The effect of tophaceous gout on the structure and function of the Achilles tendon

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MPod, PGDip (Sports Medicine),

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2015

School of Clinical Sciences

Primary Supervisor: Professor Keith Rome

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ETHICAL APPROVAL

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11 June 2013

Keith Rome
Faculty of Health and Environmental Sciences

Dear Keith

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Thank you for providing evidence as requested, which satisfies the points raised by the AUT University Ethics Committee (AUTEC).

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- A brief annual progress report using form EA2, which is available online throughhttp://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 throughhttp://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 AUTEC is notified of any adverse events or if the research does not commence. AUTEC 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.

AUTEC 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,

Madeline Banda
Acting Executive Secretary
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Institutional Approval

Keith Rome
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Dear Keith

RE: Research project A+ 5891 (Aut 13/100) The effect of chronic gouty arthritis on the structure and function of the Achilles tendon.

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Yours sincerely

On behalf of the ADHB Research Review Committee
Dr Mary-Anne Woodnorth
Manager, Research
ADHB

ABSTRACT

Gout is the most prevalent form of inflammatory arthritis in men older than forty years of age and has a significant functional and social impact. Tophaceous gout is the most progressed phase of gout and is associated with foot pain, impairment and disability in joints (first metatarsophalangeal joint) and soft tissue (Achilles tendon). The structural characteristics of the Achilles tendon (AT) enables it to withstand the large forces imposed during the gait cycle. Any alteration to the internal structure of the AT may affect the ability of the gastro-soleus complex to generate force, transfer muscle power and absorb energy during the gait cycle. Current research has reported tophus deposition in the AT. However, there is limited information on the impact of tophus on the AT structure and the impact of gait characteristics in people with gout. Therefore, the aims of this thesis were to investigate the prevalence of ultrasound (US) lesions in the AT and the gait parameters of walking velocity, ankle power and ankle range of motion in participants with tophaceous gout compared to age and sex-matched control participants. Two systematic reviews with meta-analysis were also undertaken.

The first systematic review was conducted on US lesions in the AT of people with inflammatory arthritis. The results demonstrated that the majority of studies reporting US lesions were in spondyloarthropathies, but limited data relating to tophaceous gout. The meta-analysis demonstrated the AT was significantly thicker in people with spondyloarthropathies, erosions more prevalent in both spondyloarthropathies and rheumatoid arthritis, but enthesophyte formation was not significantly more prevalent in participants with spondyloarthropathies when compared to control participants. The review highlighted inconsistencies in both defining and scoring US lesions indicative of inflammation and structural damage in people with inflammatory arthritis.

The second systematic review evaluated gait parameters in inflammatory arthritis. The findings from the review identified the most commonly assessed gait parameters used to define gait adaptation in inflammatory arthritis, with the majority of studies focusing on gait adaptation in rheumatoid arthritis. The meta-analysis demonstrated significant differences in walking velocity, cadence, stride length, double support time, ankle power and forefoot plantar pressure, but no significant differences in ankle range of motion when participants with inflammatory arthritis were compared to controls. The review

highlighted the wide range of methodologies used to acquire spatiotemporal, kinetic and plantar pressure gait parameters.

Using a case-control study experimental design, AT structure was investigated using grey-scale and power Doppler US imaging. Gait function was evaluated using three-dimensional (3D) gait analysis. Twenty four participants with tophaceous gout with a mean (SD) age of 62 (12) years old were matched with 24 age and sex-matched control participants, with a mean (SD) age of 62 (12) years old. The majority of the participants were middle aged males (92%), predominately of European ethnicity (77%). The control participants demonstrated a significantly higher number of Europeans ($p \leq 0.01$). Participants with gout had higher mean BMI compared to controls ($p < 0.01$). Participants with gout had well established disease of 17 years, with a mean serum urate level of 0.37 mmol/L. Comorbidities that included hypertension, cardiovascular disease and type 2 diabetes were found in approximately one-third of participants with tophaceous gout. The case participants with gout demonstrated had a higher prevalence of hypertension ($p < 0.01$) and cardiovascular disease ($p = 0.03$) compared to the control participants. The majority of participants with gout were prescribed allopurinol (n = 20, 83%).

