, mm	17.8 (23.4)	21.2 (26.1)	29.9 (29.7)
Patient global, mm	11.6 (18.1)	23.6 (23.3)	21.3 (21.5)
HAQ-DI	0.11 (0.22)	0.43 (0.46)	0.33 (0.49)
LLTQ daily	38.6 (3.6)	33.4 (6.6)	34.8 (8.6)
LLTQ recreational	34.3 (6.9)	21.0 (12.3)	26.8 (13.4)
MFPDI	1.8 (5.9)	13.2 (10.7)	3.1 (4.6)
Disabling foot pain, n (%)	8 (23.5%)	19 (79.2%)	16 (55.2%)
[†] Values are the mean (SD) unless indicated otherwise. VAS = Visual Analog Scale; HAQ-DI = Health Assessment Questionnaire – Disability Index; LLTQ = Lower Limb Task Questionnaire; MFPDI = Manchester Foot Pain and Disability Index.			

Table 7.7. Descriptive statistics for structural and functional outcomes [†]			
Variable	Control n = 68 joints	Gout n = 48 joints	Asymptomatic Hyperuricaemia n = 58 joints
Dorsiflexion range of motion, °	75.4 (19.3)	56.8 (21.1)	78.1 (17.2)
Plantarflexion force, N	93.0 (23.9)	72.1 (33.4)	123.3 (50.0)
Dorsiflexion force, N	61.0 (22.9)	60.5 (25.6)	61.0 (22.9)
Hallux valgus severity, n (%)	none	36 (53%)	19 (40%)
	mild	24 (35%)	28 (48%)
	moderate	15 (31%)	26 (45%)
	severe	7 (15%)	3 (5%)
Foot Posture Index	4.5 (2.9)	6.4 (3.6)	1 (2%)
[†] Values are the mean (SD) unless indicated otherwise.			

Table 7.8. Descriptive statistics for neurovascular outcomes [†]			
Variable	Control n = 68 joints	Gout n = 48 joints	Asymptomatic Hyperuricaemia n = 58 joints
Plantar Temperature, °C	23.6 (2.4)	26.1 (3.1)	24.9 (2.7)
Dorsal Temperature, °C	25.1 (2.1)	27.6 (2.9)	26.0 (2.2)
Medial Temperature, °C	24.2 (2.2)	26.6 (3.5)	25.6 (2.4)
Vibration Perception Threshold, V	17.7 (12.4)	20.9 (13.9)	18.1 (15.1)
Loss of protective sensation, n (%)	2 (3%)	10 (21%)	8 (14%)
[†] Values are the mean (SD) unless indicated otherwise.			

Table 7.9. Descriptive statistics for gait parameters [†]			
Variable	Control n = 68 feet	Gout n = 48 feet	Asymptomatic Hyperuricaemia n = 58 feet
Step length, m	0.61 (0.07)	0.56 (0.08)	0.60 (0.12)
Stride length, m	1.24 (0.14)	1.12 (0.18)	1.19 (0.25)
Support base, m	0.07 (0.03)	0.11 (0.04)	0.12 (0.04)
Step time, s	0.60 (0.05)	0.64 (0.07)	0.57 (0.06)
Swing time, s	0.45 (0.04)	0.47 (0.04)	0.42 (0.04)
Stance time, s	0.73 (0.09)	0.81 (0.09)	0.73 (0.09)
Single support time, s	0.46 (0.04)	0.47 (0.05)	0.46 (0.04)
Double support time, s	0.15 (0.04)	0.17 (0.03)	0.27 (0.11)
Velocity, m/s	1.01 (0.18)	1.05 (0.19)	0.89 (0.17)
Cadence, steps/min	101.1(10.0)	102.1 (10.14)	94.5 (9.22)
[†] Values are the mean (SD).			

Table 7.10. Descriptive statistics for peak plantar pressure (kPa) [†]			
Variable	Control n = 68 feet	Gout n = 48 feet	Asymptomatic Hyperuricaemia n = 58 feet
Heel	302.5 (73.6)	277.6 (79.5)	274.6 (53.9)
Midfoot	121.7 (42.3)	129.1 (46.4)	121.7 (42.3)
First Metatarsal	230.7 (60.6)	238.5 (60.9)	204.8 (57.7)
Second Metatarsal	322.4 (80.8)	315.6 (69.6)	300.3 (83.5)
Third to fifth metatarsals	273.6 (57.7)	272.5 (73.3)	236.2 (60.4)
Hallux	222.3 (72.5)	237.7 (80.5)	203.2 (72.5)
Lesser Toes	103.8 (46.1)	125.4 (45.0)	103.8 (46.1)
[†] Values are the mean (SD).			

Table 7.11. Descriptive statistics for pressure time integral (kPa*sec) [†]			
Variable	Control n = 68 feet	Gout n = 48 feet	Asymptomatic Hyperuricaemia n = 58 feet
Heel	61.5 (22.8)	57.4 (17.8)	52.1 (21.1)
Midfoot	27.4 (10.8)	30.0 (14.9)	18.5 (10.4)
First metatarsal	57.4 (29.2)	57.1 (23.8)	57.4 (29.2)
Second metatarsal	82.0 (31.8)	78.1 (18.4)	75.7 (22.4)
Third to fifth metatarsals	66.0 (21.5)	67.4 (22.2)	59.2 (19.3)
Hallux	42.9 (32.7)	41.8 (20.8)	35.1 (15.9)
Lesser toes	22.7 (16.0)	24.0 (12.9)	20.7 (10.1)
[†] Values are the mean (SD).			

7.3.4 Inferential statistics

7.3.4.1 Normality

The distribution of residuals from the linear models for all outcomes demonstrated sufficient normality to carry out parametric testing.

7.3.4.2 Covariates

Gender was removed from the covariate review for all outcomes due to the absence of female participants in the study. Following the covariate review for ethnicity, it was also excluded from all models as a result of statistical and clinical justification. Although there may have been an effect of ethnicity, it did not have significant influence on the estimates as the numbers in ethnic categories across the diagnostic groups were too small to account for statistically. In addition, box plots of random effects by ethnicity did not inconclusively demonstrate a marked remaining difference between the ethnicities (**Figure 7.2**). Clinically, the numbers in the ethnic categories were reflective of the ethnic composition of the true diagnostic group populations [27]. Age group achieved significance for all outcomes. The results for these variables are therefore presented adjusted for age. Additionally, for gait/dynamic outcomes BMI was also included as a covariate.

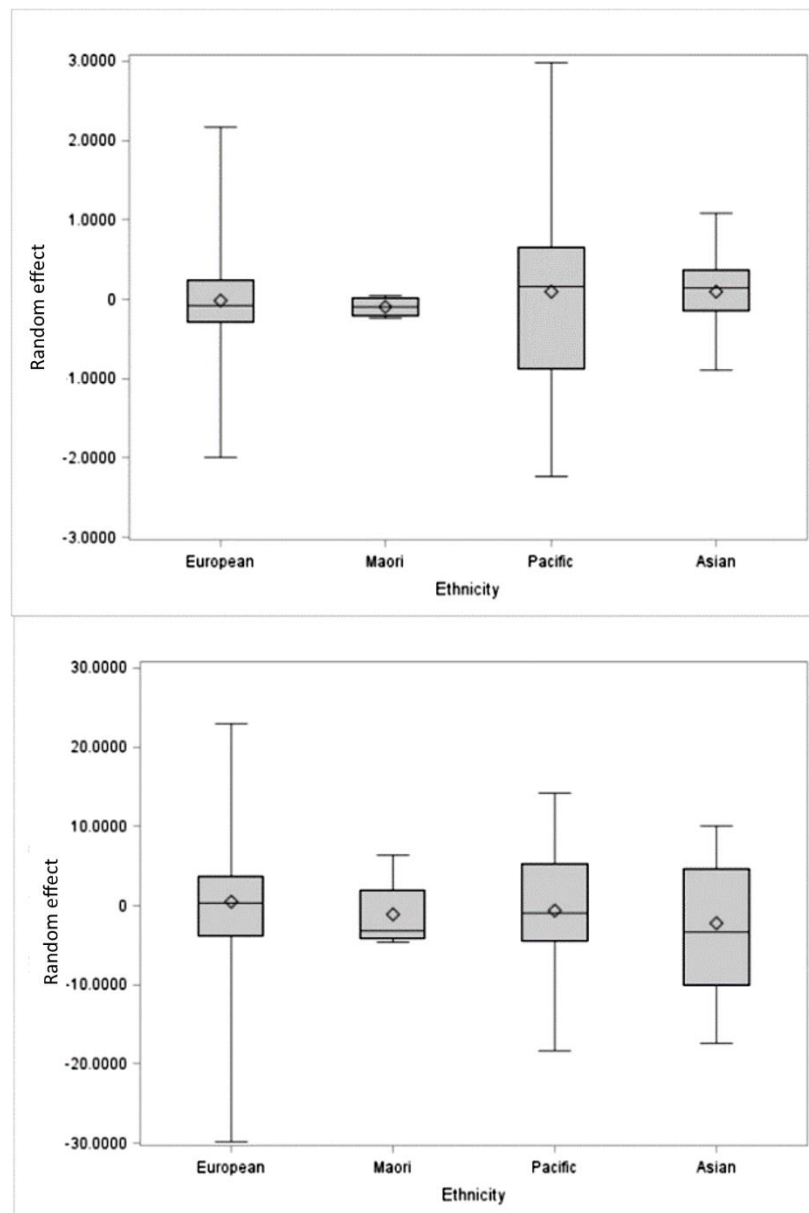


Figure 7.2 Box plots of random effects associated to each diagnostic group showing no marked difference between ethnicities

7.3.4.3 Patient-reported outcomes

The inferential analyses for patient-reported outcomes are presented in **Table 7.12**. Compared to controls, participants with gout reported significantly greater 1MTP pain ($P = 0.014$), greater patient global scores ($P = 0.034$), a greater HAQ-DI score ($P = 0.002$), a greater LLTQ daily score ($P = 0.002$), a greater LLTQ recreational score ($P < 0.001$), a greater MFPDI score ($P < 0.001$), and a higher odds of having disabling foot pain (Odds Ratio [OR] 13.4; $P < 0.001$). Participants with asymptomatic hyperuricaemia also reported a significantly greater HAQ-DI score ($P = 0.033$), a

greater LLTQ daily score ($P = 0.026$), a greater LLTQ recreational score ($P = 0.010$) and had a higher odds of having disabling foot pain ($OR\ 4.2\ P = 0.013$), compared to controls.

Table 7.12. Inferential analysis of patient-reported outcomes					
Parameter		Least-squares mean [†]	Diff.	95% CI for Diff.	<i>P</i>
1MTP pain VAS (mm)	Control	1.7			
	Gout	8.4	6.7	1.4, 12.0	0.014
	AH	6.6	4.9	-0.1, 10.0	0.055
General pain VAS (mm)	Control	18.0			
	Gout	21.8	3.8	-9.9, 17.5	0.581
	AH	29.2	11.3	-1.7, 24.3	0.088
Patient global VAS (mm)	Control	11.5			
	Gout	23.6	12.0	0.9, 23.1	0.034
	AH	21.3	9.8	-0.8, 20.3	0.068
HAQ-DI	Control	0.11			
	Gout	0.44	0.33	0.13, 0.54	0.002
	AH	0.32	0.21	0.02, 0.41	0.033
LLTQ - daily	Control	38.6			
	Gout	33.3	-5.3	-8.6, -2.0	0.002
	AH	35.0	-3.6	-6.8, -0.4	0.026
LLTQ – recreational	Control	34.2			
	Gout	20.8	-13.4	-19.0, -7.9	< 0.001
	AH	27.2	-7.0	-12.3, -1.8	0.010
MFPDI	Control	1.8			
	Gout	13.3	11.5	7.7, 15.3	< 0.001
	AH	3.0	1.2	-2.4, 4.8	0.511
		Odds Ratio [†]	95% CI for OR		<i>P</i>
Presence of disabling foot pain [‡]	Control				
	Gout	13.4	3.7, 48.7		< 0.001
	AH	4.2	1.4, 12.8		0.013
[†] Mean estimates and odds ratios are presented adjusted for age group. [‡] Reference category: no disabling foot pain. Bolded <i>P</i> values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval; AH = Asymptomatic Hyperuricaemia; VAS = Visual Analog Scale; HAQ-DI = Health Assessment Questionnaire – Disability Index; LLTQ = Lower Limb Task Questionnaire; MFPDI = Manchester Foot Pain and Disability Index.					

7.3.4.4 Structural and functional outcomes

The inferential analyses for structural and functional outcomes are presented in **Table 7.13**. Compared to controls, participants with gout had significantly reduced 1MTP dorsiflexion range of motion ($P < 0.001$), reduced 1MTP plantarflexion force ($P = 0.012$) and an increased odds of having more severe hallux valgus ($OR\ 0.3$; $P = 0.041$). Participants with asymptomatic hyperuricaemia had significantly greater 1MTP plantarflexion force ($P = 0.004$) and a higher FPI score ($P = 0.036$), compared to controls.

Table 7.13. Inferential analysis of structural and functional outcomes					
Parameter		Least-squares mean [†]	Diff.	95% CI for Diff.	P
Dorsiflexion range of motion (°)	Control	77.6			
	Gout	59.7	-17.9	-26.8, -8.9	< 0.001
	AH	76.8	-0.8	-9.3, 7.7	0.853
Plantarflexion force (N)	Control	92.0			
	Gout	71.3	-20.7	-36.9, -4.6	0.012
	AH	114.8	22.8	7.5, 38.1	0.004
Dorsiflexion force (N)	Control	57.3			
	Gout	58.0	0.8	-10.7, 12.2	0.896
	AH	65.4	8.1	-2.7, 19.0	0.139
Foot Posture Index	Control	4.8			
	Gout	6.2	1.3	-0.4, 3.1	0.134
	AH	6.6	1.8	0.1, 3.4	0.036
		Odds Ratio [†]	95% CI for OR		p
Hallux Valgus Severity [‡]	Control				
	Gout	0.28	0.08, 0.95		0.041
	AH	0.97	0.30, 3.2		0.957
[†] Mean estimates and odds ratios are presented adjusted for age group. Bolded P values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval; AH = Asymptomatic hyperuricaemia. [‡] Reference category: none (i.e. grade 0). The odds ratio represents the odds of the diagnostic group moving up one category of severity, compared to the control group moving up one category of severity.					

7.3.4.5 Neurovascular outcomes

The inferential analyses for neurovascular outcomes are presented in **Table 7.14**. Compared to controls, participants with gout had significantly increased temperature at the plantar ($P = 0.004$), dorsal ($P = 0.003$), and medial ($P = 0.004$) aspects of the 1MTP, as well as an increased odds of having loss of protective sensation ($OR\ 15.6$; $P = 0.021$).

Table 7.14. Inferential analysis of neurovascular outcomes					
Parameter		Least-squares mean [†]	Diff.	95% CI for Diff.	<i>P</i>
Plantar Temperature (°C)	Control	24.3			
	Gout	26.2	1.9	0.6, 3.1	0.004
	AH	25.1	0.8	-0.5, 2.0	0.218
Dorsal Temperature (°C)	Control	25.8			
	Gout	27.7	1.9	0.6, 3.1	0.003
	AH	26.5	0.6	-0.6, 1.9	0.295
Medial Temperature (°C)	Control	25.2			
	Gout	27.0	1.8	0.6, 3.1	0.004
	AH	25.9	0.8	-0.4, 2.0	0.219
Vibration Perception Threshold (V)	Control	17.4			
	Gout	22.0	4.6	-0.8, 10.0	0.096
	AH	17.4	0.0	-5.1, 5.2	0.986
		Odds Ratio [†]	95% CI for OR		<i>P</i>
Loss of protective sensation [‡]	Control				
	Gout	15.6	1.5, 160.9		0.021
	AH	2.6	0.2, 27.7		0.433
[†] Mean estimates and odds ratios are presented adjusted for age group. [‡] Reference category: no loss of protective sensation. Bolded <i>P</i> values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval; AH = Asymptomatic hyperuricaemia.					

7.3.4.6 Dynamic/gait outcomes

The inferential analyses for peak plantar pressure are presented in **Table 7.15**. Compared to controls, participants with gout had significantly decreased peak plantar pressure at the heel ($P = 0.012$), increased pressure at the midfoot ($P < 0.001$) and reduced pressure at the hallux ($P = 0.036$). Compared to controls, participants with asymptomatic hyperuricaemia had significantly

increased pressure at the midfoot ($P = 0.013$), increased pressure at the first metatarsal ($P = 0.015$) and increased pressure at the second metatarsal ($P = 0.007$).

Table 7.15. Peak plantar pressure (kPa)					
Parameter		Least-squares mean[†]	Diff.	95% CI for Diff.	<i>P</i>
Heel	Control	294.3			
	Gout	268.2	-26.1	-46.6, -5.6	0.012
	AH	301.9	7.6	-12.4, 27.5	0.456
Midfoot	Control	95.4			
	Gout	130.8	35.4	15.5, 55.3	< 0.001
	AH	120.1	24.7	5.3, 44.0	0.013
First Metatarsal	Control	211.5			
	Gout	229.6	18.2	-5.2, 41.5	0.127
	AH	239.7	28.3	5.6, 50.9	0.015
Second Metatarsal	Control	292.6			
	Gout	287.1	-5.5	-26.9, 15.8	0.611
	AH	321.3	28.7	7.9, 49.5	0.007
Third to Fifth Metatarsals	Control	252.3			
	Gout	244.1	-8.2	-29.6, 13.2	0.454
	AH	255.2	2.9	-17.9, 23.7	0.785
Hallux	Control	233.3			
	Gout	208.4	-24.9	-48.1, -1.6	0.036
	AH	241.9	8.6	-14.0, 31.3	0.454
Lesser Toes	Control	105.9			
	Gout	121.8	15.9	-2.8, 34.6	0.096
	AH	107.2	1.4	-16.9, 19.6	0.882
[†] Mean estimates are presented adjusted for age group and BMI. Bolded <i>P</i> values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval; AH = Asymptomatic hyperuricaemia.					

The inferential analyses for pressure time integrals are presented in **Table 7.16**. Compared to controls, participants with gout had significantly increased pressure time integrals at the midfoot ($P = 0.006$). No significant differences in pressure time integrals were observed between the participants with asymptomatic hyperuricaemia and control participants.

Table 7.16. Pressure time integrals (kPa*s)					
Parameter		Least-squares mean [†]	Diff.	95% CI for Diff.	<i>P</i>
Heel	Control	61.50			
	Gout	54.68	-6.82	-13.75, 0.12	0.054
	AH	59.83	-1.67	-8.44, 5.09	0.628
Midfoot	Control	23.48			
	Gout	32.66	9.18	2.60, 15.76	0.006
	AH	27.17	3.69	-2.72, 10.10	0.260
First Metatarsal	Control	56.24			
	Gout	54.24	-2.00	-9.50, 5.50	0.601
	AH	60.25	4.01	-3.28, 11.29	0.281
Second Metatarsal	Control	77.61			
	Gout	70.66	-6.95	-14.49, 0.59	0.071
	AH	82.15	4.54	-2.80, 11.89	0.225
Third to Fifth Metatarsals	Control	66.61			
	Gout	61.00	-5.61	-12.90, 1.68	0.132
	AH	64.42	-2.18	-9.28, 4.92	0.547
Hallux	Control	40.66			
	Gout	34.75	-5.91	-13.11, 1.29	0.108
	AH	41.74	1.08	-5.94, 8.09	0.764
Lesser Toes	Control	21.92			
	Gout	23.19	1.28	-4.94, 7.49	0.687
	AH	20.48	-1.44	-7.50, 4.62	0.642
[†] Mean estimates are presented adjusted for age group and BMI. Bolded <i>P</i> values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval; AH = Asymptomatic hyperuricaemia.					

The inferential analyses for spatial and temporal gait parameters are presented in **Table 7.17**. Compared to controls, participants with gout had significantly increased step time ($P = 0.022$), increased stance time ($P = 0.022$) and decreased velocity ($P = 0.050$). Compared to controls participants with asymptomatic hyperuricaemia had significantly increased support base ($P = 0.002$), decreased swing time ($P = 0.019$), decreased single support time ($P = 0.020$), increased double support time ($P < 0.001$) and increased cadence ($P = 0.028$).

Table 7.17. Spatial and temporal gait parameters					
Parameter		Least-squares mean[†]	Diff.	95% CI for Diff.	P
Step Length (cm)	Control	0.61			
	Gout	0.57	0.03	-0.02, 0.08	0.168
	AH	0.61	0.00	-0.05, 0.05	0.985
Stride Length (cm)	Control	1.21			
	Gout	1.14	0.07	-0.04, 0.17	0.200
	AH	1.20	0.02	-0.08, 0.11	0.763
Support Base (cm)	Control	0.08			
	Gout	0.10	-0.02	-0.03, 0.00	0.102
	AH	0.11	-0.03	-0.05, -0.01	0.002
Step Time (s)	Control	0.60			
	Gout	0.64	-0.04	-0.07, -0.01	0.022
	AH	0.57	0.03	0.00, 0.06	0.081
Swing Time (s)	Control	0.46			
	Gout	0.47	-0.02	-0.04, 0.00	0.104
	AH	0.43	0.03	0.01, 0.05	0.019
Stance Time (s)	Control	0.74			
	Gout	0.80	-0.06	-0.10, -0.01	0.022
	AH	0.72	0.03	-0.02, 0.07	0.266
Single Support Time (s)	Control	0.46			
	Gout	0.48	-0.02	-0.04, 0.00	0.092
	AH	0.43	0.03	0.00, 0.05	0.020
Double Support Time (s)	Control	0.16			
	Gout	0.16	0.00	-0.04, 0.04	0.857
	AH	0.26	-0.10	-0.14, -0.06	< 0.001
Velocity (m/s)	Control	1.03			
	Gout	0.91	0.11	0.00, 0.23	0.050
	AH	1.07	-0.05	-0.15, 0.06	0.379
Cadence (steps/min)	Control	100.9			
	Gout	95.5	5.4	-0.7, 11.5	0.080
	AH	107.3	-6.5	-12.2, -0.7	0.028
[†] Mean estimates are presented adjusted for age group and BMI. Bolded P values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval; AH = Asymptomatic hyperuricaemia.					

Chapter eight: Aim II results: Sonographic features of the 1MTP in participants with gout and asymptomatic hyperuricaemia

8.1 Introduction

This chapter presents the results related to Aim II which sought to identify sonographic features of the 1MTP in participants with gout and participants with asymptomatic hyperuricaemia. The results from the inter-rater reliability are presented, followed by the descriptive statistics and finally the inferential statistics.

8.2 Inter-rater reliability

Inter-rater reliability between the two sonographic readers is displayed in **Table 8.1** (kappa statistics) and **Table 8.2** (intra-class correlation coefficients). The inter-rater reliability was moderate for the presence of the double contour sign, tophi, erosion, synovial hypertrophy and effusion, and good for synovitis. The inter-rater reliability for the grading of features was fair to good for erosions, synovial hypertrophy and effusion and excellent for synovitis. Inter-rater reliability for tophus diameter and cartilage thickness was excellent and for erosion diameter was fair to good.

Table 8.1. Inter-rater reliability for the presence of sonographic features at the 1MTP (n = 172 joints)					
	N (%)		Percent agreement	k	95% CI for k
	Reader 1	Reader 2			
Double Contour Sign [†]	87 (51%)	51 (30%)	74.4%	0.49	0.37, 0.61
Tophus	15 (9%)	7 (4%)	94.2%	0.52	0.26, 0.78
Erosion	10 (6%)	19 (11%)	92.4%	0.52	0.29, 0.74
Effusion	31 (18%)	21 (12%)	84.9%	0.42	0.23, 0.60
Snowstorm	2 (1%)	0 (0%)	98.8%	0.00	-1.38, 1.38
Synovial hypertrophy	15 (9%)	14 (8%)	93.6%	0.59	0.36, 0.81
Synovitis	22 (13%)	21 (12%)	92.4%	0.66	0.48, 0.83
[†] Assessed at dorsal aspect of joint only. k = kappa statistic; CI = Confidence Interval.					

Table 8.2. Inter-rater reliability for the grading, size and thickness of sonographic features at the 1MTP (n = 172 joints)				
	Mean (SD)		ICC _{3,1}	95% CI For ICC
	Reader 1	Reader 2		
Tophus diameter, mm	0.8 (3.3)	0.5 (3.1)	0.86	0.81, 0.89
Erosion grade	0.4 (0.6)	0.4 (0.7)	0.72	0.64, 0.79
Erosion diameter, mm	1.2 (2.3)	0.7 (1.7)	0.60	0.50, 0.69
Effusion grade	0.8 (0.8)	0.5 (0.7)	0.50	0.38, 0.60
Synovial hypertrophy grade	0.6 (0.7)	0.2 (0.7)	0.53	0.41, 0.63
Synovitis grade	0.2 (0.5)	0.2 (0.5)	0.81	0.75, 0.85
Cartilage thickness, mm [†]	0.64 (0.20)	0.64 (0.19)	0.81	0.75, 0.86
[†] Assessed at dorsal aspect of joint only. ICC = Intra-Class Correlation Coefficient; CI = Confidence Interval.				

8.3 Descriptive statistics

Tables 8.3, 8.4 and **8.5** display the descriptive statistics for the sonographic features at the dorsal, medial and plantar aspects of the 1MTP, respectively. **Table 8.6** presents the descriptive statistics for the sonographic features at the 1MTP as a whole (i.e. features present at the dorsal, medial and/or plantar aspects of the 1MTP), which were used in the inferential analyses for Aim I. Examples of the sonographic features are displayed in **Figure 8.1** and **Figure 8.2**.

Table 8.3. Descriptive statistics for sonographic features at the dorsal 1MTP [†]				
		Control n = 68 joints	Gout n = 46 joints	Asymptomatic hyperuricaemia n = 58 joints
Double Contour Sign, n (%)		9 (13%)	17 (37%)	21 (36%)
Tophus, n (%)		0 (0%)	2 (4%)	0 (0%)
Tophus diameter, mm [‡]		0.00 (-)	7.73 (0.39)	0.00 (-)
Erosion grade, n (%)	0	65 (96%)	32 (70%)	55 (95%)
	1	3 (4%)	10 (22%)	3 (5%)
	2	0 (0%)	4 (9%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)
Erosion, n (%)		0 (0%)	4 (9%)	0 (0%)
Erosion diameter, mm [‡]		0.00 (-)	6.53 (2.46)	0.00 (-)
Effusion grade, n (%)	0	30 (44%)	23 (50%)	14 (24%)
	1	26 (38%)	20 (44%)	31 (53%)
	2	12 (18%)	3 (7%)	12 (21%)
	3	0 (0%)	0 (0%)	1 (2%)
Effusion, n (%)		12 (18%)	3 (7%)	13 (22%)
Snowstorm, n (%)		0 (0%)	0 (0%)	0 (0%)
Synovial hypertrophy grade, n (%)	0	43 (63%)	15 (33%)	33 (57%)
	1	24 (35%)	27 (59%)	22 (38%)
	2	1 (2%)	3 (7%)	1 (2%)
	3	0 (0%)	1 (2%)	2 (3%)
Synovial hypertrophy, n (%)		1 (2%)	4 (9%)	3 (5%)
Synovitis grade, n (%)	0	65 (96%)	32 (70%)	57 (98%)
	1	3 (4%)	11 (24%)	1 (2%)
	2	0 (0%)	2 (4%)	0 (0%)
	3	0 (0%)	1 (2%)	0 (0%)
Synovitis, n (%)		3 (4%)	14 (30%)	1 (2%)
Cartilage thickness, mm		0.65 (0.19)	0.61 (0.18)	0.65 (0.20)
[†] Values are the mean (SD) unless otherwise indicated. [‡] Tophus and erosion diameter values are reported based only on joints with tophi or erosions present.				

Table 8.4. Descriptive statistics for sonographic features at the medial 1MTP [†]				
		Control n = 68 joints	Gout n = 46 joints	Asymptomatic hyperuricaemia n = 58 joints
Tophus, n (%)		0 (0%)	5 (11%)	0 (0%)
Tophus diameter, mm [‡]		0.00 (-)	10.42 (6.66)	0.00 (-)
Erosion grade, n (%)	0	66 (97%)	10 (22%)	49 (85%)
	1	2 (3%)	23 (50%)	8 (14%)
	2	0 (0%)	13 (28%)	1 (2%)
	3	0 (0%)	0 (0%)	0 (0%)
Erosion, n (%) [§]		0 (0%)	13 (28%)	1 (2%)
Erosion diameter, mm [‡]		1.85 (0.92)	4.02 (1.88)	2.90 (-)
Effusion grade, n (%)	0	63 (93%)	41 (89%)	47 (81%)
	1	5 (7%)	4 (9%)	11 (19%)
	2	0 (0%)	1 (2%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)
Effusion, n (%) [§]		0 (0%)	1 (2%)	0 (0%)
Snowstorm, n (%)		0 (0%)	0 (0%)	0 (0%)
Synovial hypertrophy grade, n (%)	0	66 (97%)	30 (65%)	55 (95%)
	1	2 (3%)	15 (33%)	2 (3%)
	2	0 (0%)	1 (2%)	0 (0%)
	3	0 (0%)	0 (0%)	1 (2%)
Synovial hypertrophy, n (%) [§]		0 (0%)	1 (2%)	1 (2%)
Synovitis grade, n (%)	0	66 (97%)	31 (67%)	57 (98%)
	1	2 (3%)	12 (26%)	1 (2%)
	2	0 (0%)	3 (7%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)
Synovitis, n (%) [§]		2 (3%)	15 (33%)	1 (2%)
[†] Values are the mean (SD) unless otherwise indicated. [‡] Tophus and erosion diameter values are reported based only on joints with tophi or erosions present. [§] The overall presence of erosion, effusion and synovial hypertrophy is based on a grade of ≥ 2 ; the overall presence of synovitis is based on a grade of ≥ 1 .				

Table 8.5. Descriptive statistics for sonographic features at the plantar 1MTP [†]				
		Control n = 68 joints	Gout n = 46 joints	Asymptomatic hyperuricaemia n = 58 joints
Tophus, n (%)		0 (0%)	4 (9%)	0 (0%)
Tophus diameter, mm [‡]		0.00 (-)	18.30 (8.54)	0.00 (-)
Erosion grade, n (%)	0	68 (100%)	42 (91%)	58 (100%)
	1	0 (0%)	3 (7%)	0 (0%)
	2	0 (0%)	1 (2%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)
Erosion, n (%) [§]		0 (0%)	0 (0%)	0 (0%)
Erosion diameter, mm [‡]		0.00 (-)	3.00 (-)	0.00 (-)
Effusion grade, n (%)	0	67 (99%)	45 (98%)	50 (86%)
	1	1 (1%)	1 (2%)	7 (12%)
	2	0 (0%)	0 (0%)	1 (2%)
	3	0 (0%)	0 (0%)	0 (0%)
Effusion, n (%) [§]		0 (0%)	0 (0%)	1 (2%)
Snowstorm, n (%)		0 (0%)	0 (0%)	0 (0%)
Synovial hypertrophy grade, n (%)	0	66 (97%)	33 (72%)	56 (97%)
	1	2 (3%)	12 (26%)	1 (2%)
	2	0 (0%)	1 (2%)	1 (2%)
	3	0 (0%)	0 (0%)	0 (0%)
Synovial hypertrophy, n (%) [§]		0 (0%)	0 (0%)	1 (2%)
Synovitis grade, n (%)	0	68 (100%)	36 (78%)	58 (100%)
	1	0 (0%)	10 (22%)	0 (0%)
	2	0 (0%)	0 (0%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)
Synovitis, n (%) [§]		0 (0%)	0 (0%)	0 (0%)
[†] Values are the mean (SD) unless otherwise indicated. [‡] Tophus and erosion diameter values are reported based only on joints with tophi or erosions present. [§] The overall presence of erosion, effusion and synovial hypertrophy is based on a grade of ≥ 2 ; the overall presence of synovitis is based on a grade of ≥ 1 .				