In order to investigate specific regions of the AT, the tendon was divided into three zones (insertion, pre-insertion and proximal to mid-section). US lesions were scored using a semi-qualitative scoring system. The scoring system assessed the tophus characteristics, tendon echogenicity, tendon vascularity, tendon morphology, enthesis, bursal morphology and bone profile using binary, continuous measurement and semi-qualitative scale. As lesions were nested within participants, a general estimating equation approach was used to analyse data. The results demonstrated participants with tophaceous gout showed a significantly higher prevalence of tophus deposition ($p < 0.01$), intratendinous hyperechoic spots ($p < 0.01$) and intratendinous inflammation ($p < 0.01$) throughout all zones of the AT. There was minimal data reporting hypoechoic areas with loss of fibrillar echotexture in the AT of both the case and control participants. These findings suggest that tophus deposition and associated inflammation in the AT may be a clinically silent process, with containment of inflammation.

In the second case-control study, each participant undertook 3D gait analysis with passive lightweight markers used to track and model the lower limb in accordance with the

Oxford Foot Model. Surface electromyography signals were recorded during gait from the medial gastrocnemius, lateral gastrocnemius and tibialis anterior of both limbs. Gait measures included walking velocity, double limb support time, first metatarsophalangeal joint motion, peak ankle joint force, ankle moment and power. When compared to control participants, participants with tophaceous gout demonstrated significantly decreased walking velocity ($p < 0.01$), with a mean difference of -0.20 m/s, and an increased double limb support time ($p < 0.01$), with a mean difference of 0.05s. Peak ankle joint power was reduced with a mean difference of -0.31 W/Kg ($p = 0.01$), but peak ankle joint force, difference of 15.6N ($p = 0.25$), and peak ankle joint moments, with a mean difference of 0.06 Nm/Kg ($p = 0.16$), were not significantly different between the two groups. Medial gastrocnemius ($p = 0.04$), with a mean difference of 2.7 %MVIC/s, and lateral gastrocnemius ($p < 0.01$), mean difference of 6.2 %MVIC/s muscle activity was increased in participants with tophaceous gout. Reductions in walking velocity in the cases were associated with alterations in cadence, step length, double support time and gait cycle time. Reductions in walking velocity were also associated with decreased ankle joint angular velocity in the people with gout. With the ankle joint moments preserved and not significantly different between the two groups, the reductions in ankle joint angular velocity explain the reduced ankle joint power output. These findings highlight the importance of walking velocity and imply that walking velocity may be the central mechanism by which the body modulates gait adaptation.

The findings of the thesis are clinically relevant. When managing AT pathologies in people with tophaceous gout both structure and function must be considered. Structural integrity of the AT must be determined and the degree of gait adaptation must also be quantified to provide the clinician with a good overall perspective of functional ability. The findings are also relevant for the design of future clinical trials. The investigation of mechanical properties of the AT in people with gout is warranted. With baseline gait adaptations quantified, the impact of non-surgical interventions such as footwear, foot orthoses and strength training must also be considered for their ability to alter the process of gait adaptation in people with gout.

THESIS OUTLINE

Chapter 1 - Background to the problem, the significance of the study, provides the objectives and hypotheses for the thesis and provides an introduction to the core concepts covered in the thesis.

Chapter 2 - A systematic review of ultrasound lesions of the AT in inflammatory arthritis.

Chapter 3 - A systematic review assessing the gait characteristics in inflammatory arthritis.

Chapter 4 - The methodology of the two experimental studies.

Chapter 5 - The results from the two experimental studies.

Chapter 6 - Main discussion, strengths, limitations, and directions for future research.

Chapter 7 - The implications for practice, future research and overall conclusion.

PUBLICATIONS AND DISSEMINATIONS

1. Carroll, M., Parmar, P., Dalbeth, N., Boocock, M., Rome, K (in press). The assessment of lesions of the Achilles tendon by ultrasound imaging in inflammatory arthritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2015;45(1):103-14.