Table 8.6. Descriptive statistics for sonographic features at the 1MTP [†]				
		Control n = 68 joints	Gout n = 46 joints	Asymptomatic hyperuricaemia n = 58 joints
Double Contour Sign, n (%) [‡]		9 (13%)	17 (37%)	21 (36%)
Tophus, n (%)		0 (0%)	6 (13%)	0 (0%)
Tophus diameter, mm [§]		0.00 (-)	15.44 (9.78)	0.00 (-)
Erosion grade, n (%)	0	60 (88%)	7 (15%)	47 (81%)
	1	6 (9%)	24 (52%)	10 (17%)
	2	2 (3%)	15 (33%)	1 (2%)
	3	0 (0%)	0 (0%)	0 (0%)
Erosion, n (%)		2 (3%)	15 (33%)	1 (2%)
Erosion diameter, mm [¶]		1.85 (0.92)	4.76 (2.34)	2.90 (-)
Effusion grade, n (%)	0	27 (40%)	22 (48%)	10 (17%)
	1	29 (43%)	20 (44%)	35 (60%)
	2	12 (18%)	4 (9%)	12 (21%)
	3	0 (0%)	0 (0%)	1 (2%)
Effusion, n (%) [¶]		12 (18%)	4 (9%)	13 (22%)
Snowstorm, n (%)		0 (0%)	0 (0%)	0 (0%)
Synovial hypertrophy grade, n (%)	0	41 (60%)	12 (26%)	33 (57%)
	1	26 (38%)	29 (63%)	22 (38%)
	2	1 (2%)	4 (9%)	1 (2%)
	3	0 (0%)	1 (2%)	2 (3%)
Synovial hypertrophy, n (%) [¶]		1 (2%)	5 (11%)	3 (5%)
Synovitis grade, n (%)	0	63 (93%)	25 (54%)	56 (97%)
	1	5 (7%)	17 (37%)	2 (3%)
	2	0 (0%)	3 (7%)	0 (0%)
	3	0 (0%)	1 (2%)	0 (0%)
Synovitis, n (%) [¶]		5 (7%)	20 (44%)	2 (3%)
Cartilage thickness, mm [‡]		0.65 (0.19)	0.61 (0.18)	0.65 (0.20)
[†] Values are the mean (SD) unless otherwise indicated. [‡] Assessed at dorsal aspect of joint only. All remaining variables were assessed at dorsal, medial and plantar. [§] Tophus and erosion diameter values are reported based only on joints with tophi or erosions present. [¶] The overall presence of erosion, effusion and synovial hypertrophy is based on a grade of ≥ 2 ; the overall presence of synovitis is based on a grade of ≥ 1 .				

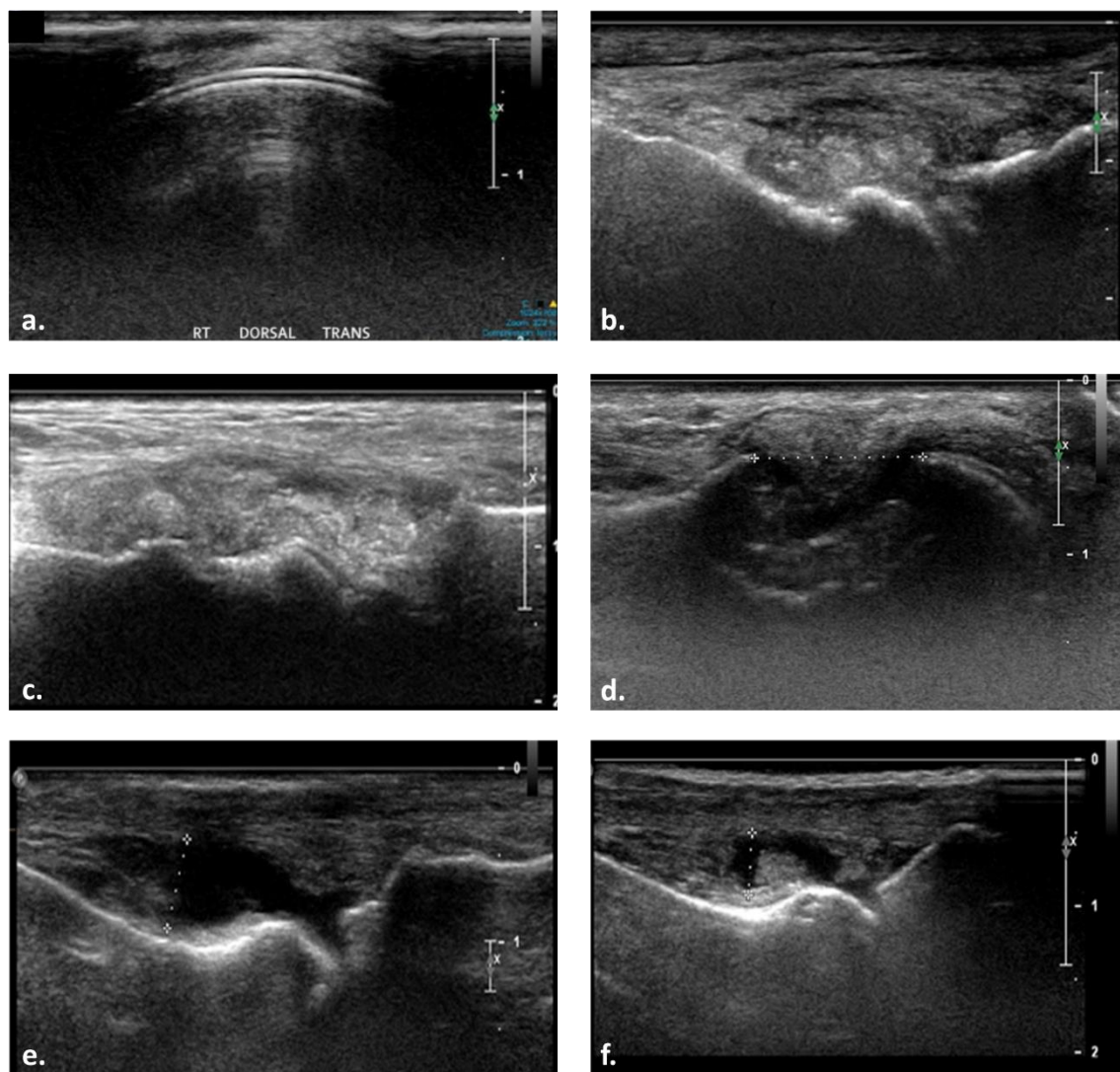


Figure 8.1 Sonographic examples of the double contour sign on the dorsal first metatarsal head (a); tophus at the dorsal aspect of the 1mtp (b, c); tophus and erosion at medial first metatarsal head (d); effusion (e); and effusion with focal synovial hypertrophy (f).

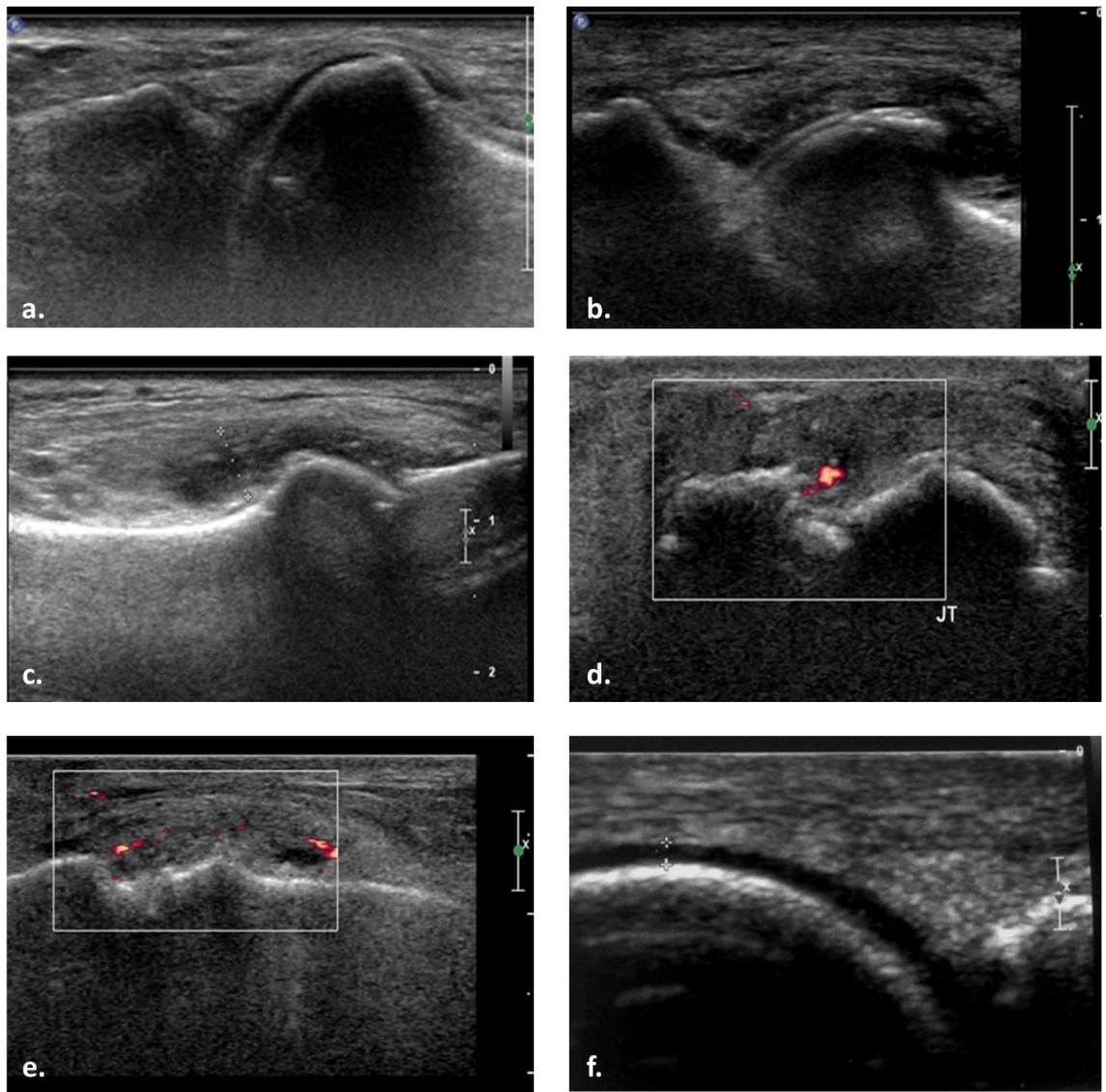


Figure 8.2 Sonographic examples of mild synovial hypertrophy (**a**); severe synovial hypertrophy (**b**, **c**); erosion and synovitis at the medial first metatarsal head (**d**); synovial hypertrophy with synovitis (**e**); and measurement of cartilage thickness at the dorsal first metatarsal head (**f**).

8.4 Inferential Statistics

8.4.1 Normality

The distribution of residuals from the linear model for tophus diameter, erosion diameter and cartilage thickness (continuous outcomes) demonstrated sufficient normality to carry out parametric testing.

8.4.2 Covariates

Gender was removed from the covariate review for all outcomes due to the absence of female participants in the study. Age group was also removed as it did not achieve significance for any sonographic feature. Following the covariate review for ethnicity, it was also excluded from all models as a result of statistical and clinical justification. Although there may have been an effect of ethnicity, it did not have significant influence on the estimates as the numbers in ethnic categories across the diagnostic groups were too small to account for statistically. Clinically, the numbers in the ethnic categories were reflective of the ethnic composition of the true diagnostic group populations [27].

8.4.3 Presence of each sonographic feature

The inferential analyses for the overall presence of sonographic features at the 1MTP is presented in **Table 8.7**. Compared to controls, both participants with gout and participants with asymptomatic hyperuricaemia had a greater odds of having the double contour sign (Odds Ratio [OR] 3.91; $P = 0.011$, OR 3.81; $P = 0.009$, respectively). Compared to controls, participants with gout also had an increased odds of having 1MTP erosions (OR 10.13; $P = 0.001$) and synovitis (OR 9.00; $P < 0.001$). No significant differences were observed for the presence of tophus, effusion or synovial hypertrophy between the groups.

Table 8.7. Odds ratios for the presence of sonographic features at the 1MTP				
		Odds Ratio[†]	95% CI for OR	P
Double Contour Sign [‡]	Gout	3.91	1.37, 11.20	0.011
	AH	3.81	1.41, 10.36	0.009
Tophus	Gout	5.08	0.96, 27.08	0.057
	AH	1.00	0.12, 8.26	1.000
Erosion [§]	Gout	10.13	2.75, 37.28	0.001
	AH	0.83	0.14, 4.88	0.828
Effusion [§]	Gout	0.45	0.13, 1.61	0.217
	AH	1.34	0.51, 3.54	0.548
Synovial hypertrophy [§]	Gout	3.25	0.67, 15.73	0.142
	AH	1.72	0.32, 9.13	0.523
Synovitis [§]	Gout	9.00	3.10, 26.08	< 0.001
	AH	0.60	0.14, 2.69	0.505
[†] Reference category = control group; All odds ratios are presented unadjusted for covariates. [‡] Assessed at the dorsal aspect of the 1MTP only. [§] The overall presence of erosion, effusion and synovial hypertrophy is based on a grade of ≥ 2 ; the overall presence of synovitis is based on a grade of ≥ 1 . Bolded <i>P</i> values indicate statistically significant differences from control group. CI = Confidence Interval.				

8.4.4 Grading of sonographic features

The inferential analyses for the grading of sonographic features at the 1MTP is presented in **Table 8.8**. Compared to controls, participants with gout had a greater odds of having more severe erosions (*OR* 101.80; *P* < 0.001), more severe synovial hypertrophy (*OR* 11.73; *P* = 0.002) and more severe synovitis (*OR* 47.51; *P* = 0.002). Compared to controls, participants with asymptomatic hyperuricaemia had a greater odds of having more severe effusion (*OR* 3.08; *P* = 0.046).

Table 8.8. Odds ratios for grading of sonographic features at the 1MTP				
		Odds Ratio[†]	95% CI for OR	P
Erosion grade	Gout	101.80	16.56, 625.68	< 0.001
	AH	1.81	0.49, 6.68	0.371
Effusion grade	Gout	0.51	0.15, 1.65	0.260
	AH	3.08	1.02, 9.31	0.046
Synovial hypertrophy grade	Gout	11.73	2.48, 55.48	0.002
	AH	1.54	0.36, 6.52	0.558
Synovitis grade	Gout	47.51	4.29, 526.07	0.002
	AH	0.46	0.05, 4.60	0.511
[†] Reference category = control group. The odds ratio represents the odds of the diagnostic group moving up one grade, compared to the control group moving up one grade. All odds ratios are presented unadjusted for covariates. Bolded <i>P</i> values indicate statistically significant differences from control group. CI = Confidence Interval.				

8.4.5 Tophus and erosion size and cartilage thickness

The inferential analyses for the size of tophi, erosions, and cartilage at the 1MTP is presented in **Table 8.9**. Compared to controls, participants with gout demonstrated significantly greater tophus diameter ($P = 0.035$) and erosion diameter ($P < 0.001$).

Table 8.9. Linear regression for size and thickness of sonographic features at the 1MTP					
		Least-squares mean[†]	Diff.	95% CI for Diff.	<i>P</i>
Tophus diameter, mm	Control	0.00			
	Gout	1.68	1.68	0.12, 0.324	0.035
	AH	0.00	0.00	-1.46, 1.46	1.000
Erosion diameter, mm	Control	0.05			
	Gout	1.55	1.50	0.84, 2.16	< 0.001
	AH	0.05	-0.00	-0.62, 0.61	0.989
Cartilage thickness average, mm	Control	0.66			
	Gout	0.64	-0.02	-0.08, 0.03	0.364
	AH	0.62	-0.01	-0.06, 0.04	0.773
[†] Mean estimates are presented unadjusted for covariates. Bolded <i>P</i> values indicate statistically significant differences from control group. Diff. = Difference in least-squares mean; CI = Confidence Interval.					

Chapter nine: Aim III results: Associations between the clinically assessed characteristics and sonographic features of the 1MTP

9.1 Introduction

This chapter presents the inferential results from Aim III which sought to investigate the associations between the clinically assessed characteristics and sonographic features. 1MTP pain, 1MTP dorsiflexion range of motion, foot pain and disability, gait velocity and 1MTP dorsal temperature were selected as the independent variables based on the results from Aim I. The double contour sign, tophus, erosion and synovitis were selected as the dependent variables based on the results from Aim II.

9.2 Associations between the double contour sign and 1MTP clinical characteristics

Associations between 1MTP clinical characteristics and the sonographic presence of the double contour sign are presented in **Table 9.1**. After accounting for the diagnostic group, presence of the double contour sign was significantly associated with higher MFPDI scores ($P < 0.001$).

Table 9.1. Association between clinical characteristics and presence of the double contour sign					
	Least squares mean		Diff.	95% CI for Diff.	<i>P</i>
	Present	Absent			
1MTPJ Pain VAS, mm	3.4	7.0	3.5	-1.0, 8.0	0.124
MFPDI	10.1	4.8	-5.4	-7.8, -2.9	< 0.001[†]
1MTPJ range of motion, °	68.8	72.2	2.4	-3.2, 8.1	0.402
1MTPJ temperature, °C	26.8	26.0	-0.8	-1.5, 0.1	0.018
Walking velocity, m/s	1.02	1.00	-0.02	-0.10, 0.05	0.521
Results are presented adjusted for diagnostic group. [†] Significantly different at Bonferroni-adjusted level of < 0.01. Bolded <i>P</i> values indicate statistically significant differences between groups. Diff. = Difference in mean estimate between presence and absence; CI = Confidence Interval; MFPDI = Manchester Foot Pain and Disability Index.					

9.3 Associations between sonographic tophus and 1MTP clinical characteristics

Associations between 1MTP clinical characteristics and the sonographic presence of tophus are presented in **Table 9.2**. After accounting for the diagnostic group, presence of tophus was significantly associated with higher MFPDI scores ($P < 0.001$), increased 1MTPJ temperature ($P = 0.005$) and reduced walking velocity ($P = 0.001$).

Table 9.2. Association between clinical characteristics and presence of tophus					
	Least squares mean		Diff.	95% CI for Diff.	P
	Present	Absent			
1MTPJ Pain VAS, mm	2.4	6.0	3.6	-7.0, 14.3	0.499
MFPDI	19.8	5.9	-13.9	-19.7, -8.1	< 0.001[†]
1MTPJ range of motion, °	55.1	71.2	16.1	2.4, 29.7	0.021
1MTPJ temperature, °C	28.6	26.2	-2.3	-3.9, 0.7	0.005[†]
Walking velocity, m/s	0.88	1.00	0.11	0.05, 0.18	0.001[†]
Results are presented adjusted for diagnostic group. [†] Significantly different at Bonferroni-adjusted level of < 0.01. Bolded <i>P</i> values indicate statistically significant differences between groups. Diff. = Difference in mean estimate between presence and absence; CI = Confidence Interval; MFPDI = Manchester Foot Pain and Disability Index.					

9.4 Associations between sonographic erosion and 1MTP clinical characteristics

Associations between 1MTP clinical characteristics and the sonographic presence of erosion are presented in **Table 9.3**. After accounting for the diagnostic group, no associations were observed between erosion and the clinical characteristics.

Table 9.3. Association between clinical characteristics and presence of erosion					
	Least squares mean		Diff.	95% CI for Diff.	P
	Present	Absent			
1MTPJ Pain VAS, mm	3.1	6.3	3.2	-6.0, 12.4	0.493
MFPDI	6.6	5.6	-1.0	-6.9, 4.9	0.745
1MTPJ range of motion, °	66.2	71.2	5.0	-4.8, 14.8	0.315
1MTPJ temperature, °C	25.1	26.2	1.1	0.1, 2.1	0.040
Walking velocity, m/s	0.95	1.00	0.05	-0.11, 0.21	0.531
Results are presented adjusted for diagnostic group. [†] Significantly different at Bonferroni-adjusted level of < 0.01. Bolded <i>P</i> values indicate statistically significant differences between groups. Diff. = Difference in mean estimate between presence and absence; CI = Confidence Interval; MFPDI = Manchester Foot Pain and Disability Index.					

9.5 Associations between sonographic synovitis and 1MTP clinical characteristics

Associations between 1MTP clinical characteristics and the sonographic presence of synovitis are presented in **Table 9.4**. After accounting for the diagnostic group, no associations were observed between synovitis and the clinical characteristics.

Table 9.4. Association between clinical characteristics and presence of synovitis					
	Least squares mean		Diff.	95% CI for Diff.	<i>P</i>
	Present	Absent			
1MTPJ Pain VAS, mm	5.7	5.7	0.0	-6.7, 6.8	0.994
MFPDI	8.4	5.8	-2.7	-6.9, 1.6	0.214
1MTPJ range of motion, °	66.3	71.0	4.7	-2.5, 12.0	0.199
1MTPJ temperature, °C	26.8	26.2	-0.6	-1.4, 0.2	0.129
Walking velocity, m/s	0.94	1.01	0.07	-0.06, 0.19	0.285
Results are presented adjusted for diagnostic group. *Significantly different at Bonferroni-adjusted level of < 0.01. Bolded <i>P</i> values indicate statistically significant differences between groups. Diff. = Difference in mean estimate between presence and absence; CI = Confidence Interval; MFPDI = Manchester Foot Pain and Disability Index.					

Chapter ten: Discussion

10.1 Introduction

The study presented in this thesis sought to identify clinical characteristics and sonographic features of the first metatarsophalangeal joint (1MTP) in participants with gout and participants with asymptomatic hyperuricaemia by comparing them to individuals with normouricaemia. Additionally, the association between clinical characteristics and sonographic features of the 1MTP was also explored. This chapter will discuss the results, including the limitations, strengths, clinical implications and future directions. The results discussed in this chapter have been published in the *Journal of Foot and Ankle Research* and *Arthritis Care & Research* [503-505] (**Appendices 9-11**).

10.2 Participant characteristics

Participants in the study presented in this thesis consisted of middle-aged males who were predominantly of European ethnicity. The higher proportion of Pacific and Māori individuals among the participants with gout is reflective of the ethnic composition of the gout population in Auckland, New Zealand from which the participants were recruited [27, 506]. The participants with gout had an average body mass index (BMI) classified as obese with many presenting with additional comorbid conditions including cardiovascular disease and diabetes. These findings are comparable to recent co-prevalence estimates in which 40% of New Zealand's gout population are recorded to have diabetes and/or cardiovascular disease [507]. This remains an important consideration in the management of people with gout, due to shared risk factors and pharmacological interactions resulting from the treatment of co-existing diseases [244].

The participants with gout had a long average disease duration, with the majority defined as having chronic tophaceous gout (Stage D under the recently proposed staging system [110]), which may be attributed to the secondary care setting from which they were recruited. Although serum urate levels were on average below the treatment target of 0.36 mmol/l, current guidelines recommend a lower target of 0.30 mmol/l for those with tophaceous gout, due to the inverse relationship between tophus regression rate and serum urate concentrations [228]. Although all but one gout participant were prescribed urate lowering therapy, sub-optimal management of serum urate is common due to the lack of understanding of the importance of pharmacological adherence [508-510].

Importantly, although all participants with gout included in the study had no clinical or self-reported evidence of acute arthritis at the time of assessment, tender and swollen joint counts were significantly higher than those observed in the control group. The frequency of disease-specific characteristics related to the 1MTP, including palpable tenderness, tophus presence and flare history, highlights the tendency for 1MTP involvement in gout and also the chronicity of pain affecting this joint [322].

The participants with asymptomatic hyperuricaemia included in this study were overweight hypertensive individuals with frequent cardiovascular disease and diuretic use which is characteristic of the disease profile seen in individuals with high serum urate concentrations [511, 512]. Average serum urate levels indicated mild hyperuricaemia, which has been associated with only a small risk of developing gout (2%) over a five year period [30]. Nevertheless, individuals with mild hyperuricaemia are still 11 times more likely to develop gout compared to individuals with normal serum urate concentrations [32].

10.3 Aim I: Clinically assessed characteristics of the 1MTP

This study also investigated patient-reported outcomes and clinician assessed characteristics of the 1MTP in participants with gout and participants with asymptomatic hyperuricaemia. Despite the absence of current symptoms of acute arthritis in the participants with gout and an absence of any signs or symptoms of gout in the participants with asymptomatic hyperuricaemia participants, both groups demonstrated significant differences from the normouricaemic controls in terms of patient-reported outcomes, functional, structural and neurovascular 1MTP characteristics and dynamic gait characteristics.

10.3.1 Patient-reported outcome measures

Clinical symptoms in gout are generally associated with acute episodes of painful inflammatory arthritis, most often at the 1MTP [144], while intercritical periods are traditionally considered to be asymptomatic remissive phases [117, 530]. However, the current findings, which support existing research [321, 376], suggest that 1MTP pain may be a chronic and persistent foot problem in people with gout. Although people with current episodes of acute gouty arthritis have been shown to experience substantial foot pain, which reduces following resolution of the flare, the pain does not completely normalise [316]. Although the presence of foot pain in the

absence of acute symptoms observed in the study presented in this thesis may be associated with residual inflammation from recent flares [316], the co-existence of tophaceous arthropathy or other conditions known to manifest in the foot, including osteoarthritis, diabetes, obesity and peripheral vascular disease, may also contribute to ongoing foot pain. In fact, a recent study reported disabling foot pain in individuals with gout was associated with older age, obesity, depression and ischaemic heart disease [322]. This is consistent with the significantly reduced overall wellbeing reported by participants with gout in the study presented in this thesis who exhibited a similar mean patient global assessment to other studies [317, 531].

Using the Health Assessment Questionnaire – Disability Index (HAQ-DI), participants with gout in the study presented in this thesis had mild activity limitation (mean score 0.44), which is consistent with previous studies in which mean HAQ-DI scores range from 0.4 to 0.9 in participants with intercritical gout [211, 212, 316-318, 532, 533]. Severe activity limitation has been reported in participants with current acute gouty arthritis (mean HAQ-DI 1.9) [316], while HAQ-DI scores range from 1.10 to 1.24 in participants with refractory chronic gout, indicating an increase to moderate disability [205, 531]. When assessing specific items of the HAQ-DI, ten Klooster et al. [211] found that activity limitation in participants with gout was primarily associated with difficulty in performing tasks related to mobility and lower extremity functioning. This aligns with the significant decrease in lower limb functioning reported by the participants with gout in the study presented in this thesis who experienced mild difficulty in performing recreational activities and moderate difficulty with activities of daily living, which is consistent with existing studies [316, 317].

Although participants with asymptomatic hyperuricaemia did not display the 1MTP-specific pain observed in the gout group, they did report greater overall foot pain and disability, reduced lower limb function and increased activity limitation compared to the normouricaemic controls. It is unclear whether this is a direct result of chronically elevated serum urate and subclinical MSU deposition, inflammation and tissue damage [125, 293, 313, 315, 382, 426], or related to co-existing conditions including hypertension, obesity, cardiovascular disease and diabetes, which have a marked association with hyperuricaemia and may display clinical manifestations in the foot and lower limb [16, 534-539].

10.3.2 Structural and functional characteristics

Several 1MTP structural and functional changes were observed in participants with gout in the study presented in this thesis. Participants with gout had a mean dorsiflexion range of motion

of 60 degrees, which was significantly lower than the normouricaemic controls and well below the 65 degrees required for efficient forward transfer of body weight during propulsion [340, 348]. Although restricted joint motion may be a result of surrounding synovial inflammation or a pain-avoidance mechanism, reduced dorsiflexion motion at this joint is a characteristic feature of 1MTP osteoarthritis and is strongly associated with radiographic evidence of cartilage loss [540]. Although the relationship between osteoarthritis and gout at the 1MTP has been previously demonstrated [361, 362, 541], it is unclear whether MSU crystals facilitate cartilage damage or whether osteoarthritis predisposes to local MSU crystal deposition [42, 43].

Participants with gout also exhibited a reduction in 1MTP plantarflexion force. Plantarflexion at the 1MTP is important for the forward transfer of body weight in normal walking [542]. Pain-avoidance gait strategies have been proposed to reduce plantarflexor muscle activity and may lead to disuse muscle atrophy [318]. In fact, a recent biomechanical study showed that foot pain and disability were correlated with not only impaired walking strategies, but also reduced ankle plantarflexion strength [319, 320]. Similarly, the authors did not observe a strength reduction in dorsiflexory muscles of the ankle which they attributed to the typical pattern of crystal deposition and patient symptoms in which anterior ankle structures are less often involved compared with posterior structures [290, 292]. This is also true of the structures surrounding the 1MTP in which imaging studies have demonstrated that the flexor hallucis longus muscle tendon is a frequent site for MSU deposition [292, 293], and that urate deposition in this tendon is highly correlated with the occurrence of 1MTP gout flares [293]. Although the impact that MSU deposition in tendons has on muscle strength remains unclear, several case studies investigating tendon ruptures of the ankle and foot in the gout population suggest that the presence of tophi may reduce the tensile capacity of tendons [306-308]. Likewise, the infiltration of tophi into muscle tissues may reduce the functional cross-sectional muscle area and thereby the potential to generate force [543].

Participants with gout in the study presented in this thesis demonstrated a greater severity of hallux valgus deformity compared to the normouricaemic control participants. This is consistent with a previous study in which clinically assessed hallux valgus was significantly more common in participants with gout when compared to control participants [376]. However, a large study involving 1,184 participants with gout found 36% had self-reported hallux valgus, which the authors reported was similar to the general population and not related to gout-specific factors including disease duration or flare history, but related only to increasing age and female gender [321]. A recent study measured hallux valgus radiographically, where it was defined as a hallux abductus angle of ≥ 20 degrees or an intermetatarsal angle of ≥ 10 degrees. The study found a high prevalence of radiography-proven hallux valgus in 72% of 43 participants with gout but

found no association between tophus size and radiographic angles or the presence of hallux valgus [544]. However, hallux valgus increases exposure of the medial articular surfaces of the 1MTP to joint damage and therefore, may facilitate MSU crystal and tophus infiltration. Thus hallux valgus may have contributed to the medial pattern of sonographic tophus and erosion observed in the study presented in this thesis. The increased frequency and severity of hallux valgus in people with gout may also be related to chronic inflammation and impaired integrity of synovial tissue and ligamentous structures responsible for maintaining normal joint alignment. Muscle imbalance, another well-known risk factor in the development of hallux valgus [545], may also be exacerbated by gout either through inflammation or muscle disuse atrophy, both of which were observed in the study presented in this thesis.

Participants with asymptomatic hyperuricaemia also demonstrated differences in structural and functional characteristics when compared to the normouricaemic controls. Their increased plantarflexory muscle strength may be related to the increased BMI in this group. Grip strength, a measure of overall muscle strength, has been shown to positively correlate with increased BMI in adults [546, 547] as it is a measure that incorporates lean muscle mass as well as adiposity. Furthermore, it is plausible that the individuals with asymptomatic hyperuricaemia lacked the same muscle disuse atrophy observed in the participants with gout because their foot and lower limb symptoms were not as marked as those reported by people with gout.

Although the mean foot posture index (6.6) observed in the participants with asymptomatic hyperuricaemia is considered within the “normal” range, they were significantly greater than the control participants who had an average of 4.8. This tendency towards a more pronated or flatter foot type, may also be attributed to the increased BMI in this group as it results in postural effects including lowering of the medial longitudinal arch [548]. The absence of a significantly flatter foot posture in those with gout, despite the similar increase in BMI, may be explained by their tendency to adjust their foot position in an attempt to “relieve” the big toe [211]. This also aligns with a reduction in the activation of the plantarflexor muscles and the eventual development of muscle disuse atrophy.

10.3.3 Neurovascular characteristics

Clinically palpable warmth is regarded as a classical feature of acute 1MTP gouty arthritis [172]. Participants with gout in the study presented in this thesis were not experiencing acute arthritis at the time of assessment, yet they presented with significant increases in 1MTP temperature

compared with normouricaemic participants, which is reflective of ongoing subclinical inflammation [549]. Dermal thermography has not been used previously to assess asymptomatic people with gout. However, it has been used as a quantifiable method in identifying people with rheumatoid arthritis that are most likely to develop future destructive disease [550] and people with type 2 diabetes that are most likely to develop ulceration [489, 551, 552]. It has been well established that MSU crystals, which promote the inflammatory response evident in acute gout, are also present in synovial fluid during intercritical periods [112], which may explain the increased temperature observed in the study presented in this thesis.

The neurological implications of gout in the foot have not yet been investigated. The study presented in this thesis has shown that people with gout have a greater likelihood of having a loss of protective sensation compared to controls, however vibration perception, as measured by a biothesiometer, was normal. This is in contrast to previous research on participants with gout with current foot ulceration, which observed normal monofilament readings and reduced biothesiometer readings [323]. Participants with asymptomatic hyperuricaemia did not demonstrate any sensation loss, suggesting that gout-specific factors may play a role in nerve dysfunction in individuals with gout. The chronic inflammation present at the 1MTP in people with gout may result in adjacent nerve fibre damage and sensation loss. Additionally, entrapment neuropathy by tophi has been reported in several case studies relating to the upper limb resulting in carpal tunnel syndromes or ulnar neuropathy suggesting tophi have the ability to compress and injure nerves [553-559]. Colchicine-induced distal sensation loss has also been reported in chronic users as a result of axonal neuropathy and denervation of unmyelinated axons [560-562]. Increased serum urate has also been associated with an increased risk of peripheral neuropathy in people with type 2 diabetes [563, 564] due to its role in causing endothelial dysfunction and oxidative stress [565-570]. However, the consequence of hyperuricaemia in the absence of diabetes has not been studied. Only four participants with gout in the study presented in this thesis had concomitant type 2 diabetes and only two of those had a loss of peripheral sensation. It is unclear if hyperuricaemia induces neural dysfunction through similar mechanism in people with gout.

10.3.4 Dynamic outcome characteristics

During barefoot walking, people with gout walked slower with increased time spent in step and stance phases compared to the normouricaemic control participants. These findings are consistent with previous research assessing people with gout during both shod and barefoot

walking [318, 320, 571]. Reduced gait speed is considered an important characteristic of impaired physical performance in daily activities in adults [572, 573] and has been associated with self-reported foot-related functional limitation in people with gout [320]. These slower walking strategies exhibited by people with gout may result from several factors including reduced lower limb and foot muscle strength [319], loss of normal joint function, particularly the reduction in 1MTP range of motion and acquired gait strategies developed in an attempt to reduce or prevent pain at the 1MTP or other sites in the foot [318, 320].

The increased midfoot and reduced hallux plantar pressures observed in people with gout are also consistent with previous research in which participants were assessed during shod walking [318]. The authors proposed that reduced peak pressure beneath the hallux in people with gout may reflect an attempt to offload pressure at the 1MTP due to pain [318], which is consistent with the patient-reported symptoms observed in the study presented in this thesis. This is further emphasised in qualitative research in which people with gout report attempting to walk more cautiously with an adjusted foot position to relieve the big toe during acute flares [211]. Additionally, the inefficient 1MTP joint motion observed in the study presented in this thesis in people with gout, may also be related to these aporulsive gait strategies by shifting weight-bearing pressure laterally away from the hallux during toe-off. In contrast to previous research assessing people with gout during shod walking [318], the study presented in this thesis also observed reduced heel pressures in participants with gout. This is consistent with the slower walking speed and may reflect an attempt to reduce impact at weight acceptance in the absence of protective footwear.

The increased peak plantar pressure noted at the first metatarsal and lesser toes is consistent with the distribution of foot ulcers commonly reported in people with gout that have a tendency to occur at areas of increased tissue stress and deformity [323]. Although traditional hypotheses attribute susceptibility for urate deposition at the 1MTP to increased loading beneath this joint during gait [353], Dalbeth and colleagues [358] recently found no association between areas of increased tissue stress in healthy individuals and areas of crystal deposition in people with gout. The increase in first metatarsal plantar pressure observed in the study presented in this thesis may therefore have occurred as a result of manifestations of the disease, rather than a cause of them. In fact, high first metatarsal peak pressures have been observed in people with symptomatic 1MTP osteoarthritis [574] suggesting it may be a mechanism developed to offload a painful 1MTP. The clinical implications for increased loading at the first metatarsal is unknown, but may play a role in triggering flares at the 1MTP in people with gout [99].

When compared to normouricaemic control participants, people with asymptomatic hyperuricaemia also exhibited altered gait parameters. They demonstrated an increased base of support, spent more time in double support, less time in single support and swing phases and walked with increased cadence. An increased base of support and double support duration are generally interpreted as adaptations made to produce a more stable and safer gait in older adults who experience mobility limitations [575-577]. The increased cadence also observed in people with asymptomatic hyperuricaemia may reflect an attempt to maintain gait velocity while retaining balance and stability. The findings from this study may provide laboratory-based biomechanical support of the reduced lower limb function and increased activity limitation reported by the participants with asymptomatic hyperuricaemia in the study presented in this thesis.

Participants with asymptomatic hyperuricaemia also differed significantly from normouricaemic control participants in terms of plantar pressure distribution in which increased pressures in the midfoot and medial metatarsals were observed. Increased midfoot pressures are characteristic of flatter foot postures [578, 579], which were also observed in this group. This increase in fore- and mid-foot plantar pressure is also consistent with that observed in obese individuals [580-582]. However, it should be noted that the analyses in the study presented in this thesis were controlled for BMI. Furthermore, obesity tends to also present with higher toe and heel pressures [580, 582], which were not observed in the study presented in this thesis, suggesting that other unknown factors are driving functional changes in people with asymptomatic hyperuricaemia.

10.3.5 Summary

The results from this clinically based investigation have shown that 1MTP pain is commonly reported by people with gout and is persistent despite the absence of acute arthritis. Clinically evident characteristics of the joint are indicative of subclinical inflammation and highlight the impact of gout on the structure and function of the 1MTP. The findings from the dynamic assessments show that people with gout also walk slower with plantar pressure patterns suggestive of propulsive and antalgic gait strategies. This study has also shown that people with asymptomatic hyperuricaemia, who do not display any signs or symptoms of gout, also experience considerable foot- and lower limb-related pain and impairment and report greater activity limitation when compared to normouricaemic controls. They also exhibit altered gait strategies and plantar loading, which may reflect their level of lower limb disability.

10.4 Aim II: Sonographic features of the 1MTP

The results from this study have shown that people with gout and with asymptomatic hyperuricaemia are more likely to demonstrate sonographic evidence of urate deposition along articular cartilage (double contour sign) at the 1MTP when compared with normouricaemic control participants. However, only those with gout demonstrated significantly more bone erosion and features of soft tissue inflammation.

The frequency of the double contour sign in the people with gout was similar to those with asymptomatic hyperuricaemia (37% and 36%, respectively) and lower in comparison to previous studies, which report a prevalence of this feature in up to 88% of 1MTPs in people with gout [381, 383, 384, 386, 389]. Although 74% of participants with gout in the study presented in this thesis had clinically evident tophi and 63% reported recent episodes of acute arthritis, indicating relatively active disease, the low frequency of the double contour sign in this group may reflect the use of urate lowering therapy and the mean serum urate level below the treatment target (< 0.36 mmol/l). Sonographic evidence of urate deposition, including both the double contour sign and tophus, have been reported to decrease or disappear following urate lowering therapy [384, 388]. This may also explain the lower frequency of tophus (13%) at the 1MTP in the participants with gout compared to previous sonographic studies, which have observed a tophus frequency of 50% to 100% at the 1MTP [114, 381, 383, 384, 388, 389, 513, 514].

The presence of intra-articular MSU crystals in people with asymptomatic hyperuricaemia may be related to signs of systemic low-grade inflammation reported in this population [324]. Studies have demonstrated strong associations between hyperuricaemia and markers of systemic inflammation including elevated levels of leucocytes, C-reactive proteins, and various inflammatory cytokines [325, 326]. It has been postulated that this systemic inflammation may be due to not only a reaction to MSU crystals, but also due to the pro-inflammatory effects of soluble uric acid [324, 515, 516]. It has also been proposed that the systemic inflammation may contribute to the link between hyperuricaemia and the increased risk of numerous comorbid conditions, including hypertension [517, 518], heart failure [519], cardiovascular disease [520, 521], stroke [522], metabolic syndrome [523] and kidney disease [524, 525], which have received considerable attention in recent research.

The double contour sign was observed in 13% of the control joints. There are several factors that may have increased the rate of false positives. Firstly, there is a strong resemblance between

the double contour sign and cartilage interface sign, with the latter often appearing as a result of increased reflectivity at a 90° insonation angle, and the former appearing dependent of the insonation angle. Secondly, the presence of even minimal joint effusion, which was observed frequently in 1MTPs in the study presented in this thesis, can also accentuate the cartilage interface sign due to enhanced reflectivity [526]. Thin or damaged cartilage, such as that seen in osteoarthritis (which is prevalent at the 1MTP [394]), may also impair visualisation of the sign [526]. The presence of osteoarthritis may have restricted joint motion and therefore the radiologist's ability to obtain adequate plantarflexion of the joint to allow sufficient visualisation of the dorsal cartilage surface during scanning.

Moderate inter-rater reliability was demonstrated in this study for the presence of the primary outcome measure, the double contour sign ($k = 0.49$). This result stands in contrast to the majority of previous ultrasound studies that report good to excellent reliability ($k = 0.68$ to 0.98) [125, 182, 383, 447, 450, 452, 453]. There are several factors that may contribute to variability between readers in interpretation of this sign. Firstly, the double contour sign is often very subtle and difficult to distinguish. Sonographers who do not routinely assess people with gout, and therefore have limited experience in detecting urate deposition, may have difficulty in differentiating the double contour sign from the normal chondrosynovial interface [527]. Importantly, dynamic confirmation of the double contour sign could not be performed in the study presented in this thesis as the presence of the sonographic features were assessed from static images. It should be noted that the two radiologists had 26 and 7 years of clinical experience, respectively; however, experience in routinely assessing people with gout was less than this. Secondly, although every effort was made to blind the sonographer performing the scans to the participant's diagnosis, recall bias in the presence of local subcutaneous tophi may have resulted in overestimation of the double contour sign and contributed to the discrepancy between the sonographic readers (the second of who did not interact with the participant).

The sonographic appearance of tophi at the 1MTP demonstrated a particular pattern of distribution in people with gout. Tophi were more commonly seen medially, followed by the plantar joint space and lastly the dorsal joint space. This is in contrast to the only existing study, which also imaged all three joint areas and reported that the dorsal joint space demonstrated the highest frequency of tophaceous material in people with gout [114]. The cause of the tendency for tophi to deposit medially is unclear but may be the limited space in the dorsal joint capsule due to constant dorsiflexion motion during gait coupled with the weight-bearing pressure on the plantar surface, which forces tophaceous material to accumulate medially.

In the study presented in this thesis, both tophi and bone erosion were noted more frequently at the medial metatarsal head. This erosion pattern is consistent with a previous study in which 92% of observed 1MTP erosions were located on the medial metatarsal head [389]. This shared distribution reflects the proposed potential for the urate and inflammatory soft tissue components of tophi to instigate bone erosions [409, 428, 528]. However, the cross-sectional nature of the study presented in this thesis limits the ability to determine whether erosions did result from local tophaceous deposition or from pre-existing osteoarthritis, which is highly prevalent at the 1MTP in people with gout [362].

Individuals with asymptomatic hyperuricaemia did not demonstrate tophi in the study presented in this thesis, in contrast to a previous study in which tophi were observed in 15% of asymptomatic individuals with a similar level of mild hyperuricaemia to participants in the study presented in this thesis (0.47 mmol/l versus 0.46 mmol/l) [513]. It is possible that the volume of urate deposition in the individuals with hyperuricaemia was not large enough to form tophi. This is consistent with a recent dual-energy computed tomography study, in which crystal deposition was observed in both gout and asymptomatic hyperuricaemia, yet the volume of crystals was much lower in the latter group compared to those with gout (mean: 0.09 cm³ versus 0.75 cm³, respectively) [382]. The authors proposed that crystal volume may be important in determining the progression to inflammatory symptomatic disease.

There was no significant loss of cartilage noted in either the participants with gout or those with asymptomatic hyperuricaemia. This is consistent with both radiographic and MRI studies that report joint space narrowing and cartilage damage are not common features in people with gout [431, 529]. Cartilage lesions in wrist and ankle joints have been reported to occur focally in association with erosion, synovitis and tophi [365, 431], which is suggestive of the direct destructive interaction between MSU crystals and chondrocytes. The study presented in this thesis only measured cartilage thickness at the central aspect of the dorsal first metatarsal head and did not assess the medial aspect where tophus and erosions were noted. Therefore, any focal cartilage loss present in these areas would not have been captured. Despite the validation of sonography for cartilage thickness in other populations [468], further validation of the use of ultrasound in measuring cartilage thickness at the 1MTP in people with gout is warranted, particularly considering that the presence of surface urate deposition and effusion enhances reflectivity and may result in overestimation of cartilage volume.

All features of synovial inflammation including effusion, synovial hypertrophy and synovitis were observed most commonly in the dorsal aspect of the joint space in comparison to the other areas imaged. The greater frequency and increased severity of synovitis in participants with gout

(who did not have a gout flare at the time of scanning) reiterates the notion that gout is a disease of chronic inflammation with a persistent subclinical immune response to MSU crystals. The current data are consistent with recent imaging studies using both MRI and ultrasound, which have reported synovial pannus in 87.5% [379] and synovitis in up to 95.8% of people with intercritical gout [443, 446]. Together, these data suggest that synovial inflammation is a common finding in people with gout, even in the absence of clinically apparent flares. Individuals with asymptomatic hyperuricaemia, despite demonstrating a similar frequency of the double contour sign at the 1MTP, did not exhibit features of synovitis. This indicates that the tissue response to MSU crystals in gout is not present in those with asymptomatic hyperuricaemia. Therefore, features other than crystal deposition, specifically soft tissue inflammation and bone erosion, may be useful in differentiating gout from asymptomatic hyperuricaemia.

The highest reliability was demonstrated for both the presence and grading of synovitis. This is reflective of the ease of visualising this feature with the colour coding capability of power Doppler, which has demonstrated excellent reliability in previous gout research [182]. Effusion was the least reliable sonographic feature, which is similar to reports of the same grading system used at the 1MTP in people with other rheumatologic conditions in which only moderate kappa and ICC scores were demonstrated for this feature [465]. This may be due to the frequency of effusion in this joint and the difficulty in differentiating pathological effusion from normal joint fluid.

In summary, the results from this sonographic study have shown that evidence of urate deposition is present at the 1MTP in individuals with gout and with asymptomatic hyperuricaemia even in the absence of symptoms of acute arthritis. However, individuals with asymptomatic hyperuricaemia lack larger urate depositions in the form of tophi, as well as features of soft tissue inflammation and bone damage at this joint. These observations suggest that the presence of sonographic synovitis and bone erosion at the 1MTP may be useful in differentiating gout from asymptomatic hyperuricaemia.

10.5 Aim III: Association between sonographic features and clinically assessed characteristics

The final aim of this study was to identify the association between clinically assessed outcomes related to pain, structure and function of the 1MTP and sonographic features of urate

deposition, bone erosion and soft tissue inflammation at the 1MTP while accounting for the diagnosis of the participant as having gout, asymptomatic hyperuricaemia or normouricaemia.

The sonographic presence of the double contour sign was associated with increased overall patient-reported foot pain and disability as assessed with the Manchester Foot Pain and Disability Index (MFPDI). This reflects the well-documented role of MSU crystals in activating inflammatory-induced pain [100, 102, 103]. This may explain the significantly higher MFPDI scores reported by the participants with asymptomatic hyperuricaemia who had never experienced clinical symptoms of gout, yet demonstrated cartilage surface crystal deposition on ultrasound. It is possible that crystal presence and associated subclinical inflammation may induce a more generalised pain that is not regarded as an acute gout flare in these individuals. It is unclear why sonographic features of soft tissue inflammation or bone disease did not demonstrate associations with patient-reported outcomes, but may be a result of the diagnostic group explaining the variation in pain, as both synovitis and erosion were observed most frequently in those with gout.

Greater foot pain and disability was also associated with tophus presence, suggesting that tophaceous gout, which may be indicative of more advanced disease, could be an important driver of pain and disability in the foot. This may be a consequence of changes to the normal biomechanical role of the 1MTP during gait, resulting in overall impaired foot function. It should be noted that the MFPDI also included items relating to self-consciousness about foot appearance and shoe wear, which has been previously documented by people with tophaceous gout of the 1MTP who struggle to find shoes appropriate for their level of deformity [333].

The presence of tophus at the 1MTP was also associated with clinically assessed increased local temperature. The presence of larger urate deposits, in the form of tophi, may represent a more progressive disease and an environment more prone to chronic inflammation, and therefore increased temperature. In contrast, no relationship was observed between synovitis (a direct measure of increased vascularisation) and increased temperature after accounting for the diagnostic group. Although it is possible that the diagnosis of the participant may have been the primary driver of the change in temperature, the majority of participants with synovitis in the study presented in this thesis had only a mild Doppler signal, which may not have been severe enough to be detected by clinical thermography. This is consistent with studies in rheumatoid arthritis that have detected sonographic evidence of synovitis despite the absence of any clinical features of inflammation [583-586].

The association between reduced walking velocity and 1MTP tophus presence supports impaired function of this joint during gait as a consequence of mechanical obstruction and

abnormal mechanical stresses in combination with pain-avoidance strategies. Research has also shown that mechanical agitation in the presence of urate enhances monosodium crystal nucleation [99], which may further facilitate inflammation-associated temperature increases.

In summary, these results have shown that sonographic features of MSU deposition, rather than soft tissue inflammation or bone erosion, are associated with patient-reported foot pain and disability, while the presence of tophus is associated with impaired functional characteristics.

10.6 Strengths and limitations

This study demonstrated several methodological strengths, however, the findings should also be considered in light of a number of limitations. Importantly, this was a novel study that comprehensively investigated characteristics of the 1MTP in people with gout and asymptomatic hyperuricaemia, many of which had not been assessed in prior research. The cross-sectional design provided an ideal snapshot of individuals with gout who were not currently flaring – a period traditionally considered to be asymptomatic and remissive – which allowed the assessment of several subclinical, and often unnoticed, disease manifestations. However, this design limits the ability to determine the cause and effect relationship between 1MTP characteristics and different disease states as well as the prognostic relevance of the subclinical ultrasound and clinical findings.

The successful recruitment of participants fulfilled the sample size requirements which were powered to detect between-group differences for the primary sonographic outcome measure in Aim II. However, with regard to Aim III, in which the associations between sonographic and clinical characteristics were investigated, the analyses were limited to a small number of carefully selected variables to avoid the issue of multiplicity and attendant increase of the Type 1 error probability. As a result there are likely additional clinical variables associated with the sonographic findings that were not assessed in the study presented in this thesis.

Although the female sex was not an exclusion criterion, all participants recruited were male. Although this is reflective of the higher representation of males with gout, research has demonstrated differences between males and females in terms of clinical features in gout, including a lower frequency of 1MTP involvement in females [587]. The current results may therefore not be generalisable to both genders. Additionally, participants with gout were recruited from secondary-care clinics and had longstanding disease with clinically evident tophus. It is possible that less severe 1MTP disease may be present in those with early gout or

without gouty tophi, who primarily present in primary-care settings. Furthermore, this study was undertaken in Auckland, New Zealand, which is well recognised for its high prevalence of gout among Pacific and Māori males, and the results may therefore not be representative of other global populations with less severe gout.

This study was undertaken prior to publication of the recent 2015 ACR/EULAR classification criteria for gout [152] and the majority of the participants with gout had not undergone microscopic assessment for urate crystals and were classified based on clinical criteria which have limited specificity [139]. The participants with hyperuricaemia and normouricaemia were classified based on a single measure of serum urate on the day of the study. Although major diurnal variation in urate is uncommon [588], mild variation in serum urate can occur. It is possible that the single measurement may have misclassified some participants, and that multiple testing of serum urate over a longer time period would have increased the accuracy of this classification criterion. Importantly, the researcher was highly competent in serum urate testing, having participated in a training course in which high intra-rater reliability was confirmed prior to data collection. It should also be noted that participants with asymptomatic hyperuricaemia had only moderately high urate levels and it is unclear whether the results would have differed if they had more severe hyperuricaemia.

The diagnostic groups were not matched for body mass index (BMI), and BMI was higher in the participants with gout and asymptomatic hyperuricaemia, compared with the normouricaemic control group. Importantly, BMI was included in the analysis models for plantar pressure and gait parameters, which are known to be influenced by body mass. However, the possibility that BMI associated with hyperuricaemia had an additional unmeasured impact on foot function cannot be excluded. In addition, participants with diabetes or a loss of peripheral sensation were not excluded, which may have influenced plantar pressure values in people with gout. Individuals with cardiovascular disease or hypertension were also not excluded, however this reflects the frequent comorbid conditions observed in clinical practice in these populations.

The patient-reported outcome tools adopted in the study varied in terms of their recall periods. The one-week recall period of the Health Assessment Questionnaire – Disability Index (HAQ-DI), Visual Analog Scales (VAS) for 1MTP pain, body pain and patient global, and the Lower Limb Task Questionnaire (LLTQ) may not capture the intermittent nature of flares in people with gout. It is likely that a substantial number of participants would not have experienced acute symptoms in the week prior to assessment. This may have resulted in an underestimate of the true level of pain, activity limitation and disability they experience. However, this was a cross-sectional study with the aim of capturing a small window of time when the patient was asymptomatic.

Nevertheless, the recall periods of established questionnaires does highlight the need for the development of a clinical measure that addresses the intermittent nature specific to gout symptoms in order to capture accurate self-reported outcomes. Furthermore, there is currently a lack of validation for the 1MTP pain VAS in people with gout, which limits the ability in interpreting and making inferences regarding the results.

Due to funding and time limitations, the sonographic assessment could not be undertaken with two radiographers assessing dynamic images. The primary outcome measure, the double contour sign, is often confirmed with dynamic assessment to differentiate it from the normal cartilage interface sign. Importantly, all features were considered present only if both musculoskeletal radiologists reported the feature as present.

Hand-held dynamometry and goniometry were used to assess muscle strength and joint motion. Although other methods commonly used in research are considered more accurate, a pragmatic approach was undertaken when selecting equipment for the clinically assessed features to ensure the assessment methods were widely available and easily usable by a clinician. Importantly, both the hand-held dynamometer and goniometer demonstrated excellent inter-session reliability in the study presented in this thesis.

10.7 Clinical implications

The extent of subclinical inflammation observed in this study questions the long-standing perception of gout as an intermittent disease interspersed with remissive phases. Most patients and practitioners do not comprehend the chronicity of gout due to the absence of signs and symptoms of ongoing crystal deposition and inflammation that occur in the periods between acute arthritis. The incorporation of imaging and clinical tools into routine assessment may be used as education means to enhance both clinicians' and patients' understanding of the concept and justification for long-term urate lowering therapy.

This study highlights the practicality of musculoskeletal ultrasound as a widely available, non-invasive and relatively low-cost imaging modality that has the ability to detect subclinical pathology in people with gout and asymptomatic hyperuricaemia. However, the findings from this study question the suitability of the 1MTP as a joint for routine sonographic assessment of the double contour sign due to its propensity for concomitant osteoarthritis and joint effusion, which greatly limit visualisation of the cartilage surface. Other joints less commonly affected by

osteoarthritis and fluid collection, such as the elbow, may provide more suitable locations for the assessment of the double contour sign.

This study has also shown the magnitude of local joint disease manifestations, specifically at the 1MTP. Clinicians may consider incorporating assessments of local joint structure and function into clinical practice, in combination with simple gait assessments in order to gauge the extent and progression of lower limb disability and impairment, which may not otherwise be apparent through observation alone. These assessments can be undertaken using clinically accessible tools including goniometers, dynamometers and dermal thermometers, in combination with standard laboratory measures.

Importantly, this study has revealed the extent of self-reported lower limb and foot pain and disability in people with asymptomatic hyperuricaemia, who also exhibit altered walking strategies when compared to healthy individuals. The association between disabling foot pain and crystal deposition observed in this study may imply that these individuals could benefit from urate lowering therapy. However, due to associated adverse events and the small number of people with hyperuricaemia who develop gout, further research is warranted before clinical recommendations can be made regarding pharmacological treatment of this condition.

10.8 Future directions

Further longitudinal studies may explore the causal relationship between subclinical 1MTP sonographic changes and structure and function of the joint, which was not possible with the cross-sectional design employed for the study presented in this thesis. By identifying clinical factors that may predispose the 1MTP to crystal deposition and/or symptomatic gout, clinicians would be provided with a means to inform early interventions that prevent progression of subsequent joint damage and improve patient outcomes.

Prospective observational studies would also be of value to assess the predictive ability of sonographically evident crystal deposition, inflammation and bone erosion at the 1MTP in the occurrence of acute 1MTP arthritis in those with intercritical gout. The long-term effects of persistent subclinical inflammation at the 1MTP in people with gout, who may not experience acute flares at the joint, would also be of interest. Additionally, determining the predictive role of the double contour sign in the induction of inflammation and symptomatic gout in those with hyperuricaemia may enhance current clinical understanding of subclinical crystal deposition in this population.

An understanding of the directional relationship between 1MTP crystal deposition and structural and functional changes would greatly improve our understanding of the pathomechanics of 1MTP gout. This knowledge would direct future research to evaluate the efficacy of non-pharmacological treatment strategies that specifically target the 1MTP in combination with urate lowering therapy. Existing research has already shown that off-the-shelf footwear featuring rocker sole characteristics, which facilitate forward transfer of body weight in the presence of inefficient 1MTP function, greatly reduces pain over an eight-week intervention period in people with gout [317]. Further work could address the individual patient in terms of their specific foot structure, function, level of deformity and symptoms through the use of customised footwear and/or orthoses that improve function, accommodate deformity, encourage efficient pressure patterns and reduce foot-related pain, disability and impairment.

Finally, current treatment guidelines addressing individuals with asymptomatic hyperuricaemia may need to be revisited considering their high level of foot pain and disability and subclinical disease findings. The association between chronically elevated serum urate levels and patient-reported outcomes is unclear and currently there is no consensus on the treatment of asymptomatic hyperuricaemia due to the small number of individuals with hyperuricaemia that develop gout [30, 32, 589] and the side effects of treatment with urate lowering therapy [590]. However, the low-grade systemic inflammation that has been reported in people with asymptomatic hyperuricaemia [325, 326] along with the results of the study presented in this thesis highlight the need for further research in this area, particularly in the evaluation of treatment strategies aimed at improving patient-reported outcomes.

Chapter eleven: Conclusion

The aim of this thesis was to investigate clinically assessed characteristics and sonographic features of the first metatarsophalangeal joint (1MTP) in gout and asymptomatic hyperuricaemia. A review of literature highlighted the long-standing recognition of gout as a condition primarily affecting the 1MTP and the importance of musculoskeletal imaging in identifying subclinical disease characteristics not only in individuals with gout but also asymptomatic hyperuricaemia. A systematic review confirmed the well-established notion that acute 1MTP arthritis is highly prevalent in people with gout and has a substantial impact on patient-reported outcomes related to foot pain and disability. It also revealed that the structure and function of the 1MTP may be impaired in people with gout.

This was the first study to comprehensively identify clinical characteristics and sonographic features of the 1MTP in people with gout and asymptomatic hyperuricaemia and to determine the association between these features. Results from the clinical assessments showed that both gout and participants with asymptomatic hyperuricaemia reported high levels of foot- and lower limb-related pain and disability when compared to the normouricaemic individuals. Additionally, people with gout demonstrated 1MTPJ-specific changes in terms of reduced joint motion and muscle strength, increased severity of hallux valgus, reduced sensation and increased temperature. These clinically evident characteristics of the joint highlight the impact of gout on the structure and function of the 1MTP. The extent of this impact was also reflected in the gait assessments in which people with gout walked slower with plantar pressure patterns suggestive of propulsive and antalgic gait strategies. This study found individuals with asymptomatic hyperuricaemia also exhibited altered gait strategies and plantar loading, which may reflect their level of lower limb disability.

The sonographic study demonstrated that features of urate deposition, soft tissue inflammation and bone erosion are common at the 1MTP in people with gout, despite the absence of clinical symptoms of acute arthritis. These results support the concept that gout is a disease of chronic inflammation with a persistent subclinical immune response to the presence of MSU crystals within joints. Furthermore, although individuals with asymptomatic hyperuricaemia lacked features of inflammation or structural joint changes on ultrasound, they demonstrated a similar frequency of subclinical urate deposition. These observations suggest that the presence of sonographic synovitis and bone erosion at the 1MTP may be useful in differentiating gout from asymptomatic hyperuricaemia.

The associations observed between the sonographic and clinical characteristics showed that sonographic features of MSU deposition, rather than soft tissue inflammation or bone erosion, were associated with patient-reported foot pain and disability, while the presence of tophus was associated with impaired functional characteristics. This may explain why the individuals with asymptomatic hyperuricaemia, who lacked sonographic features of soft tissue and bone involvement at the 1MTP, still presented with high levels of foot pain and disability and exhibited gait impairments when compared with normouricaemic individuals.

These findings provide several clinical implications, including the utility of musculoskeletal ultrasound and clinical tools to assess joint-specific disease manifestations in people with gout and asymptomatic hyperuricaemia, which may otherwise go undetected. Although the results suggested a link between urate deposition and disabling foot pain, it is unclear whether urate lowering therapy would be of benefit or should be recommended to those with asymptomatic hyperuricaemia. Further research is warranted considering the adverse events associated with pharmacological interventions and the low risk for future development of gout.

The 1MTP has been historically recognised as the most commonly affected structure in people with gout, and although several structural and functional factors were proposed in 1977 by Simkin to explain this phenomena [353], little attention has been paid to these factors over the last 40 years. This study was the first to examine clinically and sonographically assessed structural and functional characteristics of the 1MTP. The findings from this study are pivotal to future explorations of the causal relationship between the subclinical 1MTP sonographic changes and clinically assessed structure and function of the joint. Once this relationship has been established, the effectiveness of non-pharmacological interventions that specifically targets the 1MTP in people with gout and asymptomatic hyperuricaemia may be investigated with the aim of improving structure, function and patient-reported outcomes.

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Appendices

Appendix 1. The impact of gout on the foot: a review

Gout and Hyperuricemia		Review
<h3>The impact of gout on the foot: a review</h3> <p>Sarah Stewart^{1*}, Nicola Dalbeth², Keith Rome¹</p> <p>Purpose: The foot is the most commonly involved site in people with gout. This review summarises the pattern of foot involvement in gout, the impact of gout in the foot with regard to patient-reported and clinician-assessed outcomes and reviews current data addressing non-pharmacological management of the foot in people with gout.</p> <p>Findings: The first metatarsophalangeal joint and Achilles tendon are frequently affected by gout. Many factors have been proposed to explain the predilection for gout to affect the foot including reduced temperature, susceptibility to physical trauma, biomechanical loading during gait and concomitant osteoarthritis. People with gout report persistent foot-related pain and disability which is reflected in clinician-observed gait impairments, reduced foot and ankle joint function and lower limb and foot muscle weakness. Good footwear and podiatric palliative care may play an important role as part of the multidisciplinary management of gout in combination with urate lowering therapy.</p> <p>Conclusion: The exact mechanism responsible for the high frequency of gout in the foot remains unclear. However, people with gout present with chronic pain, and structural and functional impairments related to the foot which greatly affects their ability to participate in everyday activities. Health care professionals may consider local ice therapy, footwear advice and podiatric referrals as part of the management plan aimed at improving foot-related pain and gait disability in people with gout.</p> <p>Key words: Gout; Foot; Footwear; Podiatry</p> <h3>Introduction</h3> <p>Gout is one of the oldest recognised diseases and was first documented as a painful condition affecting the great toe by Egyptians in 2640 BC [1,2]. Hippocrates described this 'unwalkable disease' in the 5th century BC, which he referred to as podagra (from <i>pous</i> meaning foot and <i>agra</i> meaning prey - literally a 'foot-trap') [1]. Today, gout remains renowned for its tendency to affect the foot, manifesting clinically with painful episodes of acute arthritis resulting from an inflammatory reaction to monosodium urate (MSU) crystals which deposit in joints and soft tissues in the presence of hyperuricaemia. This article summarises the pattern of foot involvement in gout, the theories behind why gout targets the foot, the impact of foot involvement on patient-reported outcomes and foot</p> <p>structure and function, and current recommendations for non-pharmacological management of the foot in people with gout.</p> <h3>Pattern of foot involvement in gout</h3> <p>Dual-energy computed tomography has shown that the feet contain the largest volume of MSU crystal deposition when compared with other regions of the body [3-5] with between 37% and 68% of people with gout demonstrating some degree of crystal deposition within joints and soft tissue structures of the foot [4,5]. The first metatarsophalangeal joint (1MTPJ) demonstrates the highest occurrence of MSU deposits (up to 57%), followed by the ankle and midfoot joints (up to 26% and 21%, respectively) [3,5-7] (Figure 1). This is reflected in the distribution of</p>		<p>1</p> <p>Gout and Hyperuricemia. 2016; 3(1): 1-8 Access publication Mar. 2016</p> <p>¹Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand. ²Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand.</p> <p>*Corresponding author: Sarah Stewart; Health and Rehabilitation Research Institute, Auckland University of Technology, North Campus, 90 Akoranga Drive, Northcote, Auckland 0627, New Zealand; Email: sarah.stewart@aut.ac.nz</p> <p>Submitted Feb. 28, 2016; revised version accepted Mar. 14, 2016. ©2016, Gout and Hyperuricemia. Published by Dong Fong Health Co. LTD in Taiwan. All right reserved.</p>



Figure 1. Dual energy CT scan in a patient with tophaceous gout demonstrating urate deposition (green) in the joints, tendons and subcutaneous tissue of the left foot.