2. Carroll, M., Dalbeth, N., Boocock, M., Rome, K (accepted manuscript). Gait characteristics associated with the foot and ankle in inflammatory arthritis: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2015;16(1):134.

3. Carroll, M., Parmar, P., Dalbeth, N., Boocock, M., Rome, K. Gait characteristics associated with the foot and ankle in inflammatory arthritis: a systematic review and meta-analysis. Poster presentation, 2015 Australasian Podiatry Conference, Gold Coast, Australia 6-8/05/2015.

4. Carroll, M., Dalbeth, N., Boocock, M., Rome, K. The assessment of lesions of the Achilles tendon by ultrasound imaging in inflammatory arthritis: a systematic review and meta-analysis. Poster presentation, 2015 Australasian Podiatry Conference, Gold Coast, Australia 6-8/05/2015.

   This poster was awarded ‘Best Conference Poster” at the 2015 Australasian Podiatry Conference, Gold Coast, Australia.

THESIS ABBREVIATIONS

1MTP	First metatarsophalangeal joint
2MTP	Second metatarsophalangeal joint
3D	Three-dimensional
5MTP	Fifth metatarsophalangeal joint
ACR	American College of Rheumatology
ADHB	Auckland District Health Board
ANOVA	Analysis of variance
ARA	American Rheumatism Association
AS	Ankylosing spondylitis
AT	Achilles tendon
BMI	Body mass index
CI	Confidence interval
CPPD	Calcium pyrophosphate deposition
CSA	Cross-sectional area
CVD	Cardiovascular disease
DECT	Dual Energy Computed Tomography
DTS	Desktop Direct Transmission System
EMG	Electromyography
ES	Effect size
GEE	General estimating equation
GRF	Ground reaction force
GS	Grey-scale
GUESS	Glasgow ultrasound enthesis scoring system
HAQ-II	Health assessment questionnaire
Hz	Hertz
ICC	Intraclass correlation coefficients
IQR	Inter quartile range
LFIS	Leeds foot impact scale
LLTQ	Lower limb task questionnaire
MHz	Mega hertz
mm	Millimetres
MRI	Magnetic resonance imaging

MSU	Monosodium urate
MVIC	Maximum voluntary isometric contraction
NETs	Neutrophil extracellular traps
NSAIDs	Non-steroidal anti-inflammatory drugs
OMERACT	Outcome measures in rheumatology clinical trials
OR	Odds ratio
PD	Power Doppler
PMR	Polymyalgia rheumatica
PROM	Patient reported outcome measure
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
ROM	Range of motion
SD	Standard deviation
SEM	Standardised error of measurement
SENIAM	Surface electromyography for the non-invasive assessment of muscles
SLE	Systemic lupus erythematous
SMD	Standardised mean difference
SpA	Spondyloarthropathy
SSc	Systemic sclerosis
US	Ultrasound
VAS	Visual analogue scale

CHAPTER 1:

Introduction

1.1. Background to the problem

Gout is the most prevalent form of inflammatory arthritis in men older than forty years of age and has significant functional, social and financial impacts (1, 2). Gout has a special context within New Zealand society, with South Auckland being described as the 'Gout Capital' of the world due to the high prevalence within the male Māori and Pacific Island population (3). The high and increasing hospital admission rates, combined with the burden of co-morbidities is a significant current and future issue for the New Zealand health care system (4).

Gout is a disorder of purine metabolism, the biological precursor being elevated serum urate levels (hyperuricaemia). Hyperuricaemia is defined as a serum urate concentration greater than 0.42 mmol/L and can lead to the deposition of monosodium urate (MSU) crystals within articular and periarticular structures (5-7). During the course of the disease the presence of MSU crystals can clinically manifest as acute inflammatory arthritis, tophus formation, joint damage and altered tendon and ligament structure and function (8).