Figure 2. Lateral ankle and Achilles tendon tophi in a 56 year old male with gout.

patient-reported acute arthritis in which the 1MTPJ represents the most common joint (62% to 76% of patients), followed by the ankle (15% to 64%) and midfoot (20% to 57%) joints (**Figure 2**) [8-10]. While other foot joints are less frequently involved by symptoms and signs of gouty arthritis, several case studies have reported intraosseous tophi within the talus [11,12]; os trigonum [13]; phalangeal bones [14], lesser metatarsals [12,15] and sesamoid bones [16-18] with several cases also reporting fractures at sites of MSU deposition within the foot [15,19-21].

MSU crystals also deposit within certain tendon sites within the foot. The body and enthesis of the Achilles tendon are major sites for MSU crystal deposition, with a prevalence ranging from 28% in newly diagnosed gout, to 52% in patients with chronic tophaceous gout [3,5,7]. The peroneal tendons are the second most commonly affected by MSU deposits (15% to 29%) [5,7]. Tibialis posterior

and anterior tendons, and the flexor and extensor tendons of the hallux and lesser digits have also been reported as sites of MSU deposition [7]. Several case studies have reported longitudinal tears [22,23] and ruptures [24-27] associated with tophus infiltration in foot and ankle tendons.

Why does gout target the foot?

Despite a similar level of urate concentration throughout the body, it is clear that MSU crystal deposition and gout-related features have a certain propensity for the foot, and in particular the 1MTPJ. Several factors have been proposed in attempt to explain this phenomenon.

Temperature

Low temperatures substantially reduce the solubility of urate and enhance the nucleation of MSU crystals [28,29]. It has been proposed that this may contribute to the precipitation of crystals in the cooler peripheral joints of the foot, and the relative sparing of axial joints [30]. In the peripheral joints of the foot, temperature has been recorded at 35°C with a lower urate solubility measured at 0.36mmol/l [29]. Additionally, the high rate of cardiovascular disease in patients with gout [31] and the association between peripheral arterial disease and hyperuricaemia [32] places patients at an increased risk of peripheral blood flow disturbance, and thus may further encourage MSU crystal nucleation in peripheral joints. However, it has been acknowledged that this temperature mechanism cannot explain why gout targets the 1MTPJ while the lesser metatarsophalangeal joints and interphalangeal joints are less frequently involved [33,34].

Physical trauma

The susceptibility of the foot to physical trauma through daily activities, such as walking, has also been identified as an important factor contributing to the high frequency of foot involvement in gout. Mechanical agitation of solutions supersaturated with urate has been shown to enhance crystal nucleation [35], suggesting that physical trauma lowers synovial pH and increases calcium ion activity which in turn creates an environment that favours MSU crystal nucleation. The susceptibility of the foot to physical trauma may be further enhanced in patients with marked tophaceous deformity which prevents the wearing of properly fitting protective footwear [36-41].

Biomechanical loading

It has also been hypothesised that the sites in the foot frequently affected by MSU crystal deposition and structural joint damage in gout are at particular risk due to greater biomechanical loading during gait [42,43]. Repetitive loading, particularly in mal-aligned or poorly functioning joints, may lead to intra-articular debris which can provide a nucleus for crystal formation [44]. Biomechanical stress may also disrupt pre-existing deposits within the joint which may trigger the release of microcrystals and a resulting inflammatory response [43]. Conversely, Dalbeth et al. [45] recently found no association between areas of increased tissue stress in healthy individuals and areas of crystal deposition in patients with gout. However, other factors present in individuals with gout, including pre-existing osteoarthritis and other comorbid conditions may influence loading during gait and contribute to the susceptibility for MSU crystal formation and deposition at preferential sites in the foot.

Osteoarthritis

Osteoarthritis is a degenerative condition involving progressive destruction of articular cartilage at areas of abnormal biomechanical friction or stress [46]. Osteoarthritis shares gout's pattern of joint involvement in the foot with the most common joint affected being the 1MTPJ [47]. As such, it has been proposed that osteoarthritis may be associated with the frequency of local formation and deposition of MSU crystals in this joint [30,34]. In fact, strong associations have been observed between gout and conventional radiographic-proven [48] and clinically-diagnosed [49] osteoarthritis of the 1MTPJ. Furthermore, a recent dual-energy computed tomography study also found associations between the presence of MSU crystals at the 1MTPJ and coexisting conventional radiographic features of osteoarthritis, including joint space narrowing and osteophytes [50].

Although it is difficult to infer causality due to the cross-sectional nature of current studies, many researchers support the theory that degenerative cartilage predisposes to the local formation and deposition of MSU crystals [30,48,49]. It is believed that the preference for MSU crystals to deposit on cartilage surfaces is due to the facilitated nucleation and crystallization of urate by components of normal cartilage (chondroitin sulfate and phosphatidylcholine) [51]. Furthermore, the altered composition of proteoglycans in degenerative cartilage has been thought to interfere with urate crystallisation [52].

Roddy et al. [49] noted that the strength of the association between gout and osteoarthritis did not increase as the disease duration of gout increased which would be expected if joint damage was initiated and progressed by MSU crystals [49]. Conversely, Muehleman et al. [53] favoured a bidirectional association whereby degraded cartilage provides small openings for the nucleation of MSU crystals which then further perpetuates joint damage.

In contrast, although Dalbeth et al. [50] found associations between conventional radiographic features of osteoarthritis and MSU crystals, stronger relationships were found between more gout-specific conventional radiographic features and crystal presence, which supports the notion that MSU crystals may influence structural damage in gout [50]. This is supported by current research which suggests that chondrocytes directly interact with MSU crystals resulting in cartilage damage through increased production of degrading enzymes and pro-inflammatory mediators [54-56].

Foot-related pain, disability and impairment

Pain

During episodes of acute arthritis involving the foot and/or ankle, patients with gout report high levels of foot pain [57]. Although foot pain has been shown to reduce by 73% once acute gout resolves, pain scores do not completely normalise [57]. This persistent nature of foot pain in people with gout is reflected in other studies which report moderate to high levels of foot pain in the absence of acute arthritis [58-63]. In a large primary care-based study of 1,184 participants with gout, 22% reported foot pain in the past month with over two-thirds of these classified as having disabling foot pain [64]. The 1MTPJ was the most frequent site for foot pain in the past month (72%), followed by the lesser toes (67%), midfoot (62%), hallux (59%), ankle (54%), posterior heel (35%) and plantar heel (21%) [64]. High levels of persistent 1MTPJ pain in people with gout has also been observed alongside increased temperature at the 1MTPJ, further emphasising the presence of ongoing subclinical inflammation in this joint in the absence of acute arthritis [63].

Disability and impairment

Rome et al. [57] found that people with gout report high levels of foot-related impairment and disability during episodes of acute arthritis involving the foot and

ankle. The patients also indicated severe restrictions with lower-limb-related daily living and recreational activities [57]. Studies have also shown that the most common functional limitation during acute arthritis is walking-related disability with 91% to 97% of patients reporting difficulty with walking [10,65]. Furthermore, the influence of pain on walking ability during acute gouty arthritis is recognised as a discriminatory feature of the disease by patients with gout [66]. Climbing stairs and standing are also among the main concerns people with gout have with daily activity limitations [65,67].

As with pain, these functional limitations remain persistent once the symptoms of acute arthritis resolve with 54% still experiencing high levels of foot-related impairment and 35% to 60% reporting severe foot-related disability [57,59]. Not surprisingly, patients with ulcerated tophi in the feet also report moderate to high levels of foot-related disability and impairment [68]. Interestingly, individuals with asymptomatic hyperuricaemia also report greater overall foot pain and disability, reduced lower limb function and increased activity limitation compared to normouricaemic controls, even though they lack any symptoms or clinical features of gouty arthritis [63]. This may reflect the substantial degree of subclinical features, including MSU deposition and associated inflammation that have been previously observed in individuals with asymptomatic hyperuricaemia [69-71].

Functional and structural characteristics

Laboratory-based gait studies also reveal that patients with gout exhibit alterations in several gait parameters despite the absence of acute gouty arthritis [59,61]. Compared to age- and gender-matched controls, patients with gout walk slower with reduced cadence, step length and stride length and increased step and stance times while walking at comfortable self-selected speeds in their own footwear [59] and barefoot [61]. These gait patterns, primarily the shorter step and stride lengths and prolonged stance times, are reflective of not only the reduced walking velocity, but also an inability to transfer body weight forward during walking [72,73]. Although these propulsive gait strategies may reflect pain-avoidance mechanisms, they may also result from changes to foot and ankle muscle [60,63] and joint [63] function. In fact, patient-perceived foot-related functional limitations have been strongly associated with reduced step length, stride length and velocity in people with gout [61]. However, further research is warranted to determine the relationship between clinician-assessed foot and ankle function and

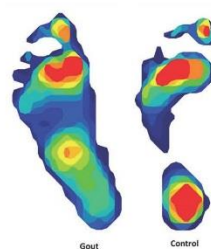


Figure 3. Typical plantar pressure patterns exhibited by a gout patient and healthy control.

gait patterns in this population.

Biomechanical research has also shown that people with gout walk with significantly reduced peak plantar pressure and pressure time integrals beneath the hallux and increased pressure time integrals beneath the midfoot compared to controls [59]. A typical plantar pressure pattern exhibited by a patient with gout is shown in **Figure 3**. Although increased midfoot pressure time integrals may be reflective of increased stance time, they may also be a result of the pes planus foot type observed in the gout population with 54% demonstrating a flat foot profile [57,59]. It has been proposed that the reduced hallux pressure is an attempt to offload pressure at the commonly affected 1MTPJ due to pain [59]. This is further emphasised in qualitative research in which patients report attempting to walk more cautiously with an adjusted foot position in an attempt to relieve the big toe [65].

A study investigating characteristics of the 1MTPJ in people with gout observed reduced 1MTPJ dorsiflexion range of motion, reduced 1MTPJ plantarflexion strength and an increased likelihood of presenting with more severe hallux valgus deformity when compared to age- and sex-matched controls [63]. These changes are likely to further contribute to inefficient foot function and the propulsive gait strategies seen in people with gout [72,73].

Patient-reported foot pain and disability have also been associated with reduced foot and ankle muscle strength in people with gout [60]. The authors reported that patients with gout demonstrated reduced muscle strength for plantarflexion, inversion and eversion of the foot compared to matched controls and found strong correlations between these strength reductions and increased foot pain and disability [60]. Although the exact cause of muscle strength reductions in gout is currently not known, it has been proposed that the pain-avoidance gait strategies employed by people with gout may contribute to reduced muscle activity and consequent disuse-related muscle atrophy [59].



Figure 4. Footwear worn by a patient with gout.

Non-pharmacological management of the foot in gout

Pharmacological treatment of gout focuses on long-term urate-lowering therapy to achieve MSU crystal dissolution alongside anti-inflammatory therapy to treat and prevent acute flares [74,75]. Non-pharmacological treatment has an important adjunctive role in gout management, providing benefits in pain and function. Here we discuss non-pharmacological management of foot disease for patients with gout.

Ice-therapy

The effectiveness of local ice therapy in the treatment of acute gouty arthritis in lower limb and foot joints has been investigated in a randomised prospective study involving 19 patients [76]. After one week, the group who received ice therapy for 30 minutes four times daily in conjunction with oral corticosteroids and colchicine achieved a significant improvement in pain on a visual analog scale compared to the control group who received pharmacological treatment alone [76]. The American College of Rheumatology guidelines have since recommended topical ice therapy by application of ice packs to inflamed joints in the treatment of acute gout [74].

Footwear

Many people with gout of the foot report difficulty in wearing shoes [37-39] and not being able to wear shoes is rated highly as an important concern [41] (Figure 4). The challenges people with gout have with wearing appropriate footwear is also highlighted in qualitative research [40,67]. Patients report an inability to wear the correct shoes required for social and work situations, hence they avoid participating in certain activities and even take

days off work [40,67].

The inability to find and wear shoes that fit properly and are appropriate to their level of pain and disability has been demonstrated in a study which characterised features of footwear worn by patients with gout [36]. Forty-four percent of patients were found to wear shoes classed as poor, including sandals, slippers and jandals (flip-flops). Over half wore shoes that were too narrow, lacked cushioning and motion control properties and were older than 12 months. Fifty-four percent of patients also wore shoes with flexion points before the level of the metatarsal heads which can limit gait efficiency by inhibiting normal 1MTPJ function during propulsion [77] and hence may exacerbate the problems of efficient toe-off observed in people with gout [59]. Furthermore, patients who wore poor footwear reported higher levels of foot-related impairment and disability [36].

A prospective intervention study, which trialled the effect of a variety of footwear on patient-reported outcomes related to the foot and lower limb, found that footwear with good characteristics significantly reduced foot pain, general pain and activity limitation over an eight week period [58]. Contrastingly, improvements in patient-reported outcomes were not seen in patients who wore footwear with poor characteristics. The authors proposed this may have resulted from certain properties of the good shoes, including excellent motion control, gel cushioning and an in-built rocker system designed to encourage heel-to-toe transition and efficient propulsion [58]. This was confirmed in a subsequent gait analysis study in which people with gout wearing the good footwear demonstrated decreased heel and lateral forefoot pressure and increased midfoot pressure compared to walking in their own shoes. These patterns are reflective of a more efficient heel to toe gait pattern [78].

Podiatric palliative care

In a recent survey in the United Kingdom, 43% of patients with gout reported consulting with their general practitioners in the past year about foot problems and 24% reported seeing a podiatrist [64]. A study of New Zealand podiatrists found that 95% managed patients with gout in their practice [79]. Podiatric interventions have been shown to reduce pain by 18% and foot disability by 23% after a single podiatry visit in a group of patients with rheumatic conditions including gout [80]. Treatments provided included callus reduction, ulcer debridement, treatment of nail conditions, clinical padding, foot orthoses, footwear advice, foot-health education and

exercise prescription.

Conclusion

The pattern of crystal deposition in individuals with gout demonstrates a clear preference for structures of the foot and ankle, in particular the 1MTPJ and Achilles tendon. Although several factors have been proposed to explain this phenomenon, it is likely that peripheral gout results from a complex interplay between several factors. The high frequency of foot involvement in gout is also reflected in the lower-limb-related functional and structural limitations observed by clinicians and reported by patients. Emerging research suggests that foot-specific interventions including footwear and podiatric care may play a role in the management of patients with gout in combination with pharmacological urate-lowering therapy.

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Conflicts of interest statement

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Gout and Hyperuricemia. 2016; 3(1): 1-8

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Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999
www.aut.ac.nz

Health and Rehabilitation Research Institute
Auckland University of Technology
North Shore Campus
90 Akoranga Drive
Northcote
Auckland 0627
New Zealand

March 13, 2017

Editor of Gout and Hyperuricemia

RE: The impact of gout on the foot: a review

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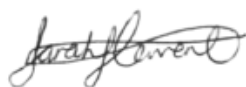
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Appendix 3. The first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a systematic review and meta-analysis

Stewart et al. *BMC Musculoskeletal Disorders* (2016) 17:69
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BMC Musculoskeletal
Disorders

RESEARCH ARTICLE

Open Access

The first metatarsophalangeal joint in gout: a systematic review and meta-analysis



Sarah Stewart^{1*}, Nicola Dalbeth², Alain C. Vandal^{3,4} and Keith Rome¹

Abstract

Background: The aim of this review was to qualitatively synthesise studies that have investigated characteristics of the first metatarsophalangeal joint (1st MTP) in gout and to undertake a meta-analysis to estimate the average prevalence of acute 1st MTP arthritis across studies in people with gout.

Methods: Studies published in English were included if they involved participants who had a diagnosis of gout and presented original findings relating to the following outcome measures associated with the 1st MTP: epidemiology; clinical features; structural and functional characteristics; and microscopic and imaging features.

Results: Forty-five studies were included in the qualitative synthesis. 1st MTP pain was a prominent feature in people with gout. People with 1st MTP gout reported walking- and general-disability. Structural and functional characteristics of 1st MTP gout included hallux valgus, osteoarthritis, and restricted joint motion. Successful crystal aspiration ranged from 81 to 91 % and positive crystal identification via microscopy ranged from 83 to 93 % in patients with a history of 1st MTP gout. Imaging features were common at the 1st MTP including the double contour sign, tophi and erosions. Eleven studies involving 2,325 participants were included in the meta-analysis, providing an estimate of the average prevalence of acute 1st MTP arthritis across studies of 73 % (95 % prediction interval 40–92 %; range 48–97 %; I² = 93 %).

Conclusions: 1st MTP acute arthritis is highly prevalent in people with gout and has a substantial impact on patient-reported pain and disability. Gout affects the structure and function of the 1st MTP. Microscopic and imaging studies have demonstrated crystal deposition and joint damage at the 1st MTP in people with gout.

Keywords: First metatarsophalangeal joint, Gout

Background

Gout, one of the most common forms of inflammatory arthritis in middle-aged men, is caused by monosodium urate (MSU) crystal deposition in joints and soft tissue [1]. Clinically, gout is characterised by painful flares of acute monoarthritis interspersed with asymptomatic periods. If left untreated, gout can progress to a chronic arthritis with tophus formation and joint damage [2].

Gout is well recognised by its predilection to affect the first metatarsophalangeal joint (1st MTP). Acute episodes of gouty arthritis at the 1st MTP are often referred to as *podagra* [3]. In recent decades, lifestyle and dietary factors associated with hyperuricaemia have become increasingly

widespread, as has the global burden of gout [4]. Gout has a major impact on health-related quality of life [5] and its tendency to affect the foot is reflected in the high levels of foot-related disability and impairment [6].

Despite the well-recognised susceptibility of the 1st MTP to acute arthritis in gout, evident by its inclusion in several gout diagnostic and classification criteria [7–10], a formal synthesis of the prevalence of acute 1st MTP arthritis in this condition has yet to be undertaken. Furthermore, the burden of 1st MTP involvement on patient-reported outcomes in gout is unclear. Despite the significant role of the 1st MTP during normal gait, particularly the forward transfer of body weight during propulsion [11, 12], it is also unclear to what extent the structure and function of the joint is compromised in people with gout. This systematic review aimed to qualitatively synthesise studies which have investigated characteristics of the

* Correspondence: sarah.stewart@aut.ac.nz

¹Faculty of Health and Environmental Sciences, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand

Full list of author information is available at the end of the article



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1st MTP in gout and to undertake a meta-analysis to provide a pooled estimate for the average prevalence of acute 1st MTP arthritis in gout across studies.

Methods

Search strategy

A comprehensive electronic search was completed in March 2015 using the following databases: Scopus (1960 to March 2015), Medline (1966 to March 2015), CINAHL (1937 to March 2015), SportsDiscus (1985 to March 2015), the Cochrane Library, ACR abstracts (2009 to 2013) and EULAR abstracts (2002 to 2012) with the search terms presented in Table 1. This search was supplemented with hand-searching of reference lists of all potentially eligible full-text articles and selected review articles.

Selection criteria

All potentially eligible articles were screened by a single author (SS) at title, abstract, and full-text stages. The review was conducted with reference to the Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA) statement [13]. Studies considered for this review were published in peer-reviewed journals and limited to randomised controlled trials, cohort studies, case-control studies and cross-sectional studies. Peer-reviewed conference proceedings and abstracts were also considered for inclusion. Case reports, case series with <5 cases and review articles were excluded.

The inclusion criteria included studies published in English, adults over 18 years old and which involved participants who had a diagnosis of gout. Included studies presented original findings relating to the following outcome measures: incidence or prevalence of acute inflammatory arthritis at the 1st MTP; clinical features of acute gouty arthritis, intercritical gout and chronic gouty arthropathy (including tophaceous gout) at the 1st MTP; structural and functional characteristics of the 1st MTP;

microscopy of the 1st MTP; and imaging features of the 1st MTP including MSU crystals, bone disease and synovial disease. Studies investigating outcomes as a measure of pharmacological, non-pharmacological and surgical intervention efficacy were excluded. Studies which assessed the 1st MTP amongst other joints, but did not report outcome measures specifically relating to the 1st MTP, were also excluded.

Data extraction

The following data was extracted from all included papers: the first author's last name, publication year, country where the study was conducted, the study design and aim(s), the outcome measure(s) reported and the characteristics of the gout participants including: sample size, gender, mean age (years), mean disease duration (years) and the method of diagnosis.

Statistical analysis

A meta-analysis was conducted to obtain an estimate of the prevalence of acute arthritis at the 1st MTP in people with gout at any point during the course of their disease. Due to the expected high prevalence of acute 1st MTP arthritis, a double arcsine transformation was adopted to address variance instability. This transformation method is the preferred transformation option as it avoids an undue large weight for studies [14]. The meta-analysis was carried out using the inverse of the variance of the transformed proportion as study weight. The pooled transformed prevalence was transformed back for the final presentation of the data. The 95 % prediction intervals for the average estimate of prevalence was also reported [15]. A random-effects model was used and the degree of heterogeneity was evaluated using the Higgins I² statistic which was interpreted as follows: I² of 25 % = low heterogeneity, I² of 50 % = medium heterogeneity, I² = 75 % = high heterogeneity [16]. Statistical analysis was undertaken in MetaXL version 2.0 (EpiGear International Pty Ltd, Brisbane, Australia).

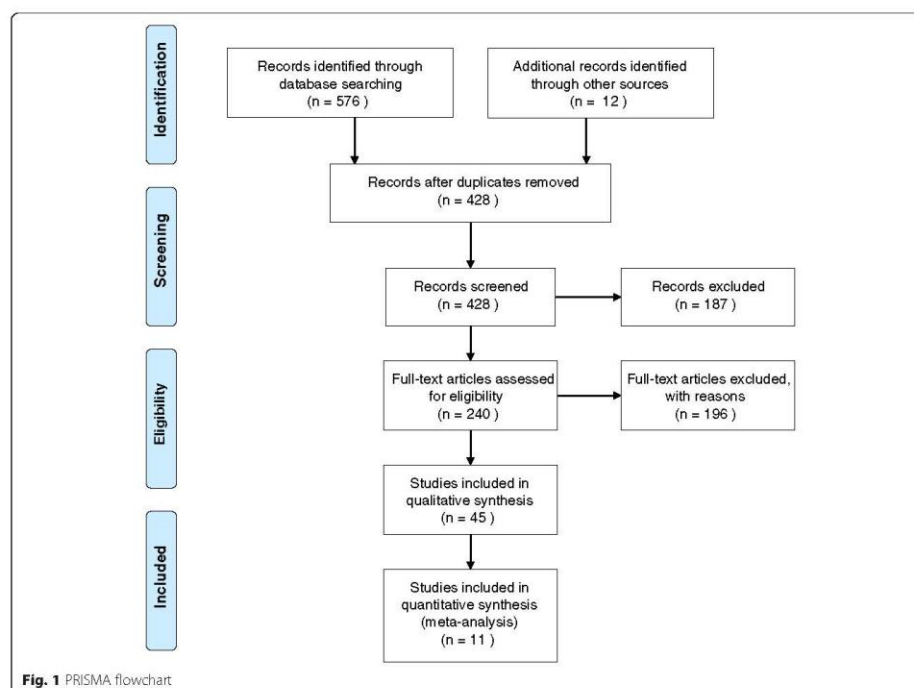
Results

Description of studies

Figure 1 shows a flow chart of the literature search. The initial search identified 576 papers through database searching and 12 papers from conference abstracts. Following the removal of 160 duplicates, 428 papers were screened, of which 240 papers were considered for further examination based upon the title and abstract. Forty-five studies met the criteria and were included in the review (including 4 conference abstracts published in peer-reviewed journals [17–20] and 2 English abstracts from non-English papers [21, 22]). Of the 45 studies, 8 were longitudinal cohort studies, 20 cross-sectional studies, 10 case-control studies, 5 retrospective

Table 1 Search terms

#1	Gout* OR uric OR urate OR hyperuric*OR toph*
#2	"First metatarsophalangeal" OR "first metatarsal phalangeal" OR hallux OR "big toe" OR "first toe" OR digit OR podagra OR "1st mtp*" OR "1 mtp*" OR foot OR feet
#3	Imaging OR sonograph* OR ultraso* OR "doppler" OR radiograph* OR xray OR "magnetic resonance" OR mri OR "computed tomograph*" OR ct OR "dect" OR "dual energy"
#4	Histol* OR microscop*
#5	Function* OR gait OR walk* OR "plantar pressure" OR motion
Final search term: #1 AND #2 AND (#3 OR #4 OR #5) (gout* OR uric OR urate OR hyperuric*OR toph*) AND ("first metatarsophalangeal" OR "first metatarsal phalangeal" OR hallux OR "big toe" OR "first toe" OR digit OR podagra OR "1st mtp*" OR "1 mtp*" OR foot OR feet) AND ((imaging OR sonograph* OR ultraso* OR "doppler" OR radiograph* OR xray OR "magnetic resonance" OR mri OR "computed tomograph*" OR ct OR "dect" OR "dual energy") OR (histol* OR microscop*) OR (function* OR gait OR walk* OR "plantar pressure" OR motion))	



studies, and 2 randomised clinical trials. Details of the 45 included studies are displayed in Table 2.

The 45 included studies involved 44 different groups of gout participants (two studies used the same participants [23, 24]) totalling a pooled sample size of 5,478 participants. Thirty-eight studies involving 5,067 participants reported gender of which 4,348 (86 %) were male. Thirty-six studies reported mean participant age which ranged from 28 years to 69 years. Twenty-nine studies reported disease duration which ranged from newly diagnosed gout to 22 years.

Five studies did not report how patients with gout were diagnosed [17, 19, 21, 25, 26]. Fifteen studies, totalling 1,773 participants included only patients with gout who were diagnosed via microscopic identification of MSU crystals in synovial fluid/tophus aspirates. Fifteen studies, totalling 1,116 participants, diagnosed gout via the 1977 ACR criteria [7] in which participants either had MSU-proven gout or met 6 of the 12 clinical criteria. Of these studies, nine reported the number of crystal-proven participants (300/656 (46 %)). Two of these studies knowingly included

patients with gout who did not meet the ACR criteria ($n = 36$). The remaining seven studies included in the review diagnosed patients with gout using other methods detailed in Table 2 [18, 20, 27–31].

The 45 studies reported on one or more of the following outcome measures relating to 1st MTP gout: epidemiology ($n = 14$, including $n = 11$ articles reporting on the prevalence of acute 1st MTP arthritis at any point during the course of the disease which were included in the meta-analysis), clinical characteristics ($n = 8$), structural characteristics ($n = 2$), functional characteristics ($n = 4$), microscopy ($n = 7$); and imaging features ($n = 19$).

Epidemiology

Acute 1st MTP arthritis presenting as the manifestation of gout at disease onset, ranged from 43 to 76 % [20, 32–35]. The frequency of acute 1st MTP arthritis as the initial manifestation of gout was not significantly different between genders [34–36]. However, acute 1st MTP arthritis at any point during the disease was significantly more frequent in men (68.6 %) compared to women (31.8 %) [34, 36]. Two studies reported 54 and 72 % of

Table 2 Details of papers included in review

Author	Location	Study design	Aim	Characteristics of gout participants	Outcome measures relevant to review
Belamy [27]	Canada	Longitudinal cohort	Natural progression of TMTP acute flares	N = 11 Male 100 % Mean age 55 years Mean disease duration 4 years Diagnosis: patients presenting with classical features of acute podagra, had experienced prior attacks of gouty arthritis and were known to be or have been hyperuricaemic.	Clinical characteristics of TMTP gout
Carter [32]	USA	Cross-sectional	The presence of synovial inflammation during intercritical gout	N = 72 Male 90 % Mean age 56 years Mean disease duration 10 years Diagnosis: ACR criteria (incl. 42 % crystal proven)	Epidemiology of TMTP gout
Dalbeth [38]	New Zealand	Cross-sectional	Scoring bone erosion in gout using CT imaging	N = 25 Male 75 % Median age 50 years Median disease duration 21 years Diagnosis: ACR criteria (incl. 44 % crystal proven)	Imaging features of the TMTP in gout
Dalbeth [33]	New Zealand	Cross-sectional	Relationship between radiographic joint damage and MSU crystal deposition using DECT imaging	N = 92 Male 95 % Mean age 58 years Mean disease duration 22 years Diagnosis: ACR criteria (incl. 48 % crystal proven)	Imaging features of the TMTP in gout
Dalbeth [34]	New Zealand	Cross-sectional	Comparison of DECT MSU deposition in people with gout and people with asymptomatic hyperuricaemia	N = 33 Male = 65 % Mean age 61 years Mean disease duration 11 years Diagnosis: MSU crystal proven	Imaging features of the TMTP in gout
Dienonchok [34]*	Thailand	Cross-sectional	Clinical pattern of gout in females and males	N = 194 Male 89 % Mean age 59 (F) 52 (M) years Mean disease duration 3 (F) 10 (M) years Diagnosis: ACR criteria (incl. 81 % crystal proven)	Epidemiology of TMTP gout
DeSouza [36]	Brazil	Cross-sectional	Clinical and laboratory features of gout in men and women	N = 58 Male 53 % Mean age 64 (F) 61 (M) years Mean disease duration 9 (F) 14 (M) years Diagnosis: ACR criteria (% crystal proven not reported)	Epidemiology of TMTP gout
Grahame [29]*	UK	Retrospective	Characteristics of patients with gout	N = 354 Male 90 % Mean age NR Mean disease duration NR Diagnosis: patients with 'recurrent acute episodes of arthritis in the presence of hyperuricaemia'	Epidemiology of TMTP gout

Table 2 Details of papers included in review (Continued)

	USA	Longitudinal cohort	Epidemiology of gout and hyperuricaemia		
Hall [28]*					
				<i>N</i> = 86 Male 87 % Mean age 58 years Mean disease duration 9 years Diagnosis: patients who met two of the following: a typical attack of arthritis characterised by acute pain, usually accompanied by swelling and heat, lasting from a few days to 2 weeks, and followed by complete remission of symptoms; an attack of arthritis exhibiting a striking and prompt response to therapeutic colchicine; the presence of hyperuricaemia.	Epidemiology of TMTP gout
Howard [67]	USA	Cross-sectional	Reliability of ultrasound for tophi and double contour sign	<i>N</i> = 50 Male 100 % Mean age 69 years Mean disease duration NR Diagnosis: ACR criteria (% crystal proven not reported)	Imaging features of the TMTP in gout
Huppertz [31]*	Germany	Case-control	Diagnostic accuracy of DECT and ultrasound for detecting MSU crystal deposition	<i>N</i> = 39 Male NR Mean age NR Disease duration newly diagnosed Diagnosis: Janssens score [10] of >8 or MSU crystal proven (46 %)	Imaging features of the TMTP in gout
Janssens [10]*	Netherlands	Cross-sectional	Validation of a diagnostic model to predict gout	<i>N</i> = 709 Male 80.5 % Mean age 59 years Mean disease duration NR Diagnosis: MSU crystal proven	Epidemiology of TMTP gout
Kawano-Muro [21]	Poland	Cross-sectional	Incidence of radiographic evidence of degenerative articular changes in patients with gout	<i>N</i> = 262 Male NR Mean age NR Mean disease duration NR Diagnosis: not reported	Imaging features of the TMTP in gout
Kennedy [30]	London	Cross-sectional	MSU crystal presence in aspirated joint fluid	<i>N</i> = 31 Male 100 % Mean age 61 years Mean disease duration 10 years Diagnosis: patients who had "previously had podagra" including 52 % who were MSU crystal proven	Microscopy in TMTP gout
Kienhorst [37]	Netherlands	Longitudinal cohort	Validation of clinical diagnosis of TMTP gout	<i>N</i> = 123 Male 85 % Mean age 59 years Mean disease duration NR Diagnosis: MSU crystal proven	Clinical characteristics of TMTP gout
Kim [68]	Korea	Cross-sectional	DECT presence of MSU deposition	<i>N</i> = 101 Male 95 % Mean age NR Mean disease duration NR Diagnosis: ACR criteria (% crystal proven not reported)	Imaging features of the TMTP in gout

Table 2 Details of papers included in review (Continued)

Kim [43]	Korea	Longitudinal cohort	Comparison of clinical outcomes of arthrodesis and tophi excision & evaluate MRI features of tophaceous gout	N = 15 Male 67 % Mean age 57 years/mean disease duration NR Diagnosis MSU crystal proven	Clinical characteristics of TMTP gout; Functional characteristics of TMTP gout; Imaging features of the TMTP in gout
Lally [35]*	USA	Retrospective	Comparison of gouty arthritis in men and women	N = 98 Male 77 % Mean age 63 (F) 63 (M) years Mean disease duration 5 (F) 14 (M) years Diagnosis MSU crystal proven	Epidemiology of TMTP gout
Mallinson [25]	Canada	Retrospective	Distribution of MSU crystal deposition in gout using DLET imaging	N = 148 Male 83 % Mean age 61 years Mean disease duration NR Diagnosis not reported	Microscopy in TMTP gout
Mijiyawa [38]*	Togo	Retrospective	Characteristics of patients with gout	N = 106 Male 99 % Mean age 53 years Mean disease duration 8 years/Diagnosis ACR criteria (incl. 17 % crystal proven)	Epidemiology of TMTP gout
Kang [41]	Korea	Longitudinal cohort	Ultrasound characteristics of gout & efficacy of intra-articular steroid injection for acute TMTP flares	N = 21 Male 86 % Mean age 64 years Mean disease duration NR Diagnosis ACR criteria (6% crystal proven not reported)	Clinical characteristics of TMTP gout; Imaging features of the TMTP in gout
Naredo [50]	Spain	Case-control	Diagnostic value of ultrasound for gout	N = 91 Male 100 % Mean age 56 years Mean disease duration 7 years Diagnosis MSU crystal proven	Imaging features of the TMTP in gout
Ordóñez [17]	Spain	Cross-sectional	Reliability of ultrasound in detection of lesion at TMTP in gout	N = 15 Male NR Mean age NR Mean disease duration NR Diagnosis not reported	Imaging features of the TMTP in gout
Octaviani [52]	France	Longitudinal cohort	Ultrasonography showing disappearance of MSU crystals following urate lowering therapy	N = 16 Male 100 % Mean age 61 years Mean disease duration 7 years Diagnosis MSU crystal proven	Imaging features of the TMTP in gout
Pascual [46]	Spain	Cross sectional	MSU crystal presence in aspirated TMTP joint fluid	N = 101 Male 98 % Mean age 56 years Mean disease duration 5 years Diagnosis ACR criteria (incl. 77 % crystal proven)	Microscopy in TMTP gout

Table 2 Details of papers included in review (Continued)

Pascual [69]	Spain	Longitudinal cohort	Disappearance of MSU crystals following urate lowering therapy	N = 18 Male 100 % Mean age 56 years Mean disease duration 10 years Diagnosis MSU crystal proven	Microscopy in TMTP gout
Pelaez-Ballestas [9]*	Mexico	Cross-sectional	Identifying criteria for diagnosis of chronic gout	N = 549 Male 96 % Mean age 50 years Mean disease duration 12 years Diagnosis MSU crystal proven	Epidemiology of TMTP gout
Radak-Petrovic [22]	Serbia	Case-control	Comparison of ultrasound and x-ray for detection of TMTP erosions	N = 30 Male NR Mean age NR Mean disease duration NR Diagnosis ACR criteria (% crystal proven not reported)	Imaging features of the TMTP in gout
Roddy [24]	UK	Case-control	Concomitant gout and osteoarthritis	N = 164 Male 81 % Mean age 63 years Mean disease duration 10 years Diagnosis 91 % met ACR criteria (% crystal proven not reported)	Epidemiology of TMTP gout: Functional characteristics of TMTP gout
Roddy [51]	UK	Cross-sectional	Ultrasound characteristics of gout	N = 40 Male 78 % Mean age 65 years Mean disease duration 13 years Diagnosis ACR criteria (incl. 53 % crystal proven)	Imaging features of the TMTP in gout
Roddy [18]	UK	Cross-sectional	Prevalence of hallux valgus, foot pain and disability in gout	N = 1184 Male 78 % Mean age 66 years Diagnosis: "Patients who had consulted their GP about gout or been prescribed allopurinol or colchicine within the preceding 2 years"	Clinical characteristics of TMTP gout; Structural characteristics of TMTP gout
Roddy [23]	UK	Case-Control	Nodal osteoarthritis and the risk of developing gout	N = 164 Male 81 % Mean age 63 years Mean disease duration 10 years Diagnosis 91 % met ACR criteria (% crystal proven not reported)	Clinical characteristics of TMTP gout; Structural characteristics of TMTP gout
Rome [45]	New Zealand	Case-control	Functional and biomechanical characteristics of gait in people with gout	N = 25 Male 75 % Mean age 61 years Mean disease duration 22 years Diagnosis ACR criteria (incl. 44 % crystal proven)	Functional characteristics of TMTP gout

Table 2 Details of papers included in review (Continued)

Author [ref]	USA	Case-control	TMTP aspiration as a diagnostic tool for gout	N = 23 Male NR Mean age NR Mean disease duration NR Diagnosis MSU crystal proven	Epidemiology of TMTP gout; Microscopy in TMTP gout
Silvera [47]	Spain	Cross-sectional	Feasibility of TMTP aspiration for gout diagnosis	N = 22 Male 83 % Mean age 61 years Mean disease duration NR Diagnosis MSU crystal proven	Microscopy in TMTP gout
Sun [53]	China	Cross-sectional	DECT imaging features of gout	N = 80 Male 94 % Mean age 52 years Mean disease duration 5 years Diagnosis ACR criteria (% crystal proven not reported)	Imaging features of the TMTP in gout
Taylor [55]*	Multinational, multicentre	Cross-sectional	Clinical, laboratory, imaging findings in gout	N = 509 Male 86 % Mean age 60 years Median disease duration 6 years Diagnosis MSU crystal proven	Epidemiology of TMTP gout; Clinical characteristics of TMTP gout
Thiele [56]	USA	Case-control	Sonographic features of gout	N = 16 Male 81 % Mean age 64 years Mean disease duration NR Diagnosis MSU crystal proven	Imaging features of the TMTP in gout
Thiele [57]	USA	Retrospective	Detection of erosions with ultrasound and conventional radiography in chronic gout	N = 42 Male NR Mean age NR Mean disease duration NR Diagnosis MSU crystal proven	Imaging features of the TMTP in gout
Vreju [19]	Romania	Longitudinal cohort	Importance of ultrasound in gout diagnosis	N = 23 Male 53 % Mean age 53 years Disease duration < 1 year Diagnosis not reported	Imaging features of the TMTP in gout
Wang [26]	Taiwan	Randomised controlled trial	Comparison of arthroscopic removal of TMTP MSU crystals with medical treatment alone	N = 28 Male 100 % Mean age 28 years Mean disease duration 2 years Diagnosis not reported	Clinical characteristics of TMTP gout; Functional characteristics of TMTP gout
Wallace [77]*	USA	Cross-sectional	Development of a criteria for the classification of arthritis due to primary gout	N = 178 Male 86 % Mean age 56 years Mean disease duration 10 years Diagnosis 88 % met ACR criteria (incl. 43 % crystal proven)	Epidemiology of TMTP gout

Table 2 Details of papers included in review (Continued)

Weinberger [48]	USA	Case-control	MSU crystals in aspirated TMTP joint fluid	N = 9 Male 100 % Mean age 54 years Mean disease duration 2 years Diagnosis: MSU crystal proven	Microscopy in TMTP gout
Wright [42]	Ireland	Case-control	Comparison of ultrasound and x-ray for detection of erosions in gout	N = 39 Male 100 % Mean age 52 years Mean disease duration 12 years Diagnosis: ACR criteria (incl. 28 % crystal proven)	Imaging features of the TMTP in gout
Zilek [20]	USA	Longitudinal cohort	Risk & predictors additional flares in newly diagnosed gout	N = 158 Male 73 % Mean age 59 years Mean disease duration Newly diagnosed Diagnosis: via the New York, Rome or ACR criteria (% crystal proven not reported)	Epidemiology of TMTP gout

*Papers included in meta-analysis; NR = Not Reported

patients with gout, respectively, experienced acute arthritis isolated to the 1st MTP [33, 37].

Eleven studies reported the prevalence of acute 1st MTP arthritis at any point during the course of the disease and were included in the meta-analysis [7, 9, 10, 28, 29, 31, 33–35, 38, 39]. The studies provided a pooled sample size of 2,464 participants. In total, 87 % were male with a mean age ranging between 50 and 63 years old. Mean or median disease duration was reported by eight studies and ranged from newly diagnosed to 14 years [7, 9, 28, 31, 33–35, 38]. Fifty-six percent of 2,110 participants from 10 studies demonstrated aspirate proven gout [7, 9, 10, 28, 31, 33–35, 38, 39]. The reported prevalence of acute arthritis at any point during the course of the disease ranged from 48 to 97 %. The pooled prevalence estimate of acute 1st MTP arthritis across studies was 73 % (95 % prediction interval: 40–92 %). The heterogeneity was high with an I^2 of 93 % (95 % CI: 90 %–96 %). Figure 2 presents the forest plot showing the pooled prevalence estimate of acute 1st MTP arthritis in gout across the included studies.

Clinical characteristics

Four studies reported the characteristics of acute 1st MTP arthritis, which included rapid onset of extremely severe pain and tenderness with moderate swelling, erythema and inflammation [27, 37, 40]. Seventy-nine percent of patients reported onset within 1 day [37]. Erythema was observed in 95 % of patients with acute 1st MTP arthritis [37]. In a study following the natural progression of acute 1st MTP arthritis for 7 days in 11 patients, improvements in erythema and juxta-articular skin temperature were observed by day four, while 1st MTP pain and swelling improved in most by day five [27]. Two studies reported pain during acute 1st MTP arthritis using 100 mm Visual Analogue Scales (VAS)

[37, 41]. Mean patient-reported pain ranged from 54.3 to 71.1 mm [37, 41].

During intercritical periods, in the absence of acute symptoms, a significantly greater number of patients with gout reported current 1st MTP pain compared to healthy matched controls (16 % vs. 6 %, respectively) [23]. One study reported 72 % of patients with long-standing gout, with a mean of 12 years disease duration, reported 1st MTP pain in the previous month [18]. During clinical examination of 78 1st MTPs from 39 patients with currently asymptomatic gout, 35 % of joints demonstrated mild tenderness, 9 % demonstrated moderate tenderness and 6 % demonstrated marked tenderness [42].

High levels of 1st MTP pain were reported in patients with chronic tophaceous gout affecting the 1st MTP [26, 43], with patients scoring a mean of 7.6 cm to 7.8 cm on a 10 cm pain VAS [43].

Structural characteristics

Structure of the 1st MTP has also been assessed in people with gout through the presence of self-reported hallux valgus, a structural forefoot deformity involving lateral deviation of the hallux at the 1st MTP [18, 23]. A case-control study involving 164 patients with gout found that self-reported hallux valgus was significantly more common in patients with gout [23]. However, a larger cohort study involving 1,184 gout participants revealed 36 % of patients had self-reported hallux valgus, which the authors reported was similar to the general population and not related to gout-specific factors [18].

Functional characteristics

Moderate to high levels of general disability and walking disability were reported using 100 mm VAS in patients with current acute 1st MTP arthritis (mean 60.0 mm to 64.1 mm) [41]. Similarly, when using the Hallux Metatarsophalangeal-Interphalangeal section of

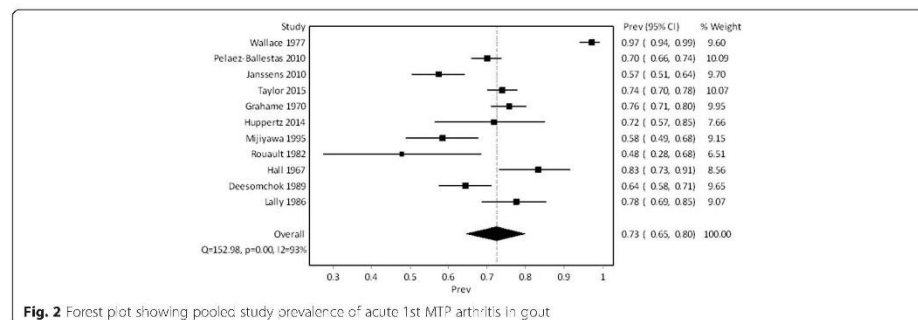


Fig. 2 Forest plot showing pooled study prevalence of acute 1st MTP arthritis in gout

the American Orthopaedic Foot and Ankle Society (AOFAS) scale [44], which provides a total score out of 100 based on pain, range of motion, joint instability and alignment, and activity- and footwear-related limitations, people with 1st MTP tophi scored between 65 and 61 out of 100, where 100 indicates an absence of pain and any joint, activity or footwear limitation [43].

A study on 164 people with gout found a significant association between acute 1st MTP arthritis and the presence 1st MTP osteoarthritis, defined as restricted motion, bony swelling and/or crepitus [24]. In a further study of patients with severe tophaceous gout the mean (SD) total range of motion at the 1st MTP was 19°, which reduced to 14° in joints which also demonstrated severe cartilage loss [43].

A study assessing foot function in 25 patients with long-standing chronic gouty arthropathy using in-shoe plantar pressure analysis found peak plantar pressure beneath the first metatarsal was greater in the gout group, although not significantly [45]. However, peak plantar pressure and pressure-time integrals beneath the hallux were significantly reduced in the gout group when compared to the controls, which the authors proposed reflected an attempt to offload pain at the 1st MTP [45].

Microscopy

The success of joint fluid acquisition for the purposes of microscopic identification of MSU crystals from the 1st MTP ranged from 81 to 91 % [30, 46, 47]. The presence of MSU crystals in 1st MTP fluid ranged from 83 to 89 % of currently asymptomatic 1st MTPs in patients with gout with a history of acute 1st MTP arthritis [39, 46]. In patients with gout with no history of acute 1st MTP arthritis, 52 to 67 % of aspirated 1st MTPs were positive for crystals [30, 39, 48]. In patients experiencing current acute 1st MTP arthritis the presence of MSU crystals ranged from 85 to 93 % [47, 49].

The occurrence of acute 1st MTP arthritis as a diagnostic feature has been compared with the presence of MSU crystals in aspirated 1st MTP fluid [10, 37]. Based on clinical characteristics of acute 1st MTP arthritis in 159 patients, general practitioners diagnosed 98 % of patients as having gout [37]. When validated against the presence of MSU crystals, a sensitivity of 0.99 and a specificity of 0.08 was demonstrated [37]. In a study of 328 patients with monoarthritis, Janssens [10] reported that the 1st MTP as the location of the monoarthritis was an independent predictor of MSU crystal presence [10].

Imaging features

Urate crystal deposition

Ultrasonography allows the visualisation of MSU crystal deposition along the surface of articular cartilage, referred

to as the 'double contour sign', the presence of which ranged from 22 to 87.5 % at the 1st MTP [41, 42, 50–52]. Naredo [50] noted the double contour sign was more frequent at the dorsal aspect of the 1st MTP (62 %) compared to the plantar aspect (23 %).

Dual-energy computed tomography (DECT) may be less sensitive than ultrasound due to the lower spatial resolution [31]. In a study of 39 patients (79 % with newly diagnosed gout) DECT detected urate crystals in 26 % of 1st MTPs, and ultrasound in 74 % of the same joints [31]. The presence of MSU deposition using DECT increased from 26 % of joints in newly diagnosed gout [25], to 36 % after 5 years disease duration [53], and 54 % in patients with 11 years mean duration [54]. In patients with tophaceous gout and a mean disease duration of 22 years, MSU crystals were present in 38 % of 184 1st MTPs [55].

In a DECT study assessing feet with current flares, the authors reported crystal deposition in 41 % of 1st MTPs in patients with 1st MTP flares, compared to 27 % of 1st MTPs in patients with current ankle flares [53]. The presence of DECT MSU crystal deposition was found to be a risk factor for acute 1st MTP arthritis (OR = 3.38;) [53].

Tophi

In sonographic studies, the presence of tophi in 1st MTPs of people with gout ranged from 50 to 100 % [41, 42, 50, 52, 56, 57]. Thiele and Schlesinger [56] noted tophi were more often seen medial and dorsal to the joint with a distinct pattern in which unformed micro-particles were seen in the dorsal proximal recess and central area while formed tophi were more frequent in the medial compartment and impinging on the dorsal proximal phalanx [56]. Using MRI, a study of 15 patients with 1st MTP tophaceous gout, reported that the medial sesamoid was the most common location for tophaceous infiltration (seen in 47 % of patients), followed by the first metatarsal shaft (40 %) and lateral sesamoid (33 %) [43]. In the majority of patients (57 %) tophi were observed both extra-articularly and intra-articularly within the 1st MTP.

Bone disease

In patients with long-standing tophaceous gout, erosions on conventional radiography were noted in 79 % of 1st MTPs [55]. Other radiographic features of bone damage have been observed frequently in the 1st MTP joints in people with gout including spur formation (40 % of joints), joint space narrowing (39 %), osteophytes (44 %), sclerosis (73 %) and periosteal new bone formation (13 %) [55]. A study of 262 patients with gout reported radiographic proven osteoarthritis (defined as destruction of the articular

surfaces) in 44 % of 1st MTPs and found a significant correlation between osteoarthritis and acute arthritis at this joint [21].

Sonographic evidence of bone erosion in 1st MTPs ranged from 40 to 67 % in patients with gout [22, 41, 42, 56, 57]. Wright [42] reported 92 % of detected erosions were present on the medial aspect of the metatarsal head, with 7 % on the dorsal metatarsal head, and the remaining 2 % on the medial aspect of the proximal phalangeal base. Erosions at the 1st MTP can be multifocal or unifocal and generally measure at least 2 mm in diameter [41, 42]. Thiele and Schlesinger [56] noted all erosions at the 1st MTP were adjacent to tophaceous material.

Using MRI, Kim [43] reported erosions and intraosseous involvement present in the first metatarsal shaft of 40 % of patients with symptomatic 1st MTP tophaceous gout. Using conventional CT, Dalbeth [58] reported 78 % of 1st MTPs had erosions present at the first metatarsal head, and 34 % had erosions at the proximal phalanx. The proportions of eroded bone were also greater at the metatarsal head compared to the proximal phalanx and were higher in those with clinically-evident tophi.

Synovial disease

Synovial disease, in the form of joint effusion, synovial hypertrophy, and synovitis has been assessed using both gray-scale and power Doppler ultrasound [41, 42, 51, 56]. Joint effusion, which has been observed in 29 to 74 % of 1st MTPs in people with gout [41, 42, 51, 56], is less specific for gout and has been seen at a similar rate in other rheumatic conditions (64 to 73 %) [42, 56]. Similarly, synovial hypertrophy is seen at a similar rate in gouty 1st MTPs (53 to 87 %) [41, 42, 51], and other rheumatic conditions (64 %) [42]. Synovitis, which can be assessed using power Doppler ultrasound has been shown to be more sensitive than clinical assessment (18 % vs. 5 %, respectively) [51]. Synovitis has been reported to occur at the 1st MTP with a mild Doppler signal in 15 %, moderate signal in 18 % and marked signal in 10 % [42]. Synovitis occurs at a significantly greater frequency in 1st MTPs in those joints with acute arthritis, with Kang [41] reporting 95 % of 1st MTPs with acute arthritis demonstrated mild to moderate power Doppler signals. However, synovitis is not specific to gout and is seen in 18 to 50 % of other inflammatory joint diseases [42, 56].

Discussion

The historical observation of gout as a condition specifically affecting the 1st MTP is reflected in modern epidemiological literature, and is evident by the pooled 73 % prevalence estimate of 1st MTP acute arthritis reported in the meta-analysis of 11 studies. The clinical diversity between these studies, which is generally considered inevitable in meta-analyses [59], may explain the wide range of

estimated prevalence values and account for the high heterogeneity observed. The included studies represented patients with gout from a wide range of countries, resulting in different participant demographics, genetic factors and lifestyle factors. Additionally, disease duration of gout participants varied considerably and is likely to impact the calculated prevalence estimate, as longer disease duration would increase the likelihood of experiencing an episode of acute 1st MTP arthritis. Furthermore, only 42 % of participants included in the meta-analysis were diagnosed with gout using the gold standard MSU crystal identification [7, 9, 10, 28, 31, 34, 35, 38, 39]. The differences in study designs adopted by the included studies (e.g. cohort, cross-sectional, case-control, retrospective and randomised controlled trial) may also have contributed to the increased heterogeneity. Nevertheless, this prevalence estimate provides useful quantitative data which corroborates the traditional notion that gout is a condition with frequent manifestations at the 1st MTP.

Pain experienced during acute 1st MTP arthritis is considerable [27, 37, 41], and remains present following the resolution of acute symptoms [18, 42]. Outcome measurement methods used for measuring 1st MTP pain varied from 5-point Likert scales [27], visual analogue scales [37, 41], simply recording whether 1st MTP pain was present or absent [23], to measuring tenderness with palpation [42]. However, it appears that 1st MTP pain is a chronic foot problem in people with gout, which is further reflected by the sub-clinical joint inflammation observed during intercritical periods [42, 51]. In patients with 1st MTP tophaceous gout, high levels of pain are coupled with reduced joint function [26, 43]. Although it is unclear whether these clinical symptoms are a consequence of pain-avoidance, joint damage, synovial inflammation, mechanical obstruction by tophi, or a combination of these factors, the clinical implications of symptomatic 1st MTP gout on the ability to undertake everyday weight-bearing activities, such as walking, are recognised as important features of the disease [41]. People with gout walk significantly slower and demonstrate gait patterns consistent with 1st MTP pain-avoidance strategies [45]. Abnormal 1st MTP loading at toe-off in patients with gout may be further exacerbated by biomechanical strain as a result of MSU deposition within the 1st MTP flexor and extensor tendons [53, 60].

As the initiation of acute gouty arthritis is not possible in the absence of MSU crystals, the susceptibility of the 1st MTP to gout over other joints must be related to certain factors which predispose to the precipitation and deposition of crystals at this site. It has been hypothesised that the predilection for MSU deposition and patient symptoms in the foot and ankle may be attributed to the biomechanical loading or physical stress during

the normal gait cycle [55, 56, 58, 60]. This is further emphasised in the distinct pattern of crystal deposition at the 1st MTP observed in imaging studies where MSU deposits have been reported to occur more often on the medial and dorsal aspects of the joint compared to the plantar aspect [50, 56, 61]. It has been proposed that this distinct pattern of crystal deposition at the 1st MTP may result from the shifting of tophaceous deposits with dorsiflexion during walking and their eventual clustering at pressure points within the joint [56].

Osteoarthritis observed at the 1st MTP has also been implicated in the co-occurrence of gout at this joint [21, 24]. However, the distinction between joint damage caused by chronic gouty arthritis and osteoarthritic joint damage is unclear, particularly due to the high prevalence of 1st MTP osteoarthritis in the general population [62].

This review has a number of limitations. Firstly, the literature search and screening was conducted by a single reviewer. Secondly, the methodology adopted may have created a selection bias through the exclusion of non-English language studies which may have resulted in an incompletely and potentially biased set of evidence. In regard to the methodologies used in included studies, most were cross-sectional descriptive studies which provide lower-level evidence and limit investigation in to the cause-effect relationship between 1st MTP characteristics and gout. Many of the studies also involved small sample sizes. Furthermore, gout disease characteristics of participants in the included studies varied and the majority of participants were diagnosed based on clinical criteria. Although this reflects diagnostic methods employed in clinical practice, there are several limitations to current classification criteria [40] and the demonstration of MSU crystals in synovial/tophus aspirates remains the only method to permit a definitive diagnosis of gout [63]. Lastly, there is an absence of a recommended outcome measure to assess patient-reported outcomes relating specifically to the 1st MTP in gout research which makes comparisons between studies challenging.

This review highlights the need for future research which adopts standardised assessment approaches when investigating patient-reported outcomes specifically relating to the 1st MTP in gout. Advanced imaging may be implemented to determine the structural characteristics of the joint in relation to clinical features, particularly how 1st MTP involvement affects patient-reported outcomes and the ability to carry out daily activities, including walking. This may direct further research which investigates the biomechanical role of the 1st MTP in the frequent occurrence of gout at this joint. By recognising the local factors that contribute to the 1st MTPs susceptibility to crystal deposition and inflammation, further studies may assess non-pharmacological interventions

that are specifically aimed at the 1st MTP including footwear, foot orthoses and foot-related health education which have previously been shown to be effective with general foot pain and disability in people with gout [64–66].

Conclusion

This review aimed to evaluate and summarise the findings from existing literature which assessed the 1st MTP in people with gout. This review confirms the long-standing notion that acute 1st MTP arthritis is highly prevalent in people with gout and has a substantial impact on patient-reported outcomes related to pain and disability. Current research also suggests that the structure and function of the 1st MTP is impaired in people with gout. This review highlights the importance of clinical, laboratory and imaging findings related to the 1st MTP in the diagnosis of gout in clinical practice and underlines the need for interventions that specifically target improvements in structure, function and patient-reported outcomes related to the 1st MTP in people with gout.

Abbreviation

1st MTP: First metatarsophalangeal joint.

Competing interests

ND has received personal fees or grants from Takeda, Teijin, Menarini, Pfizer, AstraZeneca, Ardea, and Fonterra. The other authors declare no competing interests.

Authors' contributions

SS was involved in the searches and eligibility checks, extracting of study data, conducting the meta-analysis interpreting the findings and drafting of the manuscript. ND was involved in the design of the review, interpretation of the findings and drafting of the manuscript. AV was involved in the design of the review, conducting the meta-analysis, interpreting the findings and drafting of the manuscript. KR was involved in the design of the review, interpretation of the findings and drafting of the manuscript. All authors read and approved the final manuscript.

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None.

Author details

¹Faculty of Health and Environmental Sciences, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand. ²Department of Medicine, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. ³Department of Biostatistics & Epidemiology, School of Public Health & Psychosocial Studies, Faculty of Health and Environmental Sciences, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand. ⁴Health Intelligence & Informatics, Ko Awatea, Counties Manukau Health, Private Bag 93311, Auckland 1640, New Zealand.

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Appendix 4. AUTEK ethical approval



A U T E C
S E C R E T A R I A T

18 September 2013

Keith Rome
Faculty of Health and Environmental Sciences

Dear Keith

Re: Ethics Application: 13/100 The effect of chronic gouty arthritis on the structure and function of the Achilles tendon.

The first metatarsophalangeal joint (1MTP) in gout and asymptomatic hyperuricaemia

Thank you for your request for approval of amendments to your ethics application.

I have approved minor amendments to your ethics application allowing an extension of the scope of the research and the inclusion of an additional student for a PhD qualification.

I remind you that as part of the ethics approval process, you are required to submit the following to AUTEK:

- A brief annual progress report using form EA2, which is available online through <http://www.aut.ac.nz/researchethics>. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 10 June 2016;
- A brief report on the status of the project using form EA3, which is available online through <http://www.aut.ac.nz/researchethics>. This report is to be submitted either when the approval expires on 10 June 2016 or on completion of the project.

It is a condition of approval that AUTEK is notified of any adverse events or if the research does not commence. AUTEK approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEK grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee


A u c k l a n d U n i v e r s i t y o f T e c h n o l o g y E t h i c s C o m m i t t e e

WA507 Level 5 WA Building City Campus

Private Bag 92006 Auckland 1142 Ph: +64-9-921-9999 ext 8316 email ethics@aut.ac.nz

Appendix 5. Participant information sheet


Pg 1 of 3



AUCKLAND
DISTRICT HEALTH BOARD
Te Toka Tuwai

Participant Information Sheet

September 2013



AUT
UNIVERSITY
TE WĀHANGA ARANGI O TAMAKI MAKAU RAU

The Big Toe Joint in People with Gout and People with High Uric Acid Levels

An Invitation

My name is Sarah Stewart. I'm currently doing a PhD at Auckland University of Technology (AUT) on the topic of "The Big Toe Joint in People with Gout and People with High Uric Acid Levels". I would like to invite you to participate in this research project. Participation is entirely voluntary. If you do decide to participate you may withdraw from the study at any time before the completion of the study visit without being disadvantaged in any way.

What is the purpose of this research?

New Zealand has one of the highest prevalence rates of gout in the world. Gout is a form of arthritis that is caused by an increase in uric acid levels in the blood. High uric acid levels can lead to the deposition of urate crystals in the joints which can cause painful attacks of arthritis. Previous research has found that joint damage can occur in people who have high uric acid levels even when they do not have gout. Although the big toe joint is the most common joint affected by gout, it is not well understood why. The purpose of this study is to examine the big toe joint in people with gout, people with high uric acid levels, and people with normal uric acid levels.

How was I identified and why am I being invited to participate in this research?

If you are a patient at the Auckland District Health Board you may have been invited to participate in this research if you have gout, have high uric acid levels or have normal uric acid levels. You will be able to participate in this research if you are older than 20 years of age, do not have another form of inflammatory arthritis (such as rheumatoid arthritis or psoriatic arthritis), have not had surgery to your feet or ankles in the last 3 months, have not had a lower limb amputation, are able to walk 5 meters unaided. If you have gout and experience an acute attack on the day of your study visit, we will not ask you to attend.

What will happen in this research?

You can accept this invitation to participate by signing the consent form. Participation will involve attending a single study visit at the AUT North Shore Campus, located just 2 minutes' drive from the harbour bridge. This visit is divided into two parts: an ultrasound scan and a clinical assessment. The visit will take about 1 hour and 30 minutes.

ULTRASOUND SCAN: An experienced ultrasonographer will be taking ultrasound scans of both your right and left big toe joints. He will ask you to lie back and relax on a plinth (a bed with a backrest that is able to move up and down) and will help you position your feet for scanning. The scanning should take around 30 minutes.

CLINICAL ASSESSMENT: At the clinical assessment I may or may not need to take a fingerprick blood test to measure your urate level. At the clinical assessment I will also measure your weight and height and then ask you to relax on a plinth while I examine your feet. I will be looking at the movement of your big toe joints, testing the strength of the muscles in your feet, checking the temperature of your feet and checking the nerves in your feet. I will also take some measurements while you're walking. I will then help you to fill out some simple short questionnaires that ask you about your health and your feet.

What are the discomforts and risks?

Ultrasound is an extremely safe imaging tool. It is non-invasive and painless. It does not cause ionizing radiation like x-rays and there are no known harmful effects. The ultrasonographer will apply some gel to your feet which may feel cool and a little odd, but it is essential in providing a clear and detailed ultrasound image. He will apply gentle pressure with the ultrasound probe to your big toe joint which should not cause any discomfort.

The tests I will be performing at the clinical assessment are quick and simple tests that health clinicians and researchers use all the time. None of the tests should cause you any discomfort. For those having a fingerprick blood test, it will feel like a small pinprick. You will be given a plaster to cover the prick with afterwards.

Approved by the Auckland University of Technology Ethics Committee on 18/Sept/2013 AUTEK Reference number 100/13.

How will these discomforts and risks be alleviated?

The aim is to make sure you are comfortable at all times throughout your study visit. You will have the opportunity to ask questions before you take part in the study and any time during your study visit. I will explain each clinical test to you before I perform it so you are comfortable and know what to expect. If at any time you feel discomfort, for whatever reason during any assessment please let me know.

What are the benefits?

The findings from this study may provide further support for the potential of ultrasound in the diagnosis of early gout and the prevention of further joint damage. It will also provide clinicians and researchers with an increased understanding of the disability and functional impairment experienced by those with gout and high uric acid levels. Furthermore, by identifying a relationship between the ultrasound features of the joint and clinically assessed features will give us a valuable insight into the characteristics of the joint that are associated with joint damage. This may direct future research which evaluates incorporating non-pharmacological interventions that address functional aspects of the joint. This may lead to an improvement in the big toe joint and foot function and may reduce the frequency of painful big toe joint gout flares, thus increasing the health-related quality of life for those with gout.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of your participation in this study, rehabilitation and compensation for injury by accident may be available from the Accident Compensation Corporation, providing the incident details satisfy the requirements of the law and the Corporation's regulations.

How will my privacy be protected?

Your name and birthdate will not be used in this research or published in any form. All information you provide will be kept confidential and access to any information will be restricted only to the researchers.

What are the costs of participating in this research?

There will be no monetary cost to you if you choose to participate in this research. It will only cost approximately 1 hour and 30 minutes of your time. Tea and coffee will be provided and we will reimburse you with any travel costs to and from the study visit.

What opportunity do I have to consider this invitation?

You have until July 2013 to consider this invitation. Please contact me as soon as you decide to take part so we can arrange a time for you to attend the study visit that suits you.

How do I agree to participate in this research?

If you agree to take part in this study, or have any questions please contact me, Sarah Stewart, by 0800 number, txt message, or email (see contact details below). We can arrange a time for you to attend the study visit that suits you. When you attend the study visit could you please bring with you the signed Consent Form attached to this Information Sheet, and if possible a list of your current medications.

Will I receive feedback on the results of this research?

Results will be made available to you at the completion of the study, and will be in the form of a written summary. If you wish to receive this, please indicate on the relevant section of the Consent Form. Please provide either your postal address or your email address on the Consent Form so we can send the results to you. Any papers that may be published arising from the research can be accessed on request.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Professor Keith Rome, *keith.rome@aut.ac.nz*, 921 9999 ext 7688.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTC, Dr Rosemary Godbold, *rosemary.godbold@aut.ac.nz*, 921 9999 ext 6902.

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Maori Research Committee or Maori Research Advisor by telephoning 09 4868920 ext 3204

Whom do I contact for further information about this research?