Clinically apparent gout is characterised by three overlapping phases, (i) acute arthritis with (ii) asymptomatic intervals (inter-critical gout) and (iii) chronic gouty arthritis or tophaceous gout (9) that may emerge over a period of 1 to 4 decades (10). Tophaceous gout is the most progressed phase of gout and is associated with pain, inflammation, joint deformity and/or joint destruction, and tophus deposition in joints and subcutaneous tissues (11). Tophus formation has been identified as a risk factor for development of musculoskeletal disability, implicated in the pathogenesis of joint damage, the mechanical obstruction of joint movement and is linked to a reduction in quality of life (12-14). Tophi are defined as granulomatous lesions surrounding a core of MSU crystals, encased by dense connective tissue and represent a complex and organised chronic inflammatory response to MSU crystals (15). Tophi have a tendency to deposit in the enthesis and body of extensor tendons such as the Achilles tendon (AT) (16). A recent study has highlighted the significance of the AT as a site for tophus deposition in a cohort of 92 participants with tophaceous gout, with urate deposition recorded in 39% of all ATs (17).

Tophaceous gout is associated with the development of musculoskeletal foot pain, impairment and disability and has been associated with reduced walking velocity (18). However, overall gait strategy has not been defined in tophaceous gout, with only one study assessing spatiotemporal (time and distance) and plantar pressure parameters, but not kinematic or kinetic gait parameters (18). Rome (18) speculated that alterations in gait strategy may result from a pain avoidance strategy and ultimately lead to weakness in the ankle plantar flexors.

The AT is the strongest tendon in the human body and is subjected to large stresses (up to 12.5 times bodyweight) during strenuous activities such as running and jumping (19). The AT is a conjoined tendon of the two heads of the gastrocnemius and with the soleus muscle; this is often referred to as the 'gastro-soleus complex' (20). The primary role of the gastro-soleus complex is plantarflexion of the foot and ankle during gait (21). Prime activity occurs from approximately 10-50% of the cycle with peak activity at approximately 40% (22, 23).

Ultrasound (US) imaging provides a non-invasive technique to aid diagnosis, monitor disease progression and provide insights into pathological changes in musculoskeletal disease (24). US imaging is able to detect various specific and non-specific US lesions in gout. Non-specific features include those findings that may be common amongst other forms of inflammatory arthritis such as: joint effusion, synovitis, hypervascularisation, bony erosion and proliferative new bone formation (25). To date there is limited data relating to the structural properties of the AT in people with gout.

The presence of tophaceous deposits within the AT may have significant effects on the internal structure leading to: impaired tendon healing, reduced tensile strength and ultimately reduced functional ability. Impaired healing of the AT results in the breakdown of two key functions: the ability to absorb load and the ability to transmit load (26). Alteration to AT function may modify coordinated movements of the hip, knee and ankle joints during gait, leading to functional adaptation such as reduced ankle power and reduced ankle range of motion (27). However, no research to date has investigated the gait parameters of ankle power and ankle range of motion in people with tophaceous gout.

1.2. Significance of the study

Tophaceous gout places a significant economic burden on the health care system and has a direct effect on ability to work, work productivity and a reduced quality of life (28-31). Impaired quality of life in patients with tophaceous gout is largely associated with clinical and musculoskeletal co-morbidity rather than the presence of gout itself (31). A high percentage of patients with tophaceous gout develops severe musculoskeletal deformities that may lead to functional disability (13, 32, 33).

The mechanical structure of the AT enables it to withstand the large forces imposed during the gait cycle. Any alteration to the internal structure of the tendon may affect the ability of the gastro-soleus complex to generate force, transfer muscle power and absorb energy during the gait cycle (34). The mechanical efficacy and structure of the AT may be significantly affected by the clinical manifestations of tophaceous gout (35). The presence of tophi within the tendon may alter the collagen structure and prolong inflammatory responses, leading to the development of a mechanically weakened AT. Consequently, adaptations to gait strategy such as reduced walking velocity, reduced ankle range of motion and reduced ankle power may occur.