Researcher Contact Details: Sarah Stewart, *sarah.stewart@aut.ac.nz*, 0221642962

Project Supervisor Contact Details: Professor Keith Rome, *keith.rome@aut.ac.nz*, 921 9999 ext 7688.

Appendix 6. Participant consent form

Consent Form



Project title: *The big toe joint in people with gout and people with high uric acid levels*

Project Supervisor: *Prof. Keith Rome*

Researcher: *Sarah Stewart*

- ☐ I have read and understood the information provided about this research project in the Information Sheet dated 18 September 2013.
- ☐ I have had an opportunity to ask questions and to have them answered.
- ☐ I have been given sufficient time to discuss with family/whānau or a friend when a decision is required.
- ☐ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ☐ I am not suffering from a form inflammatory arthritis (such as rheumatoid arthritis or psoriatic arthritis). I have not had any foot and/or ankle surgery in the past 3 months, have not had lower limb amputation, and I am able to walk 5 meters unaided.
- ☐ I understand that the ultrasound images will be used for academic purposes only and will not be published in any form outside of this project without my written permission.
- ☐ I agree to provide a finger-prick blood test to measure the uric acid level in my blood (please tick one): N/A ☐ Yes ☐ No
- ☐ I wish to have my finger-prick test strip returned to me in accordance with right 7 (9) of the *Code of Health and Disability Services Consumers' Rights* (please tick one):
Yes ☐ No ☐
- ☐ I agree to take part in this research.
- ☐ I wish to receive a copy of the report from the research (please tick one):
If yes, then please provide postal/email details below. Yes ☐ No ☐

Participant's name:.....

Participant's signature:.....

Participant's Contact Details (if appropriate):.....

.....

Date:.....

*Approved by the Auckland University of Technology Ethics Committee on 18 September 2013 AUTEC
Reference number 100/13*

Appendix 7. Clinical Report Form

Patient ID.....

Date:

Participant meets diagnostic group criteria:

- ☐ **Gout:** has a diagnosis of gout according to the ACR criteria
- ☐ **Asymptomatic hyperuricaemia:** has no history of gout, does not meet ACR criteria, and has a serum urate level of $\geq 0.41\text{mmol/L}$
- ☐ **Healthy control:** has no history of gout, does not meet ACR criteria, and has a serum urate level of $< 0.41\text{mmol/L}$

Participants meets criteria:

- ☐ older than 20 years of age
- ☐ does not have a history of other inflammatory arthritis
- ☐ is not experiencing an acute flare at the time of the clinical visit
- ☐ has not had foot and/or ankle surgery in the past 3 months
- ☐ does not have lower limb amputation
- ☐ is able to walk 5 meters unaided

- ☐ Consent Form signed
- ☐ Participant Information Sheet given to participant
- ☐ Participant reimbursed for travel to AUT
- ☐ Clinical Report Form completed
- ☐ Ultrasound Assessment completed

Patient ID.....

Participant Demographic and Medical Data

NHI:

Age (years):

Gender: Male / Female

Ethnicity: European / Māori / Pacific Island / Asian

Weight (Kg):

Height (m):

Patient agrees to their GP/Rheumatologist getting information about their assessments Y / N

Medications (name and dosage):

Diuretics (if yes, state)

Allopurinol

Colchicine

Probenecid

Benzbromarone

Febuxostat

NSAID

Prednisone

Current Medical History:

Hypertension Y / N

Cardiovascular Disease Y / N

Diabetes Y / N

Serum urate (mmol/L):

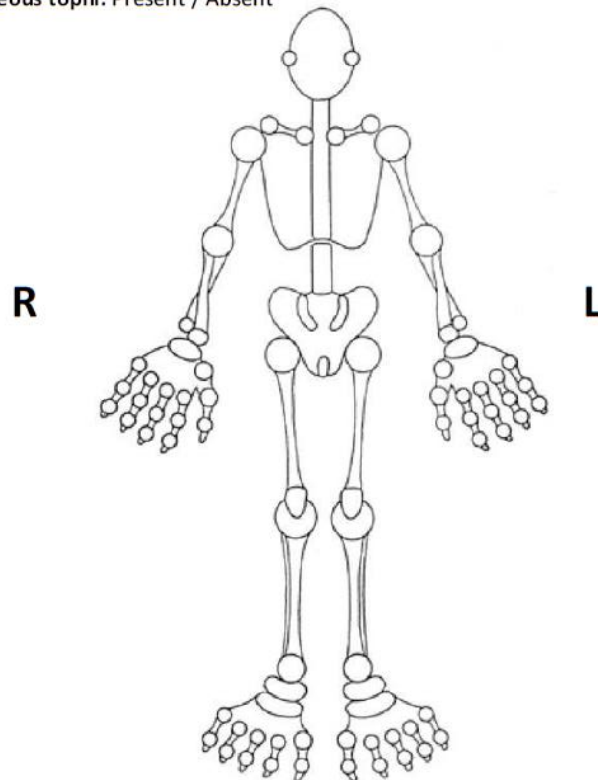
Patient ID.....

Gout only

Disease Duration (years):

Diagnostic Criteria: Aspirate proven / Microscopy / Clinical

Subcutaneous tophi: Present / Absent



Total Tophus count:

Foot tophus count, RIGHT:

LEFT:

1MTP tophus, RIGHT: Present / Absent LEFT: Present / Absent

Number of acute flares in last 3 months:

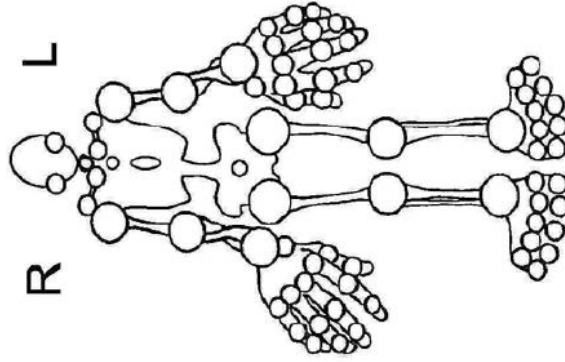
Number of acute flares at 1MTP in last 3 months:

Flare at 1MTP anytime during disease history:

RIGHT Y / N

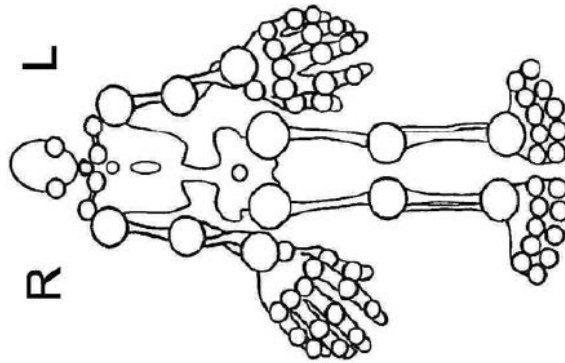
LEFT Y/N

SWOLLEN JOINTS



Total Swollen Joints

TENDER JOINTS



Total Tender Joint

Patient ID.....

Session 1

Dorsiflexion ROM	Right	Left
Test 1	___°	___°
Test 2	___°	___°
Test 3	___°	___°

Session 2 (if applicable)

Dorsiflexion ROM	Right	Left
Test 1	___°	___°
Test 2	___°	___°
Test 3	___°	___°

Session 1

Plantarflexion strength	Right	Left
Test 1	___N	___N
Test 2	___N	___N
Test 3	___N	___N

Session 2 (if applicable)

Plantarflexion strength	Right	Left
Test 1	___N	___N
Test 2	___N	___N
Test 3	___N	___N

Session 1

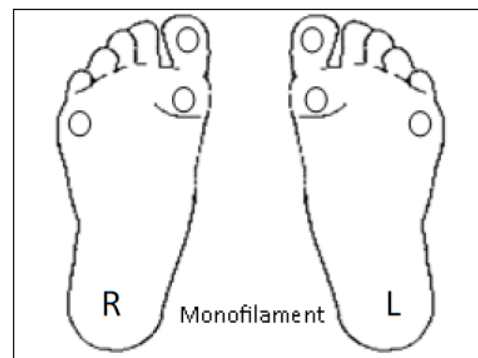
Dorsiflexion strength	Right	Left
Test 1	___N	___N
Test 2	___N	___N
Test 3	___N	___N

Session 2 (if applicable)





Dorsiflexion strength	Right	Left
Test 1	___N	___N
Test 2	___N	___N
Test 3	___N	___N

Temperature	Plantar		Medial		Dorsal	
	Right	Left	Right	Left	Right	Left
Test 1	___°	___°	___°	___°	___°	___°
Test 2	___°	___°	___°	___°	___°	___°
Test 3	___°	___°	___°	___°	___°	___°

Biothesiometer	Right	Left
Test 1	___V	___V
Test 2	___V	___V
Test 3	___V	___V



Patient ID.....

Hallux Valgus Severity		Right	Left
		0 / 1 / 2 / 3	0 / 1 / 2 / 3
0		1	
2		3	

Foot Posture Index	Left	Right
Talar head position*	_____	_____
Malleolar curvature	_____	_____
Calcaneal position	_____	_____
TN joint prominence	_____	_____
MLA congruence*	_____	_____
Forefoot position	_____	_____
Total	____ / +12	____ / +12

MatScan - three trials obtained for each foot	
GaitMat - three trials obtained	

Appendix 8. Ultrasound assessment form

Ultrasound Assessment Form									
PID _____									
Sonographic Feature	Joint Location	Right	Left	Right	Left	Right	Left	Right	Left
Double Contour Sign	Dorsal metatarsal head	0/1	0/1						
	Dorsal phalangeal base	0/1	0/1						
	Medial metatarsal head	0/1	0/1						
	Medial phalangeal base	0/1	0/1						
Intra-articular Tophi	Plantar metatarsal head	0/1	0/1						
	Plantar phalangeal base	0/1	0/1						
	Dorsal proximal space	0/1	0/1						
	Dorsal distal space	0/1	0/1						
Erosions	Medial proximal space	0/1	0/1						
	Medial distal space	0/1	0/1						
	Plantar proximal space	0/1	0/1						
	Plantar distal space	0/1	0/1						
Synovial Hypertrophy	Dorsal metatarsal head	0/1/2/3	0/1/2/3						
	Dorsal phalangeal base	0/1/2/3	0/1/2/3						
	Medial metatarsal head	0/1/2/3	0/1/2/3						
	Medial phalangeal base	0/1/2/3	0/1/2/3						
Joint effusion	Plantar metatarsal head	0/1/2/3	0/1/2/3						
	Plantar phalangeal base	0/1/2/3	0/1/2/3						
	Dorsal joint membrane	0/1/2/3	0/1/2/3						
	Plantar joint membrane	0/1/2/3	0/1/2/3						
Synovitis (Power Doppler signal)	Dorsal joint compartment	0/1/2/3	0/1/2/3						
	Plantar joint compartment	0/1/2/3	0/1/2/3						
	Medial joint compartment	0/1/2/3	0/1/2/3						
	Dorsal joint compartment	0/1/2/3	0/1/2/3						
Snowstorm Appearance	Plantar joint compartment	0/1	0/1						
	Medial joint compartment	0/1	0/1						
	Dorsal synovial compartment	0/1	0/1						
	Plantar synovial compartment	0/1	0/1						
Cartilage Thickness	Dorsal metatarsal head	__mm	__mm						
	Dorsal phalangeal base	__mm	__mm						
	Medial metatarsal head	__mm	__mm						
	Medial phalangeal base	__mm	__mm						
Snowstorm Appearance	Plantar metatarsal head	__mm	__mm						
	Plantar phalangeal base	__mm	__mm						
	Dorsal joint compartment	0/1	0/1						
	Plantar joint compartment	0/1/2/3	0/1/2/3						

Appendix 9. Characteristics of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a cross-sectional observational study

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RESEARCH

Open Access



Characteristics of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a cross-sectional observational study

Sarah Stewart^{1*}, Nicola Dalbeth^{2,3}, Alain C. Vandal^{4,5} and Keith Rome¹

Abstract

Background: This study aimed to identify patient-reported outcomes and clinician-assessed characteristics of the first metatarsophalangeal joint (1MTPJ) in people with gout and with asymptomatic hyperuricaemia by comparing them to normouricaemic controls.

Methods: Twenty four people with gout (without current symptoms of acute arthritis), 29 with asymptomatic hyperuricaemia and 34 age- and sex-matched controls participated in this cross-sectional observational study. Patient-reported outcomes included 1MTPJ pain, foot pain and disability, body pain, lower limb function, activity limitation and overall wellbeing. Clinician-assessed characteristics of the 1MTPJ included range of motion (ROM), plantar- and dorsi-flexion force, foot posture, temperature and hallux valgus severity.

Results: Compared to controls, participants with gout reported greater 1MTPJ pain ($p = 0.014$), greater foot pain and disability ($p < 0.001$), increased odds of having disabling foot pain (odds ratio (OR) 13.4, $p < 0.001$), decreased lower limb function for daily living ($p = 0.002$) and recreational ($p < 0.001$) activities, increased activity limitation ($p = 0.002$), reduced overall wellbeing ($p = 0.034$), reduced ROM ($p < 0.001$), reduced plantarflexion force ($p = 0.012$), increased 1MTPJ plantar ($p = 0.004$), dorsal ($p = 0.003$) and medial ($p = 0.004$) temperature and had increased odds of having more severe hallux valgus (OR 0.3 $p = 0.041$). Compared to controls, participants with asymptomatic hyperuricaemia had increased odds of having disabling foot pain (OR 4.2, $p = 0.013$), increased activity limitation ($p = 0.033$), decreased lower limb function for daily living ($p = 0.026$) and recreational ($p = 0.010$) activities, increased 1MTPJ plantarflexion force ($p = 0.004$) and a more pronated foot type ($p = 0.036$).

Conclusions: People with gout demonstrate 1MTPJ-specific changes indicative of subclinical inflammation, even in the absence of acute arthritis. People with asymptomatic hyperuricaemia, who exhibit no features or symptoms of gout, also report high levels of foot- and lower limb-related pain and disability.

Keywords: Gout, First metatarsophalangeal joint, Patient-reported outcomes

Background

Gout is the most common form of inflammatory arthritis in middle-aged men [1, 2]. Abnormally high levels of urate in the blood, termed hyperuricaemia (defined as ≥ 0.41 mmol/L), is the most important risk factor in the development of gout [3]. The prevalence of gout and hyperuricaemia is increasing worldwide [4–7]. Hyperuricaemia can lead to the formation and deposition of

monosodium urate (MSU) crystals in joints and soft tissues, and consequent clinical manifestations of gout, including episodes of acute gouty arthritis and tophus formation [8, 9]. Not all individuals with hyperuricaemia develop clinical features of gout [10–12]. However, recent imaging studies have reported the presence of MSU crystal deposition and subclinical joint- and extra-articular-damage in people with asymptomatic hyperuricaemia [13–19]. The clinical significance of these findings is currently unclear [20].

* Correspondence: sarah.stewart@aut.ac.nz

¹Department of Podiatry, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand
Full list of author information is available at the end of the article



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Acute gouty arthritis most commonly affects the first metatarsophalangeal joint (1MTPJ) [11, 21–23]. Advanced imaging studies have shown MSU crystal deposition frequently occurs within this joint not only in people with gout [24–26], but also in people with asymptomatic hyperuricaemia [14, 16]. People with gout report significant foot pain and report impairments and disability with everyday activities, including walking [27, 28]. In fact, they exhibit plantar pressure patterns and gait strategies consistent with an attempt to offload pain at the 1MTPJ [29]. Despite the importance of 1MTPJ function, particularly during the propulsive phase of gait [30, 31], the effect of gout and asymptomatic hyperuricaemia on patient-reported outcomes and clinical characteristics of the joint is unclear. This study therefore aims to identify patient-reported and clinician-assessed characteristics of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia by comparing them to normouricaemic controls.

Methods

Participants

This investigation was a cross-sectional observational study. Gout participants were recruited from Auckland District Health Board, Auckland, New Zealand. All participants fulfilled the 1977 preliminary American Rheumatism Association classification criteria for gout [21]. Participants without gout were recruited from Auckland University of Technology (AUT) staff. Non-gout participants underwent serum urate capillary testing on the day of the study using a Reflotron® Plus (Roche Diagnostics Ltd., New Zealand) and were stratified into either the asymptomatic hyperuricaemic group (serum urate ≥ 0.41 mmol/L) or the normouricaemic control group (serum urate < 0.41 mmol/L). The three groups were age- and sex-matched. Participants were excluded if they were under 20 years of age; had a history of other inflammatory arthritis; were experiencing acute arthritis at the time of the clinical visit; had foot and/or ankle surgery in the previous 3 months; had a history of 1MTPJ surgery; lower limb amputation; or were unable to walk 10 m unaided. Ethical approval for the study was obtained from the AUT Ethics Committee (13/100) and locality assessment was obtained from Auckland District Health Board (A + 5891). All participants provided written informed consent prior to data collection.

All data were collected by a single researcher and registered podiatrist (SS). Demographic data were obtained from all participants including age, gender, ethnicity, body mass index (BMI), current medications and medical history. Additionally, gout disease characteristics were documented for gout participants including disease duration, flare history, and tophus presence.

Patient-reported outcomes

Both right and left 1MTPJ pain, general body pain and patient global over the past week were assessed using 100 mm Visual Analogue Scales (VAS). Foot pain and disability was assessed using the 19-item Manchester Foot Pain and Disability Index (MFPDI) [32]. Each item was answered 'none of the time' (scored as 0), 'on some days' (scored as 1) or 'on most/every day(s)' (scored as 2) in the past month and a total score out of 38 was summated for each participant. Additionally, it was noted whether each participant had the presence of disabling foot pain, defined as at least one item scored as 1 or 2 [32]. The Health Assessment Questionnaire - Disability Index (HAQ-DI) [33] was used to measure activity limitation in which participants were asked to rate their ability to perform 10 tasks in the past week (without difficulty = 0, some difficulty = 1, much difficulty = 2, or unable = 3). The scores were summated and divided by 10 to give an overall value between 0 (minimal loss of function) and 3 (completely disabled). The Lower Limb Task Questionnaire (LLTQ) [34] was used to measure lower limb function related to two sections: activities of daily living (LLTQ daily) and recreational activities (LLTQ recreational). For each section participants were asked to rate their difficulty with 10 activities in the past 24 h (unable = 0, severe difficulty = 1, moderate difficulty = 2, mild difficulty = 3, and no difficulty = 4) from which a total score out of 40 was calculated.

Clinician-assessed outcomes

Passive, non-weight-bearing 1MTPJ dorsiflexion range of motion (ROM) was measured using a hand-held goniometer (Whitehall Manufacturing Ltd., California, USA) in accordance with the procedure outlined by Hopson and McPoil [35]. Participants were positioned seated with knees extended and the ankle in neutral. Lines were drawn on the medial aspect of the foot along the sagittal bisections of the first metatarsal and proximal phalanx. The examiner applied a dorsiflexion force to the hallux until it could no longer be passively moved into further extension. The angle between the two bisection lines was measured from the goniometer. Three repeated measurements of right and left feet were taken.

Isometric muscle force for plantarflexion and dorsiflexion of the 1MTPJ was measured using a CITEC hand-held dynamometer (CIT Technics, Haren, Netherlands). Participants were positioned seated with knees extended and the foot stabilised in a custom-made device comprised of two wooden boards angled at 90°. The plantar foot was positioned against the vertical board with the ankle in a neutral position. Velcro straps were applied across the dorsum of the foot and lower leg, to isolate the 1MTPJ and to ensure the lower leg was held stationary. Strength was assessed using the 'make' technique in which

the examiner held the dynamometer stationary while the participant exerted maximal force against it [36]. The dynamometer was positioned against the plantar aspect of the interphalangeal joint during plantarflexion testing and on the dorsal aspect of the hallux during dorsiflexion [37]. Three consecutive contractions of three to five seconds were recorded for each muscle group for each foot.

Hallux valgus severity was assessed using the Manchester Scale [38] which is comprised of four photographs graded as 0 being 'no deformity', 1 being 'mild deformity', 2 being 'moderate deformity' and 3 being 'severe deformity'. The participant was asked to stand in a relaxed weight-bearing position while the examiner used the photographs to grade the deformity on each foot.

Foot type was assessed using the 6-item Foot Posture Index (FPI-6) [39] with the participant standing in a relaxed weight-bearing position. Each FPI criterion was scored on a five-point scale (-2 to +2) and a total score calculated for each foot ranging from -12 (highly supinated) to +12 (highly pronated).

Temperature of the 1MTPJ was measured using a DermaTemp 1001 (Exergen Corporation, Massachusetts), which is a hand-held infrared thermographic scanner with an in-built sensor. Participants were given adequate equilibration time in the room (thermostatically controlled at $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$). Temperatures were recorded from medial, dorsal and plantar sites of the 1MTPJ. Three readings for each site were repeated for each foot.

Where repeated measurements were taken, they were not averaged, but instead included as separate observations in the analysis as described below.

Data analysis

Demographic and medical data were described as mean (SD) for continuous data and frequency (%) for categorical data. All continuous outcomes were reviewed for normality using the residuals from a linear model, which included relevant demographic covariates and the participant group as the independent variables. Appropriate regression models were identified for each outcome measure. Linear regression models were used for all continuous outcome measures. For the presence of disabling foot pain (a dichotomous outcome measure) logistic regression was used. For hallux valgus severity, an ordinal outcome measure, multinomial regression with cumulative logit link was used. Where appropriate, models accounted for repeated measures taken from right and left feet of each participant through using a mixed models approach in which a participant-specific random effect and participant-nested random effects for foot-side were added to the model. This analysis produces results identical to an analysis of measures averaged for each foot-side that would allow for a between-foot-side correlation, and also allows for any

reweighting required due to missing values. For 1MTPJ temperature, which was measured at three sites (forming a natural vector of related variables) in addition to the participant and foot-side random effects, a heterogeneous compound symmetry covariance structure was employed, which allowed for separate variances for each site, as well as different covariances (but equal correlations) between each pair of sites.

Adjustments for gender, age group and ethnicity, which were entered into each model simultaneously, were considered only if their level of observed significance achieved at least 10 % on an F-test (or equivalent deviance test (i.e. Wald test) for categorical variables). Potential covariates were also explored by reviewing box plots of random effects by covariate group. A single-adjusted model was sought for each category of clinically-assessed outcome measures (i.e. patient-reported outcomes, structural and functional outcomes and neurovascular outcomes). Two contrasts were considered: gout vs. control and asymptomatic hyperuricaemia vs. control, which were always tested separately. All hypothesis tests (excluding covariate testing) were carried out at a 5 % level of significance against two-sided alternatives. No adjustment for multiplicity was used, but all test-statistics, their null distributions and their observed significance levels were reported. Data were analysed using IBM SPSS Statistics version 20 and SAS version 9.3.

Results

A total of 87 participants were included with 24 in the gout group, 29 in the asymptomatic hyperuricaemic group and 34 controls. Demographic and clinical characteristics for the three groups are shown in Table 1. All participants were male with a mean (SD) age of 58 (15) years and predominantly of European ethnicity ($n = 68$, 81 %). The control group had a significantly lower mean BMI compared to the gout ($p < 0.001$) and asymptomatic hyperuricaemic participants ($p < 0.001$). Compared to controls, participants with gout had a significantly higher frequency of NSAID use ($p = 0.004$). The control group had a significantly lower prevalence of hypertension compared to the gout ($p = 0.001$) and asymptomatic hyperuricaemic groups ($p = 0.023$) and a significantly lower prevalence of cardiovascular disease compared to the gout group ($p = 0.019$). People with gout also had significantly higher mean tender ($p = 0.032$) and swollen joints counts ($p < 0.001$) compared to controls.

Disease characteristics for the gout group are shown in Table 2. Gout participants were found to have a long disease duration with a mean (SD) of 17 (11) years, with 71 % ($n = 17$) having tophaceous gout and 96 % ($n = 23$) on urate lowering therapy. The majority of participants with gout reported a history of acute 1MTPJ arthritis on either foot ($n = 21$, 88 %).

Table 1 Demographic and medical characteristics

Variable	Gout	Asymptomatic hyperuricaemia	Control
N	24	29	34
Gender, male, n (%)	24 (100 %)	29 (100 %)	34 (100 %)
Age, years, mean (SD)	58 (13)	58 (19)	58 (14)
Ethnicity, n (%)	European 14 (58 %)	European 24 (83 %)	European 30 (88 %)
	Maori 1 (4 %)	Maori 0 (0 %)	Maori 1 (3 %)
	Pacific 5 (21 %)	Pacific 3 (10 %)	Pacific 0 (0 %)
	Asian 4 (17 %)	Asian 2 (7 %)	Asian 3 (9 %)
BMI, kg/m ² , mean (SD)	30.2 (4.0)*	29.3 (5.9)*	25.0 (2.9)
Diuretic use, n (%)	3 (12 %)	7 (24 %)	4 (12 %)
NSAID use, n (%)	14 (58 %)*	11 (38 %)	7 (21 %)
Prednisone use, n (%)	5 (21 %)	0 (0 %)	0 (0 %)
Hypertension, n (%)	17 (70 %)*	16 (55 %)*	9 (26 %)
Cardiovascular disease, n (%)	7 (29 %)*	5 (17 %)	1 (3 %)
Diabetes, n (%)	4 (17 %)	1 (3 %)	2 (6 %)
Urate, mmol/l			
Mean (SD)	0.35 (0.10)	0.46 (0.05)*	0.32 (0.06)
Range	0.24 - 0.63	0.41 - 0.63	0.20 - 0.40
1MTPJ tenderness, n (%)			
Right	4 (17 %)	1 (0 %)	0 (0 %)
Left	3 (12 %)	0 (0 %)	1 (3 %)
1MTPJ swelling, n (%)			
Right	1 (4 %)	0 (0 %)	0 (0 %)
Left	0 (0 %)	0 (0 %)	0 (0 %)
66/68 joint count, mean (SD)			
Tender	2.7 (6.1)*	1.5 (1.9)	0.6 (1.2)
Swollen	1.0 (1.7)*	0.2 (0.7)	0.0 (0.0)

*Significantly different from controls ($p < 0.05$)**Table 2** Gout disease characteristics

Variable	Gout
Classification criteria	Aspirate proven 6 (25 %)
	Clinical criteria 18 (75 %)
Disease duration, years, mean (SD)	17 (11)
Age of onset, years, mean (SD)	41 (18)
Acute flares in preceding 3 months, mean (SD)	1.3 (1.4)
1MTPJ flares in preceding 3 months, n (%)	6 (25 %)
History of 1MTPJ flares, n (%)	21 (88 %)
Presence of subcutaneous tophi, n (%)	17 (71 %)
Presence of 1MTPJ tophi, n (%)	6 (25 %)
Number of tophi in feet, mean (SD)	1.9 (3.5)
Total number of tophi, mean (SD)	6.1 (8.7)
Colchicine use, n (%)	13 (54 %)
Urate lowering therapy ^a , n (%)	23 (96 %)
Allopurinol use, n (%)	19 (79 %)
Probenecid use, n (%)	3 (12 %)
Benzbromarone use, n (%)	2 (8 %)
Febuxostat use, n (%)	2 (8 %)

^a3 patients were taking >1 urate lowering agent

The distribution of residuals from the linear models for all outcome measures demonstrated sufficient normality to carry out parametric testing. All final models were adjusted for age group. Table 3 displays the mean estimates and inferential statistics for all patient-reported outcomes. Compared to controls, participants with gout reported significantly greater 1MTPJ pain ($p = 0.014$), greater patient global scores ($p = 0.034$), a greater HAQ-DI score ($p = 0.002$), a greater LLTQ daily score ($p = 0.002$), a greater LLTQ recreational score ($p < 0.001$), a greater MFPDI score ($p < 0.001$), and a higher odds of having disabling foot pain (OR 13.4; $p < 0.001$). Participants with asymptomatic hyperuricaemia also reported a significantly greater HAQ-DI score ($p = 0.033$), a greater LLTQ daily score ($p = 0.026$), a greater LLTQ recreational score ($p = 0.010$) and had a higher odds of having disabling foot pain (OR 4.2 $p = 0.013$), compared to controls.

Table 4 displays the mean estimates and inferential statistics for all clinician-assessed outcomes. Compared to controls, participants with gout had significantly reduced 1MTPJ ROM ($p < 0.001$), reduced 1MTPJ plantarflexion force ($p = 0.012$), an increased odds of having more severe hallux valgus (OR 0.3; $p = 0.041$) and increased temperature at the plantar ($p = 0.004$), dorsal ($p = 0.003$),

Table 3 Patient-reported outcomes

Parameter		Mean estimate	Diff.	95 % CI		p
				Lower	Upper	
1MTP pain VAS (mm)	Control (ref.)	1.7				
	Gout	8.4	6.7	1.4	12.0	0.014
	Asymptomatic hyperuricaemia	6.6	4.9	-0.1	10.0	0.055
General pain VAS (mm)	Control (ref.)	18.0				
	Gout	21.8	3.8	-9.9	17.5	0.581
	Asymptomatic hyperuricaemia	29.2	11.3	-1.7	24.3	0.088
Patient global VAS (mm)	Control (ref.)	11.5				
	Gout	23.6	12.0	0.9	23.1	0.034
	Asymptomatic hyperuricaemia	21.3	9.8	-0.8	20.3	0.068
HAQ-DI	Control (ref.)	0.11				
	Gout	0.44	0.33	0.13	0.54	0.002
	Asymptomatic hyperuricaemia	0.32	0.21	0.02	0.41	0.033
LLTQ - daily	Control (ref.)	38.6				
	Gout	33.3	-5.3	-8.6	-2.0	0.002
	Asymptomatic hyperuricaemia	35.0	-3.6	-6.8	-0.4	0.026
LLTQ - recreational	Control (ref.)	34.2				
	Gout	20.8	-13.4	-19.0	-7.9	<0.001
	Asymptomatic hyperuricaemia	27.2	-7.0	-12.3	-1.8	0.010
MFPSI	Control (ref.)	1.826				
	Gout	13.3	11.5	7.7	15.3	<0.001
	Asymptomatic hyperuricaemia	3.0	1.2	-2.4	4.8	0.511
			Odds ratio	95 % CI for OR		p
				Lower	Upper	
Presence of disabling foot pain	Control (ref.)					
	Gout		13.4	3.69	48.68	<0.001
	Asymptomatic hyperuricaemia		4.2	1.36	12.8	0.013

and medial ($p = 0.004$) aspects of the 1MTPJ. Participants with asymptomatic hyperuricaemia had significantly greater 1MTPJ plantarflexion force ($p = 0.004$) and a higher FPI score ($p = 0.036$), compared to controls.

Discussion

This study investigated patient-reported outcomes and clinician-assessed characteristics of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia. Despite the absence of current symptoms of acute arthritis in the gout participants and an absence of any signs or symptoms of gout in the asymptomatic hyperuricaemic participants, both groups reported high levels of foot- and lower limb-related pain and disability. Additionally, people with gout demonstrated 1MTPJ-specific changes related to pain, joint motion, muscle strength, hallux valgus severity and temperature.

Clinical symptoms in gout are generally associated with acute episodes of painful inflammatory arthritis,

most often at the 1MTPJ [21], while intercritical periods are considered to be 'asymptomatic' remissive phases [40, 41]. However, our findings, which support existing research [42, 43], suggest that 1MTPJ pain may be a chronic and persistent foot problem in people with gout. These results may be explained by the presence of sub-clinical inflammation, which is further emphasised by the increased 1MTPJ temperature observed in the gout participants in this study [44]. It has been well established that MSU crystals, which promote the inflammatory response evident in acute gout, are also present in synovial fluid during intercritical periods [45]. Furthermore, imaging studies have frequently observed synovitis in gout patients in the absence of clinically evident inflammation [25, 46, 47]. The clinical relevance of persistent inflammation at the 1MTPJ in people with gout is uncertain.

This study has also identified a number of structural and functional changes at the 1MTPJ in people with

Table 4 Clinician-assessed outcomes

Parameter		Mean estimate	Diff.	95 % CI		p
				Lower	Upper	
ROM (°)	Control (ref.)	77.6				
	Gout	59.7	-17.9	-26.8	-8.9	<0.001
	Asymptomatic hyperuricaemia	76.8	-0.8	-9.3	7.7	0.853
Plantarflexion force (N)	Control (ref.)	92.0				
	Gout	71.3	-20.7	-36.9	-4.6	0.012
	Asymptomatic hyperuricaemia	114.8	22.8	7.5	38.1	0.004
Dorsiflexion force (N)	Control (ref.)	57.3				
	Gout	58.0	0.8	-10.7	12.2	0.896
	Asymptomatic hyperuricaemia	65.4	8.1	-2.7	19.0	0.139
Foot Posture Index	Control (ref.)	+4.8				
	Gout	+6.2	1.3	-0.4	3.1	0.134
	Asymptomatic hyperuricaemia	+6.6	1.8	0.1	3.4	0.036
Plantar temperature (°C)	Control (ref.)	24.3				
	Gout	26.2	1.9	0.6	3.1	0.004
	Asymptomatic hyperuricaemia	25.1	0.8	-0.5	2.0	0.218
Dorsal temperature (°C)	Control (ref.)	25.8				
	Gout	27.7	1.9	0.6	3.1	0.003
	Asymptomatic hyperuricaemia	26.5	0.6	-0.6	1.9	0.295
Medial temperature (°C)	Control (ref.)	25.2				
	Gout	27.0	1.8	0.6	3.1	0.004
	Asymptomatic hyperuricaemia	25.9	0.8	-0.4	2.0	0.219
				95 % CI for OR		p
				Lower	Upper	
Hallux Valgus Severity ^a	Control (ref.)					
	Gout		0.284	0.085	0.947	0.041
	Asymptomatic hyperuricaemia	0.968	0.968	0.296	0.957	

^aReference category: none (i.e. grade 0). The odds ratio represents the odds of the diagnostic group moving up one category of severity, compared to the control group moving up one category of severity

gout. Although restricted 1MTPJ motion may be a result of surrounding synovial inflammation or a pain-avoidance mechanism, previous research has regarded reduced 1MTPJ motion in people with gout as a clinical measure of osteoarthritis [43]. It has been suggested that osteoarthritis may predispose to localised MSU crystal deposition and thus may explain the tendency for gout to affect the 1MTPJ [43, 44]. However, it remains uncertain whether osteoarthritis precedes gout or whether joint damage results from chronic gouty arthritis and/or mechanical obstruction by tophi [45].

Participants with gout also exhibited a reduction in 1MTPJ plantarflexion force. Considering the importance of 1MTPJ plantarflexion force during the forward transfer of body weight in normal walking [46], we speculate that reduced strength in this muscle group may be related to the propulsive gait patterns

previously observed in people with gout who demonstrated reduced peak pressure beneath the hallux [26]. The authors proposed this was a pain-avoidance strategy, which would reduce plantarflexor muscle activity and may lead to disuse muscle atrophy.

Although participants with asymptomatic hyperuricaemia did not display the 1MTPJ-specific changes observed in the gout group, they did report greater overall foot pain and disability, reduced lower limb function and increased activity limitation compared to the normouricaemic controls. It is unclear whether this is a direct result of chronically elevated serum urate and subclinical MSU deposition, inflammation and tissue damage [13–18] or related to co-existing conditions including hypertension, obesity, cardiovascular disease and diabetes, which have a marked association with hyperuricaemia and may display clinical manifestations in the foot and lower limb [48–54].

The association between chronically elevated serum urate levels and patient-reported outcomes is unclear and currently there is no consensus on the treatment of asymptomatic hyperuricaemia due to the small number of hyperuricaemic individuals that develop gout [10, 55] and the side effects of treatment with urate lowering therapy [56, 57]. However, the low-grade systemic inflammation, which has been reported in patients with asymptomatic hyperuricaemia [58, 59] along with the results of the current study highlight the need for further research in this area, particularly in the evaluation of treatment strategies aimed at improving patient-reported outcomes.

Our findings should be considered in light of several limitations. Firstly, our study included only male participants so our results cannot be generalisable to both genders. Secondly, we did not exclude participants with diabetes, cardiovascular disease and hypertension, which may have impacted our results. The majority of patients with gout had advanced disease with tophi, and it is possible that less severe 1MTPJ disease may be present in those with early gout or without gouty tophi. Lastly, the cross-sectional nature of our study design limits the ability to determine the cause and effect relationship between 1MTPJ characteristics and different disease states.

Further research may employ methods of advanced imaging to identify subclinical characteristics of gouty arthritis at the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia in correlation to clinically-assessed features of the joint. Considering the lower-limb related functional impairments reported by gout and asymptomatic hyperuricaemic participants in the current study, future research may also investigate how this is reflected in gait parameters. The findings from this study may be useful in directing future research, which evaluates the efficacy of non-pharmacological treatment strategies, such as footwear [60, 61] and orthoses, which specifically target the 1MTPJ in combination with urate lowering therapy.

Conclusion

In conclusion, this study has shown that 1MTPJ pain is commonly reported by people with gout during inter-critical periods. Clinician-assessed characteristics of the joint, including reduced motion and increased temperature, are indicative of subclinical inflammation and highlight the impact of gout on the structure and function of the 1MTPJ. This study has also shown that people with asymptomatic hyperuricaemia, who do not display any signs or symptoms of gout, also experience considerable foot- and lower limb-related pain and impairment and report greater activity limitation when compared to normouricaemic controls.

Competing interests

ND has received consulting fees, speaker fees or grants from the following companies: Takeda, Teijin, Menarini, Pfizer, Ardea, AstraZeneca, Savient, Fonterra, Metabolex. The other authors declare no competing interests.

Authors' contributions

SS participated in the conception and design of the study, undertook data acquisition and participated in analysis and interpretation of the data. ND participated in the conception and design of the study and interpretation of the data. AV participated in the conception and design of the study and the analysis and interpretation of the data. KR participated in the conception and design of the study and interpretation of the data. All authors were involved in drafting and revising of the manuscript and read and approved the final version to be published.

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Author details

¹Department of Podiatry, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand.

²Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. ³Department of Rheumatology, Auckland District Health Board, P.O. Box 92189, Auckland, New Zealand.

⁴Department of Biostatistics & Epidemiology, Faculty of Health and Environmental Sciences, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand. ⁵Health Intelligence & Informatics, Ko Awatea, Counties Manukau Health, Private Bag 93311, Auckland 1640, New Zealand.

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Appendix 10. Spatiotemporal gait parameters and plantar pressure distribution during barefoot walking in people with gout and asymptomatic hyperuricemia: comparison with healthy individuals with normal serum urate concentrations

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Spatiotemporal gait parameters and plantar pressure distribution during barefoot walking in people with gout and asymptomatic hyperuricemia: comparison with healthy individuals with normal serum urate concentrations

Sarah Stewart^{1*}, Nicola Dalbeth^{2,3}, Alain C. Vandal^{4,5} and Keith Rome¹

Abstract

Background: To identify spatiotemporal gait parameters and plantar pressure distribution during barefoot walking in people with gout and people with asymptomatic hyperuricemia by comparing them to healthy individuals with normal serum urate concentrations.

Methods: Eighty-seven participants were included: 24 with gout, 29 with asymptomatic hyperuricemia and 34 age- and sex-matched normouricemic control participants. Spatiotemporal parameters of gait were assessed during level barefoot walking using a GAITRite® walkway. Peak plantar pressure and pressure time integrals were recorded using a TekScan MatScan®. Results were adjusted for age and body mass index.

Results: Compared to normouricemic control participants, participants with gout demonstrated increased step time ($P = 0.022$) and stance time ($P = 0.022$), and reduced velocity ($P = 0.050$). Participants with gout also walked with decreased peak pressure at the heel ($P = 0.012$) and hallux ($P = 0.036$) and increased peak pressure ($P < 0.001$) and pressure time integrals ($P = 0.005$) at the midfoot. Compared to normouricemic control participants, participants with asymptomatic hyperuricemia demonstrated increased support base ($P = 0.002$), double support time ($P < 0.001$) and cadence ($P = 0.028$) and reduced swing time ($P = 0.019$) and single support time ($P = 0.020$) as well as increased pressure at the midfoot ($P = 0.013$), first metatarsal ($P = 0.015$) and second metatarsal ($P = 0.007$).

Conclusion: During barefoot walking, people with gout walk slower with plantar pressure patterns suggestive of propulsive and antalgic gait strategies. Individuals with asymptomatic hyperuricemia also demonstrate altered barefoot gait patterns when compared to normouricemic control participants. Clinicians may consider dynamic gait outcomes when assessing and managing foot and lower limb related pain and disability in individuals with gout and asymptomatic hyperuricemia.

Keywords: Gout, Asymptomatic hyperuricemia, Gait, Plantar pressure

* Correspondence: sarah.stewart@aut.ac.nz

¹Department of Podiatry, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand
Full list of author information is available at the end of the article



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Background

People with gout experience flares of severe inflammatory arthritis as a response to the presence of urate crystals deposited in joints and soft tissues [1, 2]. Gout most commonly affects peripheral structures of the foot and ankle with a propensity for the first metatarsophalangeal joint and Achilles tendon [3, 4]. Although elevated serum urate (hyperuricemia) is required for the development of gout, not all individuals with hyperuricemia develop symptomatic acute gouty arthritis [5]. However, advanced imaging studies have identified urate deposition and joint damage in foot and ankle structures in individuals with asymptomatic hyperuricemia [6–10].

People with gout report chronic and persistent foot and lower limb impairments, even in the absence of acute arthritis [11–16]. Furthermore, foot-related disability has been associated with altered gait parameters in people with gout [16] and may be mirrored in their plantar pressure patterns which have been proposed to reflect pain-avoidance strategies [13]. Individuals with asymptomatic hyperuricemia, who lack any current or previous symptoms of acute gouty arthritis or clinical evidence of urate deposition, also report disabling foot pain and experience lower limb impairments and activity limitations compared to healthy individuals with normal urate levels [14]. However, it is unknown whether their gait and plantar pressure patterns also differ from healthy normouricemic individuals.

Previous plantar pressure research in gout has been undertaken with patients wearing their own footwear [13]. Many people with tophaceous gout of the foot report difficulty in wearing and finding footwear that is appropriate to their level of pain, disability and deformity [17–22]. Footwear worn by people with gout has been shown to be poorly fitting with minimal cushioning and motion control properties [23]. Furthermore, over half of people with gout wear shoes with flexion points proximal to the level of the metatarsal heads which can limit gait efficiency by inhibiting normal first metatarsophalangeal joint function during propulsion [24] and hence may exacerbate the problems of efficient toe-off observed in people with gout during shod walking [13]. Considering the important influence of footwear on foot function, assessment of plantar pressure without the confounding effect of footwear is warranted.

This study aimed to identify spatiotemporal gait parameters and plantar pressure distribution during level barefoot walking in people with gout and people with asymptomatic hyperuricemia by comparing them to normouricemic control participants.

Methods

Participants

This investigation was a cross-sectional observational study. Ethical approval for the study was obtained from

the Auckland University of Technology Ethical Committee (13/100) and Locality Assessment was obtained from the Auckland District Health Board (ADHB) Research Office (A + 5891). All participants provided written informed consent prior to data collection.

Participants with gout were recruited from the ADHB rheumatology clinic and met the 1977 preliminary American Rheumatism Association (ARA) classification criteria for gout [25]. Participants without gout were recruited from the local community and were to have no history of acute arthritis nor meet the ARA criteria. Participants without gout underwent serum urate testing on the day of the study using a Reflotron® Plus capillary test and were stratified into either the asymptomatic hyperuricemic group (serum urate ≥ 0.41 mmol/L) or the normouricemic control group (serum urate < 0.41 mmol/L, 6.8 mg/dL). The three diagnostic groups were age- and sex-matched. Participants were excluded if they were under 20 years of age; had a history of other inflammatory arthritis; were experiencing an acute flare at the time of the clinical visit; had foot and/or ankle surgery in the previous 3 months; had lower limb amputation; or were unable to walk 5 m unaided.

All data were collected during a single session at the Auckland University of Technology Podiatry Clinic (Auckland, New Zealand) by a single researcher (SS). Demographic data were obtained from all participants including age, gender, ethnicity, body mass index (BMI), current medications and medical history. Peripheral sensation was assessed using a 10 g Semmes-Weinstein monofilament at the plantar hallux, first metatarsal head and fifth metatarsal head. A loss of protective sensation for each foot was defined if absent in at least two of the three sites. Additionally, gout disease characteristics were documented for participants with gout including disease duration, flare history, presence of subcutaneous tophi and tophus count.

Gait parameters

Spatial and temporal parameters of gait during level barefoot walking were collected using the GAITRite system (CIR Systems, Inc., New Jersey, US). The GAITRite is a 700 cm \times 90 cm electronic walkway with an active sensor area of 610 cm long and 60 cm wide. The active area contains 23,040 embedded pressure-activated sensors with a spatial resolution of 1.27 cm and a sampling rate of 120 Hz. All data was processed and stored by an IBM compatible computer using GAITRite® gold, Version 3.2b software. Participants were instructed to walk at their own comfortable walking speed [26] from a point 100 cm before the walkway and finishing 100 cm past its end to ensure that when they reached the walkway they were walking at a normal speed and momentum. Three trials of barefoot walking were recorded for

each participant with adequate rest time between trials. Prior to calculation of the gait parameters, the data was reviewed on the monitor screen to ensure that right and left footfalls had been correctly identified, and any footfall not completely on the walkway at either end was removed. For each trial the following temporal and spatial parameters for right and left feet were calculated: velocity (m/s), cadence (steps/min), step length (cm), stride length (cm), support base (cm), step time (s), swing time (s), stance time (s), and single and double support time (s).

Plantar pressure

Dynamic plantar pressure measurements were captured during level barefoot walking using the TekScan MatScan® system (Boston, MA, USA). The system consists of a 5 mm thick platform (432 × 368 mm), comprising of 2288 resistive sensors (1.4 sensors/cm²) which sample data at a frequency of 40 Hz. Data was collected using the two-step gait initiation protocol [27] which required the participant to step on the platform on their second step. Prior to data acquisition participants were instructed to familiarise themselves with the protocol and line themselves up with the platform to ensure their second step landed in the sensing area. Participants were instructed to walk at their own natural comfortable walking speed and to continue walking past the platform for at least two more steps which ensured that a constant velocity and momentum had been reached and pressure data reflected their normal gait. Three trials were recorded for each foot. The Research Foot® Version 6.61 was used to mask the foot into seven regions representing the heel, midfoot, first metatarsal, second metatarsal, metatarsal three to five, the hallux, and the lesser toes (Fig. 1). This masking method has demonstrated excellent reliability for the calculation of pressure parameters (ICCs 0.96 to 0.99) [28]. Peak plantar pressure (kPa) and pressure time integrals (kPa·s) were computed from the software for each masked region.

Statistical analysis

All continuous outcomes were reviewed for normality using the residuals from a linear model which included relevant demographic covariates and the diagnostic group as the independent variable. Mixed linear regression models were used which accounted for repeated measures taken from right and left feet of each participant in which participant-specific and participant-nested random effects for foot-side were added to the models. This analysis produces results identical to an analysis of measures averaged for each foot-side (if there are no missing values) that allows for a between-foot-side correlation as well as any reweighting required due to missing values. For the spatiotemporal gait parameters the

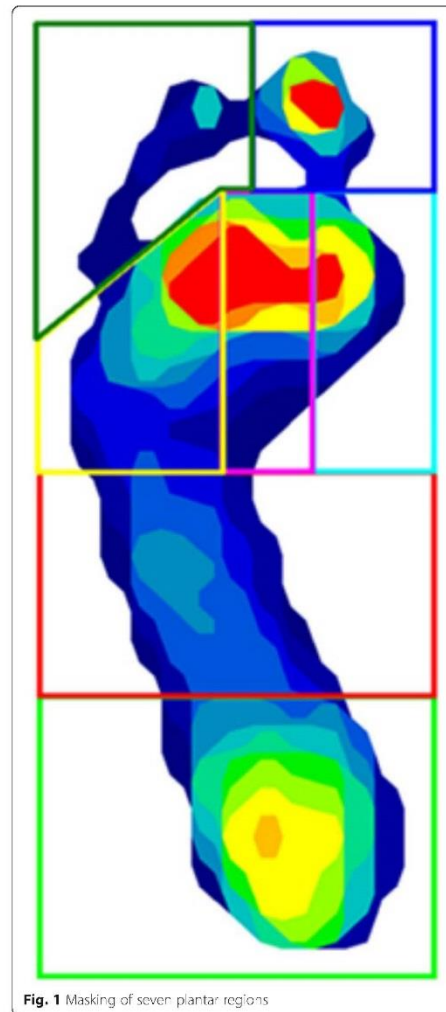


Fig. 1 Masking of seven plantar regions

models also accounted for the time-based repeated-measures using a scaled identity repeated covariance structure which assumed the repeated-measures were independent and shared a common variance. For peak plantar pressure and pressure time integrals, which were measured at seven sites on the plantar foot (forming a natural vector of related variables), in addition to the side- and time-based repeated measures, a heterogeneous

compound symmetry covariance structure was employed which allowed for separate variances for each site, as well as different covariances (but equal correlations) between each group of sites.

Adjustments for age group, ethnicity and BMI, which were entered into each model simultaneously, were considered only if their level of observed significance achieved at least 10 % on an F-test. These covariates were not expected to behave as confounders due to the frequency matching, but had the potential to decrease residual variance as possible independent variables. Potential covariates were also explored by reviewing box plots of random effects by covariate group.

Two comparisons were considered: gout vs. normouricemic control and asymptomatic hyperuricemic vs. normouricemic control, which were always tested separately. All hypothesis tests (excluding covariate testing) were carried out at a 5 % level of significance against two-sided alternatives. No adjustment for multiplicity was used, but all test-statistics (least-squares (L-S) means), their null distributions and their observed significance levels were reported. Data were analysed using IBM SPSS Statistics version 20 and proc-mixed in SAS version 9.3.

Sample size

The study was powered to test hypotheses regarding pre-planned analyses comparing normouricemic control parameters with asymptomatic hyperuricemic and gout parameters respectively. With respect to this analysis, the target figures of 21 participants in the gout group, 29 in the asymptomatic hyperuricemia group and 34 in the normouricemic control group are sufficient to detect unadjusted effect sizes on continuous outcomes of 0.7

and 0.8 (moderate to large) between control and each of the asymptomatic hyperuricemia and the gout group, respectively. The achieved sample size improved on these figures.

Results

Participant characteristics

A total of 87 participants were included: 24 with gout, 29 with asymptomatic hyperuricemia and 34 normouricemic controls. Demographic and clinical characteristics for the three groups are shown in Table 1. All participants were male with a mean (SD) age of 58 (15) years and predominantly of European ethnicity ($n = 68$, 81 %). The normouricemic control group had a significantly lower mean BMI compared to the gout ($P < 0.001$) and asymptomatic hyperuricemic ($P < 0.001$) groups. The normouricemic control group had a significantly lower prevalence of hypertension compared to the gout ($P = 0.001$) and asymptomatic hyperuricemic ($P = 0.023$) groups and a significantly lower prevalence of cardiovascular disease compared to the gout group ($P = 0.019$). Disease characteristics for the gout group are shown in Table 2. Participants with gout were found to have a mean (SD) disease duration of 17 (11) years, with 71 % ($n = 17$) having tophaceous gout and 96 % ($n = 23$) on urate lowering therapy.

The distribution of residuals from the linear models for all outcome measures demonstrated sufficient normality to carry out parametric testing. The effect of age group and BMI as covariates were included in the final models for all gait and plantar pressure parameters. Table 3 displays the mean estimates and inferential statistics for the spatial and temporal gait parameters.

Table 1 Demographic and medical characteristics. Data are presented as mean (SD) unless otherwise specified

Variable	Normouricemic control	Gout	Asymptomatic Hyperuricemia
N	34	24	29
Gender, male, n (%)	34 (100 %)	24 (100 %)	29 (100 %)
Age, years	58 (14)	58 (13)	58 (19)
Ethnicity, n (%)	European 30 (88 %) Māori 1 (3 %) Pacific 0 (0 %) Asian 3 (9 %)	European 14 (58 %) Māori 1 (4 %) Pacific 5 (21 %) Asian 4 (17 %)	European 24 (83 %) Māori 0 (0 %) Pacific 3 (10 %) Asian 2 (7 %)
BMI, kg/m^2	25.0 (2.9)	30.2 (4.0) [†]	29.3 (5.9) [†]
Diuretic use, n (%)	4 (12 %)	3 (12 %)	7 (24 %)
Hypertension, n (%)	9 (26 %)	17 (70 %) [†]	16 (55 %) [†]
Cardiovascular disease, n (%)	1 (3 %)	7 (29 %) [†]	5 (17 %)
Diabetes, n (%)	2 (6 %)	4 (17 %)	1 (3 %)
Loss of protective sensation, n (%)	Right 1 (3 %) Left 1 (3 %)	Right 4 (17 %) Left 6 (25 %)	Right 4 (14 %) Left 4 (14 %)
Serum urate	0.32 (0.06) mmol/L 5.3 (1.0) mg/dL	0.35 (0.10) mmol/L 5.8 (1.7) mg/dL	0.46 (0.05) mmol/L [†] 7.6 (0.8) mg/dL

[†]Significantly different from normouricemic control group ($p < 0.05$)

Table 2 Gout disease characteristics. Data are presented as mean (SD) unless otherwise specified

Variable	Gout
Disease duration, years	17 (11)
Age of onset, years	41 (18)
Number of flares in preceding 3 months	1.3 (1.4)
Presence of subcutaneous tophi, n (%)	17 (71 %)
Foot tophus count	1.9 (3.5)
Total tophus count	6.1 (8.7)
Colchicine use, n (%)	13 (54 %)
Urate lowering therapy, n (%)	23 (96 %)

Compared to normouricemic control participants, participants with gout had significantly increased step time ($P = 0.022$), increased stance time ($P = 0.022$) and decreased velocity ($P = 0.050$). Compared to normouricemic control participants, participants with asymptomatic hyperuricemia had significantly increased support base ($P = 0.002$), reduced swing time ($P = 0.019$), decreased single support time ($P = 0.020$), increased double support time ($P < 0.001$) and increased cadence ($P = 0.028$).

Table 4 displays the mean estimates and inferential statistics for peak plantar pressure. Compared to normouricemic control participants, participants with gout had significantly reduced pressure at the heel ($P = 0.012$) and hallux ($P = 0.036$) and increased pressure at the

Table 3 Spatial and temporal gait parameters. Results are presented adjusted for age and BMI

Parameter		Least-squares mean	Diff.	95 % CI		p
				Lower	Upper	
Step Length (cm)	Normouricemic control	0.61				
	Gout	0.57	0.03	-0.02	0.08	0.168
	Asymptomatic hyperuricemia	0.61	0.00	-0.05	0.05	0.985
Stride Length (cm)	Normouricemic control	1.21				
	Gout	1.14	0.07	-0.04	0.17	0.200
	Asymptomatic hyperuricemia	1.20	0.02	-0.08	0.11	0.763
Support Base (cm)	Normouricemic control	0.08				
	Gout	0.10	-0.02	-0.03	0.00	0.102
	Asymptomatic hyperuricemia	0.11	-0.03	-0.05	-0.01	0.002
Step Time (s)	Normouricemic control	0.60				
	Gout	0.64	-0.04	-0.07	-0.01	0.022
	Asymptomatic hyperuricemia	0.57	0.03	0.00	0.06	0.081
Swing Time (s)	Normouricemic control	0.46				
	Gout	0.47	-0.02	-0.04	0.00	0.104
	Asymptomatic hyperuricemia	0.43	0.03	0.01	0.05	0.019
Stance Time (s)	Normouricemic control	0.74				
	Gout	0.80	-0.06	-0.10	-0.01	0.022
	Asymptomatic hyperuricemia	0.72	0.03	-0.02	0.07	0.266
Single Support Time (s)	Normouricemic control	0.46				
	Gout	0.48	-0.02	-0.04	0.00	0.092
	Asymptomatic hyperuricemia	0.43	0.03	0.00	0.05	0.020
Double Support Time (s)	Normouricemic control	0.16				
	Gout	0.16	0.00	-0.04	0.04	0.857
	Asymptomatic hyperuricemia	0.26	-0.10	-0.14	-0.06	<0.001
Velocity (m/s)	Normouricemic control	1.03				
	Gout	0.91	0.11	0.00	0.23	0.050
	Asymptomatic hyperuricemia	1.07	-0.05	-0.15	0.06	0.379
Cadence (steps/min)	Normouricemic control	100.9				
	Gout	95.5	5.4	-0.7	11.5	0.080
	Asymptomatic hyperuricemia	107.3	-6.5	-12.2	-0.7	0.028

Table 4 Peak plantar pressure (kPa). Results are presented adjusted for age and BMI

Parameter		Least-squares mean	Diff.	95 % CI		p
				Lower	Upper	
Heel	Normouricemic control	294.3				
	Gout	268.2	-26.1	-46.6	-5.6	0.012
	Asymptomatic hyperuricemia	301.9	7.6	-12.4	27.5	0.456
Midfoot	Normouricemic control	95.4				
	Gout	130.8	35.4	15.5	55.3	<0.001
	Asymptomatic hyperuricemia	120.1	24.7	5.3	44.0	0.013
First Metatarsal	Normouricemic control	211.5				
	Gout	229.6	18.2	-5.2	41.5	0.127
	Asymptomatic hyperuricemia	239.7	28.3	5.6	50.9	0.015
Second Metatarsal	Normouricemic control	292.6				
	Gout	287.1	-5.5	-26.9	15.8	0.611
	Asymptomatic hyperuricemia	321.3	28.7	7.9	49.5	0.007
Third to Fifth Metatarsals	Normouricemic control	252.3				
	Gout	244.1	-8.2	-29.6	13.2	0.454
	Asymptomatic hyperuricemia	255.2	2.9	-17.9	23.7	0.785
Hallux	Normouricemic control	233.3				
	Gout	208.4	-24.9	-48.1	-1.6	0.036
	Asymptomatic hyperuricemia	241.9	8.6	-14.0	31.3	0.454
Lesser Toes	Normouricemic control	105.9				
	Gout	121.8	15.9	-2.8	34.6	0.096
	Asymptomatic hyperuricemia	107.2	1.4	-16.9	19.6	0.882

midfoot ($P < 0.001$). Compared to normouricemic control participants, participants with asymptomatic hyperuricemia had significantly increased pressure at the midfoot ($P = 0.013$), first metatarsal ($P = 0.015$) and second metatarsal ($P = 0.007$). Examples of typical plantar pressure patterns for normouricemic controls and people with asymptomatic hyperuricemia and gout are presented in Fig. 2. Table 5 displays the mean estimates and inferential statistics for the pressure time integrals. Compared to normouricemic control participants, participants with gout had significantly increased pressure time integrals at the midfoot ($P = 0.006$), but no other differences were observed. No differences were observed for pressure time integrals between the asymptomatic hyperuricemic participants and the normouricemic control participants ($P > 0.05$).

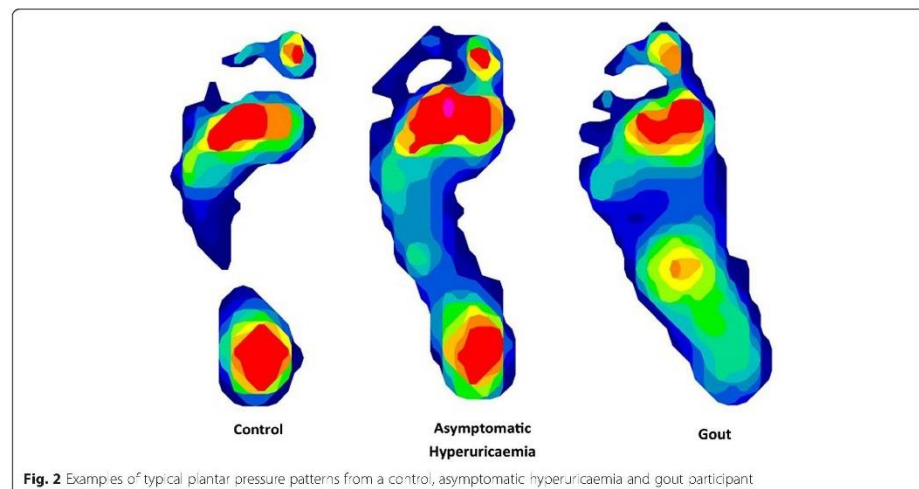
Discussion

Our study shows that people with gout and people with asymptomatic hyperuricemia both demonstrate variations in gait parameters and plantar pressure distribution during level barefoot walking when compared to normouricemic control participants.

During barefoot walking, people with gout walked slower with increased time spent in step and stance phases compared to the normouricemic control participants.

These findings are consistent with previous research assessing people with gout during both shod and barefoot walking [13, 16, 29]. Reduced gait speed is considered an important characteristic of impaired physical performance in daily activities in adults [30, 31] and has been associated with self-reported foot-related functional limitation in people with gout [16]. Functional gait limitations exhibited by people with gout may result from several factors including reduced lower limb muscle strength [15], loss of normal joint function [14] and acquired gait strategies developed in an attempt to reduce or prevent pain [13, 16].

The increased midfoot and reduced hallux plantar pressures observed in people with gout are also consistent with previous research in which participants were assessed during shod walking [13]. Previous studies have proposed that reduced peak pressure beneath the hallux in people with gout may reflect an attempt to offload pressure at the first metatarsophalangeal joint due to pain [13]. This is further emphasised in qualitative research in which people with gout report attempting to walk more cautiously with an adjusted foot position to relieve the big toe during acute flares [32]. Additionally, inefficient first metatarsophalangeal joint function, previously observed in people with gout [14], may further contribute to the propulsive gait strategies observed in the current study. In contrast

**Table 5** Pressure time integral (kPa·s). Results are presented adjusted for age and BMI

Parameter		Least-squares mean	Diff.	95 % CI		p
				Lower	Upper	
Heel	Normouricemic control	61.50				
	Gout	54.68	-6.82	-13.75	0.12	0.054
	Asymptomatic hyperuricemia	59.83	-1.67	-8.44	5.09	0.628
Midfoot	Normouricemic control	23.48				
	Gout	32.66	9.18	2.60	15.76	0.006
	Asymptomatic hyperuricemia	27.17	3.69	-2.72	10.10	0.260
First Metatarsal	Normouricemic control	56.24				
	Gout	54.24	-2.00	-9.50	5.50	0.601
	Asymptomatic hyperuricemia	60.25	4.01	-3.28	11.29	0.281
Second Metatarsal	Normouricemic control	77.61				
	Gout	70.66	-6.95	-14.49	0.59	0.071
	Asymptomatic hyperuricemia	82.15	4.54	-2.80	11.89	0.225
Third to Fifth Metatarsals	Normouricemic control	66.61				
	Gout	61.00	-5.61	-12.90	1.68	0.132
	Asymptomatic hyperuricemia	64.42	-2.18	-9.28	4.92	0.547
Hallux	Normouricemic control	40.66				
	Gout	34.75	-5.91	-13.11	1.29	0.108
	Asymptomatic hyperuricemia	41.74	1.08	-5.94	8.09	0.764
Lesser Toes	Normouricemic control	21.92				
	Gout	23.19	1.28	-4.94	7.49	0.687
	Asymptomatic hyperuricemia	20.48	-1.44	-7.50	4.62	0.642

to previous research assessing people with gout during shod walking [13], the current study also observed reduced heel pressures in participants with gout. This is consistent with the slower walking speed and may reflect an attempt to reduce impact at weight acceptance in the absence of protective footwear.

When compared to normouricemic healthy control participants, people with asymptomatic hyperuricemia also exhibited altered gait parameters. They demonstrated an increased base of support, spent more time in double support, less time in single support and swing phases and walked with increased cadence. An increased base of support and double support duration are generally interpreted as adaptations made to produce a more stable and safer gait in older adults who experience mobility limitations [33–35]. The increased cadence also observed in people with asymptomatic hyperuricemia may reflect an attempt to maintain gait velocity while retaining balance and stability. The findings from this study may provide laboratory-based biomechanical support of patient-reported outcomes in which people with asymptomatic hyperuricemia have reported reduced lower limb function and increased activity limitation compared to normouricemic control participants [14].

Participants with asymptomatic hyperuricemia also differed significantly from normouricemic control participants in terms of plantar pressure distribution in which increased pressures in the midfoot and medial metatarsals were observed. Increased midfoot pressures are characteristic of flatter foot postures [36, 37] which have been observed in people with asymptomatic hyperuricemia [14]. This increase in fore- and mid-foot plantar pressure is consistent with that observed in obese individuals [38–40]. However, it should be noted that the analyses in the current study were controlled for BMI. Furthermore, obesity tends to also present with higher toe and heel pressures [38, 40], which were not observed in the current study, suggesting that other factors are driving functional changes in people with asymptomatic hyperuricemia.

The findings from this study should be considered in light of several limitations. Firstly, the participants with gout were recruited from secondary care clinics and may not be representative of those with less severe gout seen in primary care. We did not match groups for BMI, and BMI was higher in the participants with gout and asymptomatic hyperuricemia, compared with the normouricemic control group. Importantly, BMI was included in the analysis models. We cannot exclude the possibility that BMI associated with hyperuricemia had additional unmeasured impact on foot function. Also, we did not exclude participants with diabetes or a loss of peripheral sensation, which may have influenced plantar pressure values in people with gout, reflecting the frequent comorbid conditions observed in clinical practice.