There is a limited body of research investigating specific biomechanical function in the lower limb and foot in tophaceous gout (13, 18). Based on the current data it is unclear what adaptations occur to gait strategy in people with tophaceous gout. This necessitates research to investigate clinical disease activity in the AT, assessment of the structural alterations in the AT and examination of gait strategy in people with tophaceous gout. The current research will aid in the understanding of potential pathways leading from underlying disease process to localised impairment and enable the development of disease-stage targeted treatment.

1.3. Objectives of the thesis

1. Systematically review the literature and where appropriate conduct meta-analysis pertaining to:
   (a) Lesions of the AT assessed by US imaging.
   (b) Gait characteristics associated with AT in inflammatory arthritis.

2. To assess US lesions of the AT using US imaging between participants with tophaceous gout and age and sex matched control participants.

3. To investigate the differences in the kinematic, kinetic and spatiotemporal gait parameters between participants with tophaceous gout and age and sex matched control participants.

4. To evaluate the relationship between 3D gait parameters and the US lesions of the AT.

1.4. Hypotheses

1. Participants with tophaceous gout have a higher prevalence of US lesions in the AT compared to control participants.

2. There are significant differences US lesions in the AT in participants with tophaceous gout compared to control participants.

3. Walking velocity is significantly reduced in participants with tophaceous gout compared to control participants.

4. Ankle power is significantly reduced in participants with tophaceous gout compared to control participants.

5. There is a significant difference in ankle range of motion in participants with tophaceous gout compared to control participants.

6. There is a relationship between ankle power, ankle range of motion, walking velocity and ultrasound lesions in the AT in participants with tophaceous gout.

1.5. Gout: A New Zealand context

The most recent prevalence estimates indicate that gout is more common among Māori and Pacific Islanders, males, people with advancing age and people living in socio-economically deprived areas (36). The prevalence of gout in New Zealand was first measured in 1956 in Māori, 1958 in Europeans and 1980 in Pacific Islanders (37-39). Prevalence rates for males and females have been reported to range from 4.5%-13.9 % and 0-2% in Māori's, 0.7-5.8% and 0-0.9% in Europeans and 5.3-14.9% and 0.6%- 4.1% in Pacific Islanders (36). Gout prevalence rates from previous New Zealand studies are displayed in Table 1.1. Winnard (36) investigated prevalence estimates in the New Zealand population using national level health data sets (Table 1.2).

Winnard (36) described the epidemiology of hospital admissions associated with gout in New Zealand. Using hospital admissions data from a ten year period (1999 to 2009) the co-morbidities associated with gout were analysed. Data were analysed from two groups. In group one there were 10,241 admissions for gout and in group two 34,318 admissions due to complications caused by gout. Results demonstrated gout patients admitted to hospital were more likely to be Māori or Pacific Islander and have had 3-7 co-morbidities such as: hypertension, cardiovascular disease, diabetes mellitus and chronic renal disease.

Table 1.1: Gout Prevalence from Previous New Zealand Studies

Ethnicity	Year	Study population	Prevalence (%)	
			Male	Female
European	1958	Rotorua, European (random population sample)	0.7%	0.0%
	1966	Carterton, European (cluster sampling)	1.9%	0%
	1992	Rotorua, European (random population sample)	5.8%	0.6%
	2006	South Auckland, general practice database	4.1%	0.1%
	2009	National health database	3.7%	0.9%
Māori	1956	Whanau-a-Apanui, Māori (census)	8.2%	1.6%
	1958	Rotorua, Māori (random population sample)	6.0%	0.0%
	1963	Ruatahuna, Māori (census)	4.5%	2.0%
	1963	Māori	8.8%	0.8%
	1966	Ruatahuna, Tikitiki, Rotorua, Māori (census)	10.4%	1.8%
	1984	Māori (working age adults from a motor assembly plant)	8.0%	NA
	1992	Rotorua and Ruatahuna, Māori (census)	13.9%	1.9%
	2006	South Auckland, general practice database	9.3%	2.6%
	2009	National health database	11.7%	4.0%
Pacific	1980/1	Migrants from Tokelau (census)	13.9%	1.9%
	2006	South Auckland, general practice database	9.3%	2.6%
	2009	National health database	11.7%	4.0%

Note. From National prevalence of gout derived from administrative health data in Aotearoa New Zealand, Winnard (36). Reprinted with permission.