This study highlights the need for future research to provide insight into the dynamic function of the foot, which may assist in the development of interventions for pressure-related foot complaints in people with gout. The relationship between lower limb function during gait and specific locations of joint involvement in gout may also contribute to knowledge in this field of research. An understanding of the impact of comorbid conditions in people with asymptomatic hyperuricemia on functional limitation may also be of interest. The efficacy of non-pharmacological interventions, in combination with pharmacological treatment, aimed at improving lower limb function and patient-reported pain and disability in individuals with gout and asymptomatic hyperuricemia also warrants further investigation.

Conclusions

In summary, the findings from this study provide novel information regarding plantar pressure distribution during barefoot walking in individuals with gout. The findings are consistent with previous biomechanical research in gout in which patients walk slower with increased midfoot and decreased hallux peak pressures which are suggestive of propulsive and antalgic gait strategies. This is the first study to assess gait and plantar pressure characteristics in individuals with asymptomatic hyperuricemia. The results have shown that even in the absence of symptomatic gout, people with hyperuricemia exhibit altered gait strategies and plantar loading which may reflect their previously reported high levels of lower limb impairment and disability.

Ethics, consent and permissions

Ethical approval was obtained for this study and all participants provided written informed consent.

Abbreviation

BMI: body mass index.

Competing interests

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Authors' contributions

SS participated in the conception and design of the study, undertook data acquisition and participated in analysis and interpretation of the data. ND participated in the conception and design of the study and interpretation of the data. AV participated in the conception and design of the study and the analysis and interpretation of the data. KR participated in the conception and design of the study and interpretation of the data. All authors were involved in drafting and revising of the manuscript and read and approved the final version to be published.

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Author details

¹Department of Podiatry, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand. ²Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. ³Department of Rheumatology, Auckland District Health Board, P.O. Box 92189, Auckland, New Zealand. ⁴Department of Biostatistics & Epidemiology, Faculty of Health and Environmental Sciences, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand. ⁵Health Intelligence & Informatics, Ko Awatea, Counties Manukau Health, Private Bag 93311, Auckland 1640, New Zealand.

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Appendix 11. Ultrasound features of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: comparison with normouricaemic individuals

Original Article

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Ultrasound features of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: comparison with normouricaemic individuals

Sarah Stewart^a, BHSc (Hons.), corresponding author: 0064 21 176 7690;
sarah.stewart@aut.ac.nz

Nicola Dalbeth^{b,c}, MBChB, MD, FRACP

Alain C. Vandal^{d,e}, MA, PhD

Bruce Allen^f, MBChB, FRANZCR

Rhian Miranda^g, MBChB, FRANZCR

Keith Rome^a, BSc (Hons), FPodM, MSc, PhD

^aDepartment of Podiatry, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand Zealand.

^bFaculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.

^cDepartment of Rheumatology, Auckland District Health Board, P.O. Box 92189, Auckland, New Zealand.

^dDepartment of Biostatistics & Epidemiology, Faculty of Health and Environmental Sciences, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand.

^eHealth Intelligence & Informatics, Ko Awatea, Counties Manukau Health, Private Bag 93311, Auckland 1640, New Zealand.

^fHorizon Radiology, Auckland University of Technology North Shore Campus, AA Building, 90 Akoranga Drive, Northcote, Auckland, New Zealand.

^gAuckland City Hospital Radiology, Auckland District Health Board, P.O Box 92189, Auckland, New Zealand.

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Accepted Article

ABSTRACT

Objective. The first metatarsophalangeal joint (1MTPJ) is frequently affected in gout. The aim of this study was to identify ultrasound features of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia compared with normouricaemic controls.

Methods. Participants with gout (n=23), asymptomatic hyperuricaemia (n=29) and age- and sex-matched normouricaemic control participants (n=34) underwent a grey-scale and power Doppler ultrasound assessment of bilateral 1MTPJs by a single musculoskeletal radiologist. No participants had clinical evidence of joint inflammation at the time of scanning. The static images were later read by two musculoskeletal radiologists for the presence of the double contour sign, tophus, erosion, effusion, synovial hypertrophy, synovitis and cartilage thickness.

Results. Compared to normouricaemic control participants, participants with gout and participants with asymptomatic hyperuricaemia had more frequent double contour sign (odds ratio (OR) 3.91, $P=0.011$ and OR 3.81, $P=0.009$, respectively). Participants with gout also had more erosion (OR 10.13, $P=0.001$) and synovitis (OR 9.00, $P<0.001$) and had greater tophus and erosion diameters ($P=0.035$ and $P<0.001$, respectively). More severe erosion and synovitis grades and a less severe effusion grade were independently associated with gout compared with asymptomatic hyperuricaemia ($R^2 = 0.65$, $p < 0.001$).

Conclusion. Urate deposition, synovitis and bone erosion are common at the 1MTPJ in people with gout, even in the absence of flare. Although individuals with asymptomatic hyperuricaemia lack ultrasound features of inflammation or structural joint changes, they demonstrate a similar frequency of urate deposition.

SIGNIFICANCE AND INNOVATIONS

- Ultrasound features of urate deposition, soft tissue inflammation and bone erosion are common at the 1MTPJ in people with gout, despite the absence of clinical symptoms of acute arthritis.
- People with asymptomatic hyperuricemia lack features of inflammation and structural joint changes on ultrasound, but demonstrate a similar frequency of subclinical urate deposition.

Gout results from the formation and deposition of monosodium urate (MSU) crystals in structures of the musculoskeletal system in the presence of hyperuricaemia [1]. MSU crystals have the potential to initiate inflammatory responses resulting in painful episodes of arthritis [2, 3]. Although hyperuricaemia is required for the development of symptomatic gout, many individuals with hyperuricaemia are clinically asymptomatic [4].

Despite a similar level of urate concentration throughout the body, MSU crystal deposition and gout-related features have a certain propensity for the first metatarsophalangeal joint (1MTPJ). Most people with gout experience acute 1MTPJ arthritis at some point during the course of the disease [5]. Furthermore, people with gout report consistent 1MTPJ pain even after the resolution of clinical evidence of acute arthritis [6, 7]. The function of the 1MTPJ is also impaired in people with gout [8, 9]. It is unclear why gout has a predilection to affect the 1MTPJ, but may be associated with biomechanical loading or physical stress during the normal gait cycle [10, 11], or the co-occurrence of 1MTPJ osteoarthritis [12, 13].

High-resolution ultrasound has recently gained substantial interest in the assessment of individuals with gout due to its ability to visualise not only soft tissue inflammation (through its power Doppler capability) and joint damage, but also MSU crystal deposition. The ultrasound presence of MSU crystals along the surface of articular cartilage (the double contour sign) is the most well-recognised ultrasound feature in people with gout and has been included in the 2015 ACR/EULAR Gout Classification Criteria [14]. However, the double contour sign bears close resemblance to bone interface reflections frequently seen in healthy joints, which increases the rate of false-positives [15-17]. The double contour sign has also been observed in individuals with asymptomatic hyperuricaemia [18-21]. Despite this evidence of crystal deposition in people with asymptomatic hyperuricaemia, very few

studies have systematically assessed for features of soft tissue inflammation and joint damage in this population [20-22]. The aim of this study was to identify ultrasound features of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia by comparing them with healthy normouricaemic controls.

PATIENTS AND METHODS

Participants

Participants with gout were recruited from Auckland District Health Board, New Zealand. All participants fulfilled the 1977 preliminary American Rheumatism Association (ARA) classification criteria for gout [33]. Participants without gout were recruited from Auckland University of Technology (AUT) staff. Participants without gout underwent serum urate capillary testing on the day of the study using a Reflotron® Plus (Roche Diagnostics Ltd., New Zealand) and were stratified into either the asymptomatic hyperuricaemic group (serum urate ≥ 6.9 mg/dL) or the normouricaemic control group (serum urate < 6.9 mg/dL). The three groups were age- and sex-matched. Participants were excluded if they were aged under 20 years; had a history of other inflammatory arthritis; were experiencing acute arthritis at the time of the study; had foot and/or ankle surgery in the previous three months; had a history of 1MTPJ surgery; or lower limb amputation. Ethical approval for the study was obtained from the AUT Ethics Committee (13/100). All participants provided written informed consent prior to data collection. Demographic data were obtained from all participants including age, gender, ethnicity, body mass index (BMI), current medications and medical history. Additionally, gout disease characteristics were documented for participants with gout including disease duration, flare history and tophus presence.

Ultrasound image acquisition

The ultrasound examination was performed at the AUT Horizon Scanning Clinic by a single experienced musculoskeletal radiologist (BA) who was blinded to all clinical features including gout status and serum urate results. A Phillips iU22 diagnostic ultrasound machine (Bothell, Washington, USA) with a 10 MHz, 55mm linear array transducer was used. Bilateral 1MTPJs were scanned with participants positioned supine with legs extended. A water-based gel was applied to the skin to optimise transducer-skin contact and to provide an acoustic interface. The dorsal, medial and plantar aspects of each joint were scanned using a multi-planar technique in which transverse and longitudinal planes were imaged. Each joint was maximally dorsiflexed and plantarflexed by the radiologist during scanning to ensure direct visualisation of the articular surfaces. Each joint was scanned in B-mode grey scale and then using power Doppler. Power Doppler involved the use of a standardised pulse frequency of 400 to 500 Hz and low wall filters with the gain adjusted to a level just below the disappearance of the colour signs under the bony cortex.

Ultrasound image interpretation

Two musculoskeletal radiologists (BA and RM) who were blinded to all clinical features, including gout status and serum urate results, and to each other's scores, independently reviewed the static images for eight ultrasound features: the double contour sign, tophus, erosion, effusion, snowstorm appearance, synovial hypertrophy, synovitis and cartilage thickness (defined in Supplementary Table 1). In accordance with previous research and the

Outcome Measures in Rheumatology group (OMERACT) recommendations, cartilage-related features (double contour sign and cartilage thickness) were assessed at the dorsal aspect of the 1MTPJ [23]. All remaining ultrasound features were assessed at the dorsal, medial and plantar aspects. The double contour sign, tophus and the snowstorm appearance were recorded as either present or absent at the 1MTPJ, while erosions, joint effusion, synovial hypertrophy and synovitis were graded using a four-grade semi-quantitative scale (grade 0=absent; grade 1=mild; grade 2=moderate; grade 3=severe) [24, 25]. For erosions, joint effusion and synovial hypertrophy the feature was considered present if graded ≥ 2 [24]. Synovitis was considered present if graded as ≥ 1 [25]. Additionally, the largest diameter of the largest tophus and erosion in each 1MTPJ was recorded using digital callipers. Thickness of the articular cartilage covering the dorsal first metatarsal head was also assessed by measuring the longest diameter using digital callipers [26].

Statistical Analysis

Demographic and medical data were described as mean (SD) for continuous data and frequency (%) for categorical data. The inter-reader reliability for the presence of each ultrasound feature was assessed using Cohen's kappa (k) in which values of 0 to 0.2 were considered poor; 0.2 to 0.4 fair; 0.4 to 0.6 moderate; 0.6 to 0.8 good; and 0.8 to 1.0 excellent [27]. The inter-reader reliability for cartilage thickness, tophus and erosion diameters and the severity grading for erosions, effusion, synovial hypertrophy and synovitis was assessed using intra-class correlation coefficients (ICC) which were interpreted using the following benchmarks: ≥ 0.75 excellent reliability; 0.40 to 0.75 fair to good reliability; and < 0.40 poor reliability [28]. For the purpose of the inferential analyses, ultrasound feature

grades and thickness measures were calculated by taking the mean of the two readers. For dichotomous outcome measures (i.e. scored as either present or absent), the feature was considered present only if scored as present by both readers. For outcome measures assessed at dorsal, medial and plantar sites of the 1MTPJ, the maximum grade and thickness measures were used. Binary logistic regression was used to determine between-group differences for the presence of the double contour sign, tophus, erosion, effusion, snowstorm appearance, synovial hypertrophy and synovitis. Additionally, to determine between-group differences in grading of erosions, effusion, synovial hypertrophy and synovitis, multinomial regression with cumulative logit link was used. For the continuous outcome measures (tophus size, erosion size and cartilage thickness) linear regression models were used. All continuous outcomes were reviewed for normality using the residuals from a linear model with the participant group as the independent variable. All models accounted for repeated measures taken from right and left feet through using a mixed-models approach in which a participant-specific random effect and participant-nested random effect for foot-side were added to the model. This analysis produces results identical to an analysis of measures averaged for each foot-side that would allow for a between-foot-side correlation and also allows for any reweighting required due to missing values. Adjustments for gender, age, ethnicity and BMI, which were entered into each model simultaneously, were considered only if their level of observed significance achieved at least 10% on the relevant deviance test (Wald test for categorical data or F-test for continuous data). Potential covariates were also explored by reviewing box plots of random effects by covariate group. Two contrasts were considered: gout vs. control and asymptomatic hyperuricaemia vs. control, which were always tested separately. To determine which ultrasound features were associated with a diagnosis of gout or

asymptomatic hyperuricaemia, a stepwise linear regression was undertaken which included tophus presence, double contour sign presence, erosion grade, effusion grade, synovial hypertrophy grade and effusion grade. For the purpose of this analysis, ultrasound features were considered present in each gout and asymptomatic hyperuricaemic participant if present in at least one foot, while for graded variables, the highest grade from both feet was used. All hypothesis tests (excluding covariate testing) were carried out at a 5% level of significance against two-sided alternatives. No adjustment for multiplicity was used, but all test-statistics, their null distributions and their observed significance levels were reported. Data were analysed using IBM SPSS Statistics version 20 and R version 3.2.3.

Sample size calculation

A sample size calculation was undertaken based on adjusted pooling of data derived from studies available at the time of the study conception which had reported the prevalence of the double contour sign at the 1MTPJ in people with gout, asymptomatic hyperuricaemia and/or healthy controls [7, 19, 21, 29, 30]. From these studies the expected prevalence rates of the double contour sign were calculated as 20.6% in gout, 15.4% in asymptomatic hyperuricaemia and 0% in healthy controls. As both 1MTPs in each participant were to be scanned, the required sample size was divided by two and increased by a design effect factor of 1.1 (corresponding to a small intra-class correlation coefficient of approximately 0.1) to account for association in the probability of the double contour sign within a participant. Sample sizes were Familywise Error Rate-adjusted for multiplicity using a Bonferroni correction. The calculated sample sizes were 21 with gout, 29 with asymptomatic hyperuricaemia and 34 healthy controls. These sizes provide approximately 80% power to

detect a difference between asymptomatic hyperuricaemia and controls and 87% power to detect a difference between gout and controls at a Bonferroni-corrected significance level of 5% against two-sided alternatives.

RESULTS

All participants were men with a mean age of 58 years and predominantly of European ethnicity (Table 1). Participants with gout and asymptomatic hyperuricaemia had significantly higher BMI compared to the controls ($p < 0.05$). Participants with gout had a mean (SD) disease duration of 18 (11) years. Eighty-three percent had a history of 1MTPJ acute arthritis and 26% had clinical evidence of 1MTPJ tophi. Six (26%) of participants with gout were crystal-proven, with the remaining ($n = 17$, 74%) fulfilling the ARA clinical criteria.

Inter-reader reliability was moderate for the presence of the double contour sign, tophi, erosion, synovial hypertrophy and effusion, and good for synovitis (Table 2). The inter-reader reliability for the grading of features was fair to good for erosion, synovial hypertrophy and effusion and excellent for synovitis. Inter-reader reliability for tophus diameter and cartilage thickness was excellent and for erosion diameter was fair to good.

The descriptive statistics for the sonographic features used in the inferential analyses are displayed in Supplementary Table 2. The double contour sign was the most common ultrasound feature of urate deposition and was present in a similar number of 1MTPJs in both gout ($n=17$, 37%) and asymptomatic hyperuricaemia groups ($n=21$, 36%). However, only the gout group displayed tophus at the 1MTPJ ($n=6$, 13%). Synovitis was most common in the gout group ($n=20$, 44%) compared to the control ($n=5$, 7%) and asymptomatic

hyperuricaemic groups (n=2, 3%). However, joint effusion was observed more frequently in the asymptomatic hyperuricaemic group (n=13, 22%) compared to the gout group (n=4, 9%). Synovial hypertrophy was less commonly observed and seen in only 2% to 11% of joints. Bone erosion was present in 15 (33%) 1MTPs in the gout group and in only 2 (3%) and 1 (2%) of the control and asymptomatic hyperuricaemic groups, respectively. Cartilage thickness was similar across all groups. Supplementary Tables 3 to 5 show the descriptive statistics for ultrasound features present at each of the dorsal, medial and plantar aspects of the 1MTPJ, respectively. The snowstorm appearance was absent in all participants so was excluded from the inferential analysis.

The distribution of residuals from the linear models for all continuous outcome measures demonstrated sufficient normality to carry out parametric testing. All final models were unadjusted for covariates which did not achieve significance. The overall presence of ultrasound features at the 1MTP demonstrated significant between-group differences (Table 3). Compared to controls, both participants with gout and with asymptomatic hyperuricaemia had a greater odds of having the double contour sign (OR 3.9; $P=0.011$, OR 3.8; $P=0.009$, respectively). Compared to controls, participants with gout also had an increased odds of having 1MTPJ erosions (OR 10.13; $P=0.001$) and synovitis (OR 9.0; $P<0.001$). Participants with gout also had a non-significant trend towards an increased odds of having 1MTPJ tophus compared to controls (OR 5.08; $P=0.057$). No significant differences were observed for the presence of effusion or synovial hypertrophy between the groups.

Between-group differences were observed for the grading of ultrasound features at the 1MTPJ (Table 4). Compared to controls, participants with gout had a greater odds of having more severe erosions (OR 101.80; $P<0.001$), more severe synovial hypertrophy (OR 11.73;

$P=0.002$) and more severe synovitis (OR 47.51; $P=0.002$). Compared to controls, participants with asymptomatic hyperuricaemia had a greater odds of having more severe effusion (OR 3.08; $P=0.046$). Compared to controls, participants with gout demonstrated significantly greater tophus diameter ($P=0.035$) and erosion diameter ($P<0.001$) (Table 5).

Using stepwise linear regression analysis, a more severe erosion and synovitis grade and a less severe effusion grade were independently associated with gout compared with asymptomatic hyperuricaemia (model $R^2=0.65$, $p<0.001$) (Table 6).

DISCUSSION

This study has shown that ultrasound features of urate deposition, soft tissue inflammation and bone damage at the 1MTPJ are present in people with gout despite the absence of clinical symptoms of acute arthritis. In contrast, despite a similar frequency of subclinical urate deposition at the 1MTPJ, individuals with asymptomatic hyperuricemia do not demonstrate features of inflammation or bone erosion on ultrasound. However, they did display a similar frequency of urate deposition at the 1MTPJ.

This study has shown that the double contour sign is significantly more frequent in those with gout. Thirty-seven percent of participants with asymptomatic hyperuricaemia in the current study also demonstrated the double contour sign on ultrasound which is consistent with existing research [18-21] and emphasises the extent of subclinical crystal deposition in individuals with asymptomatic hyperuricaemia.

The frequency of the double contour sign in the patients with gout was similar to those with asymptomatic hyperuricaemia (37% vs. 36%). Although 74% of participants with gout had

clinically-evident tophi and 63% reported recent episodes of acute arthritis, the relatively low frequency of the double contour sign may reflect the use of urate lowering therapy and the mean serum urate level below the treatment target (< 6 mg/dl). Sonographic evidence of urate deposition including both the double contour sign and tophus have been reported to decrease or disappear following urate lowering therapy [31, 32]. This may also explain the lower frequency of tophus (13%) at the 1MTP in our participants with gout compared to previous sonographic investigations which have observed a tophus frequency of 50% to 100% at the 1MTP [7, 10, 30-35].

In the current study, both tophi and bone erosion were noted more frequently at the medial metatarsal head (Supplementary Tables 3 to 5). This erosion pattern is consistent with previous studies in which 46% to 92% of observed 1MTP erosions were located on the medial metatarsal head [7, 36]. This distribution of tophaceous material reflects the strong association between the urate crystal and inflammatory soft tissue components of tophi and the presence of bone erosions [37-39].

Our multiple regression analysis suggests that features other than crystal deposition, specifically synovitis and bone erosion, may be useful in differentiating gout from asymptomatic hyperuricaemia. The greater frequency and increased severity of synovitis in participants with gout (who did not have a gout flare at the time of scanning) suggests that gout is a disease of chronic inflammation with a persistent subclinical immune response to MSU crystals. Individuals with asymptomatic hyperuricaemia, despite demonstrating similar frequency of double contour sign at the 1MTPJ, did not exhibit features of synovitis, indicating that the tissue response to MSU crystals in gout is not present in those with asymptomatic hyperuricaemia. Our data are consistent with recent imaging studies using

both ultrasound and MRI which have reported synovial pannus in 87.5% [40] and synovitis in up to 95.8% of people with intercritical gout [41, 42]. Together, these data suggest that synovial inflammation is a common finding in patients with gout, even in the absence of clinically apparent flares. The relevance of synovial inflammation in predicting future gout flares or joint damage is currently unknown.

Moderate inter-reader reliability was demonstrated in this study for the presence of the double contour sign ($k = 0.49$) which is in contrast to the majority of previous ultrasound studies which report good to excellent reliability ($k = 0.68$ to 0.98) [18, 30, 43-47]. There are several factors which may have influenced the reliability of this sign in the current study.

Firstly, there is a strong resemblance between the double contour sign and cartilage interface sign, with the latter often appearing as a result of increased reflectivity at a 90° insonation angle, and the former appearing dependant of the insonation angle. Dynamic conformation of the double contour sign could not be performed in the current study as the presence of the sonographic features were assessed from static images. Secondly, the presence of even minimal joint effusion, which was observed frequently in 1MTPJs in the current study, can also accentuate the cartilage interface sign due to enhanced reflectivity [15]. Thin or damaged cartilage, such as that seen in osteoarthritis (which is prevalent at the 1MTPJ) [48], may also impair visualisation of the double contour sign [15]. Importantly, in our analyses, all features were considered present only if both musculoskeletal radiologists reported the feature as present.

The findings from this study should be considered in light of several limitations. Firstly, participants with gout were recruited from secondary-care clinics and had longstanding disease, and it is possible that the findings are not generalizable to people with gout treated

in primary-care. It should also be noted that this study was undertaken prior to publication of the recent 2015 ACR/EULAR classification criteria for gout [14] and the majority of the participants with gout had not undergone microscopic assessment for urate crystals and were classified based on clinical criteria which has limited specificity [49]. Also, the participants with normouricaemia were included based on a single measure of serum urate on the day of the study. Although major diurnal variation in urate is uncommon [50], mild variation in serum urate can occur. It is possible that the single measurement may have misclassified some participants with asymptomatic hyperuricaemia and normouricaemia groups, and that multiple testing of serum urate over a longer time period would have increased the accuracy of this inclusion criterion. Furthermore, participants with asymptomatic hyperuricemia had relatively low hyperuricaemia and it is unclear whether the results would have differed if they had higher urate levels. The cross-sectional nature of study does not allow us to determine the prognostic relevance of asymptomatic ultrasound findings. Future studies may consider the relationship between ultrasound features suggestive of gouty arthritis and clinically-assessed structural and functional characteristics of the 1MTPJ. A longitudinal follow-up to determine the predictive appeal of ultrasound in the development of symptomatic gout in those with asymptomatic hyperuricaemia may also be of value.

In conclusion, this study has shown that compared to normouricaemic controls, ultrasound features of urate deposition, soft tissue inflammation and bone erosion are common at the 1MTPJ in people with gout, despite the absence of clinical symptoms of acute arthritis. Furthermore, although individuals with asymptomatic hyperuricemia lack features of inflammation or structural joint changes on ultrasound, they demonstrate a similar frequency of subclinical urate deposition. Features other than crystal deposition, specifically

synovitis and bone erosion, may be useful in differentiating gout from asymptomatic hyperuricaemia. These data support the concept that gout is a disease of chronic inflammation with a persistent subclinical immune response to the presence of MSU crystals within joints.

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TABLES

Table 1. Demographic characteristics.

Variable	Control	Gout	Asymptomatic hyperuricaemia
N	34	23	29
Gender, male, n (%)	34 (100)	23 (100)	29 (100)
Age, years	58 (14)	58 (14)	58 (19)
	European 30 (88)	European 14	European 24 (83)
	Maori 1 (3)	(61)	Maori 0 (0)
Ethnicity, n (%)	Pacific 0 (0)	Maori 1 (4)	Pacific 3 (10)
	Asian 3 (9)	Pacific 4 (17)	Asian 2 (7)
		Asian 4 (17)	
BMI, kg/m ²	25.0 (2.9)	30.8 (3.8) [†]	29.3 (5.9) [†]
Diuretic use, n (%)	4 (12)	3 (13)	7 (24)
NSAID use, n (%)	7 (21)	14 (61) [†]	11 (38)
Prednisone use, n (%)	0 (0)	5 (22)	0 (0)
Hypertension, n (%)	9 (26)	16 (70) [†]	16 (55) [†]
Cardiovascular disease, n (%)	1 (3)	6 (26) [†]	5 (17)
Diabetes, n (%)	2 (6)	4 (17)	1 (3)
Serum urate, mg/dl	5.4 (1.0)	5.9 (1.7)	7.7 (0.8) [†]
Serum urate, mg/dl, range	3.4 – 6.7	4.0 – 10.6	6.9 – 10.6
Highest ever serum urate,	-	10.1 (2.2)	-

25

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Ultrasound of the 1MTPJ in gout and AH

mg/dl			
1MTP tenderness, n (%)	1 (3)	6 (26)	1 (3)
1MTP swelling, n (%)	0 (0)	1 (4)	0 (0)
Tender joint count (/68)	0.6 (1.2)	2.6 (6.4) [†]	1.5 (1.9)
Swollen joint count (/66)	0.0 (0.0)	0.9 (1.2) [†]	0.2 (0.7)
Crystal-proven gout, n (%)	-	6 (26)	-
Disease duration, years	-	18 (11)	-
Age of onset, years	-	40 (19)	-
Acute flare in preceding 3 months, n (%)	-	15 (63)	-
Number of acute flares in preceding 3 months	-	1.4 (1.4)	-
1MTP flares in preceding 3 months, n (%)	-	6 (26)	-
History of 1MTP flares, n (%)	-	19 (83)	-
Presence of subcutaneous tophi, n (%)	-	17 (74)	-
Presence of 1MTP tophi, n (%)	-	6 (26)	-
Colchicine use, n (%)	-	13 (57)	-
Urate lowering therapy [‡] , n (%)	-	22 (96)	-
Allopurinol use, n (%)	-	18 (79)	-
Probenecid use, n (%)	-	3 (13)	-
Benzbromarone use, n (%)	-	2 (9)	-

Febuxostat use, n (%) - 2 (9) -

Values presented as mean (SD) unless otherwise indicated. [†]Significantly different from control group ($p < 0.05$). [‡]3 patients were taking >1 urate lowering agent. BMI = body mass index; NSAID = non-steroidal anti-inflammatory drugs.

Table 2. Inter-reader reliability of ultrasound features at the 1MTPJ[†]

	N (%)		Percent agreement	k	95% CI for k	
	Reader 1	Reader 2			Lower	Upper
Double contour sign presence	87 (51)	51 (30)	74.4%	0.49	0.37	0.61
Tophus presence	15 (9)	7 (4)	94.2%	0.52	0.26	0.78
Erosion presence	10 (6)	19 (11)	92.4%	0.52	0.29	0.74
Effusion presence	31 (18)	21 (12)	84.9%	0.42	0.23	0.60
Snowstorm presence	2 (1)	0 (0)	98.8%	-	-	-
Synovial hypertrophy presence	15 (9)	14 (8)	93.6%	0.59	0.36	0.81
Synovitis presence	22 (13)	21 (12)	92.4%	0.66	0.48	0.83
	Mean (SD)			ICC _{3,1}	95% CI for ICC	
	Reader 1	Reader 2			Lower	Upper
Tophus diameter, mm	0.8 (3.3)	0.5 (3.1)		0.86	0.81	0.89
Erosion grade	0.4 (0.6)	0.4 (0.7)		0.72	0.64	0.79
Erosion diameter, mm	1.2 (2.3)	0.7 (1.7)		0.60	0.50	0.69
Effusion grade	0.8 (0.8)	0.5 (0.7)		0.50	0.38	0.60

Ultrasound of the 1MTPJ in gout and AH

Synovial hypertrophy grade	0.6 (0.7)	0.2 (0.7)	0.53	0.41	0.63
Synovitis grade	0.2 (0.5)	0.2 (0.5)	0.81	0.75	0.85
Cartilage thickness, mm [†]	0.64 (0.20)	0.64 (0.19)	0.81	0.75	0.86

[†]n=172 joints. k = kappa statistic; ICC = Intra-class Correlation Coefficient; CI = Confidence Interval.

Table 3. Odds ratios for the presence of ultrasound features at the 1MTPJ

		N (%)	Odds Ratio [†]	95% CI for OR		p
				Lower	Upper	
Double Contour Sign	Control	9 (13%)				
	Gout	17 (37%)	3.91	1.37	11.20	0.011
	AH	21 (36%)	3.81	1.41	10.36	0.009
Tophus	Control	0 (0%)				
	Gout	6 (13%)	5.08	0.96	27.08	0.057
	AH	0 (0%)	1.00	0.12	8.26	1.000
Erosion [‡]	Control	2 (3%)				
	Gout	15 (33%)	10.13	2.75	37.28	0.001
	AH	1 (2%)	0.83	0.14	4.88	0.828
Effusion [‡]	Control	12 (18%)				
	Gout	4 (9%)	0.45	0.13	1.61	0.217
	AH	13 (22%)	1.34	0.51	3.54	0.548
Synovial hypertrophy [‡]	Control	0 (0%)				
	Gout	1 (2%)	3.25	0.67	15.73	0.142

Ultrasound of the 1MTPJ in gout and AH

	AH	2 (3%)	1.72	0.32	9.13	0.523
	Control	5 (7%)				
Synovitis [‡]	Gout	20 (44%)	9.00	3.10	26.08	<0.001
	AH	2 (3%)	0.60	0.14	2.69	0.505

[†]Reference category = control group; All odds ratios are presented unadjusted for

covariates. [‡]The overall presence of erosion, effusion and synovial hypertrophy is based

on a grade of ≥ 2 ; the overall presence of synovitis is based on a grade of ≥ 1 . CI =

Confidence Interval; OR = Odds Ratio.

Table 4. Odds ratios for grading of ultrasound features at the 1MTPJ

		Odds Ratio [†]	95% CI for OR		<i>p</i>
			Lower	Upper	
Erosion grade	Gout	101.80	16.56	625.68	<0.001
	AH	1.81	0.49	6.68	0.371
Effusion grade	Gout	0.51	0.15	1.65	0.260
	AH	3.08	1.02	9.31	0.046
Synovial hypertrophy grade	Gout	11.73	2.48	55.48	0.002
	AH	1.54	0.36	6.52	0.558
Synovitis grade	Gout	47.51	4.29	526.07	0.002
	AH	0.46	0.05	4.60	0.511

[†]Reference category = control group. The odds ratio represents the odds of the diagnostic group moving up one grade, compared to the control group moving up one grade. All

odds ratios are presented unadjusted for covariates. CI = Confidence Interval; OR = Odds

Ratio

Table 5. Linear regression for size and thickness of ultrasound features at the 1MTPJ

		Least-squares mean ^a	Diff.	95% CI for Diff.		p
				Lower	Upper	
Tophus diameter, mm	Control	0.00				
	Gout	1.68	1.68	0.12	0.32	0.035
	AH	0.00	0.00	-1.46	1.46	1.000
Erosion diameter, mm	Control	0.05				
	Gout	1.55	1.50	0.84	2.16	<0.001
	AH	0.05	-0.00	-0.62	0.61	0.989
Cartilage thickness average, mm	Control	0.66				
	Gout	0.64	-0.02	-0.08	0.03	0.364
	AH	0.62	-0.01	-0.06	0.04	0.773

^aMean estimates are presented unadjusted for covariates. Diff. = Difference in least-squares mean; CI = Confidence Interval.

Table 6. Stepwise linear regression analysis of ultrasound features independently associated with gout compared with asymptomatic hyperuricaemia

Variables included	Standardised β	Partial R^2 change	p	Model	Variables excluded
Erosion grade	0.59	0.49	< 0.001	$R^2 = 0.65$;	Tophus; double
Synovitis grade	0.39	0.16	< 0.001	$F = 32.22$;	contour sign;
Effusion grade	-0.26	0.07	0.002	$P < 0.001$	synovial hypertrophy grade.