Table 1.2: Gout Prevalence in New Zealand from National Level Health Data Sets

Population	Prevalence (%)
Overall	2.7
People ≥ 20	3.8
European males	3.7
European females	0.9
Māori males	11.7
Māori females	4.0
Pacific males	13.5
Pacific females	4.1

Note. From National prevalence of gout derived from administrative health data in Aotearoa New Zealand, Winnard (36). Reprinted with permission.

1.6. Gout: Pathophysiology

Gout is a disorder of purine metabolism and results from urate crystal deposition in and around joints (8). Hyperuricaemia occurs when serum urate levels exceed urate solubility, which occurs at 0.41 mmol/L (40, 41). Hyperuricaemia is a risk factor in the development of gout but does not inevitably cause gout (42, 43). Langford (44) followed a patient cohort over a 14 year period and reported that in those with a serum urate level between 0.39-0.44 mmol/L only 12% developed gout. Urate is the final metabolite of endogenous and dietary purine metabolism (45, 46). Purines are organic substances found in many proteins derived from animals and plants and are one of the classes of substances from which the nucleic acids are constructed (40). The serum urate level in a given individual is determined by the amount of purines synthesised and ingested, the amount of urate produced by purines, and the amount of uric acid excreted by the kidneys and the gastrointestinal tract (47). Renal mechanisms are responsible for hyperuricaemia in approximately 90% of individuals, with patients who overproduce uric acid representing only 10-15% of hyperuricaemia cases and patients who under-excrete representing approximately 80-90% of hyperuricaemia cases (47).

Apart from the concentration of urate the solubility of MSU crystals is modulated by several factors. These include: trauma or irritation, tissue pH, tissue temperature, intra

articular hydration state, concentration of cations, and the presence of extracellular proteins such as proteoglycans, collagens and chondroitin sulphate (9, 47). Release of MSU crystals into the joint space may initiate a dramatic acute inflammatory reaction. Urate crystals are directly able to initiate, amplify or sustain an intense inflammatory attack because of their ability to stimulate the synthesis and release of humoral and cellular inflammatory mediators (47). Resident tissue cells such as macrophages and monocytes react to crystal deposition by the uptake of crystals through phagocytosis within the synovial lining (48). The stage of differentiation of the monocyte and macrophage has been identified as the factor that determines the host response (48). The subsequent recruitment of inflammatory leukocytes to the site of MSU crystal deposition accounts for the release of inflammatory mediators and the inflammatory manifestations found in acute gout (48).

1.7. Gout: Classification

In 1977 the American Rheumatism Association (ARA) published preliminary criteria for the classification of gout for population-based epidemiological research (49). The preliminary criteria for the classification of gout are presented in Table 1.3. A combination of microscopic identification of MSU crystals in synovial fluid or tophus or 6 more of these features is highly suggestive of gout. A new classification criteria for gout has recently been developed by an international collaborative working group (50). The new classification criteria for gout represent an advance over previous criteria, with improved performance characteristics and incorporation of newer imaging modalities.

Table 1.3: ARA preliminary criteria for the classification of gout

MSU crystals in joint fluid during attack
More than one acute attack of acute arthritis
Maximum inflammation developed within one day
Monoarthritis attack
Redness observed over joints
First metatarsophalangeal joint painful or swollen
Unilateral metatarsophalangeal joint attack
Unilateral tarsal joint attack
Hyperuricaemia
Asymptomatic swelling within a joint on x-ray
Subcortical cysts without erosions on x-ray
Joint fluid culture negative for organisms during attacks

Note. From Preliminary criteria for the classification of the acute arthritis of primary gout. Wallace (49). Reprinted with permission.

Traditionally, hyperuricaemia and gout has been classified into four disease stages: (1) asymptomatic hyperuricaemia (high serum urate but no clinical symptoms); (2) acute gouty arthritis (sustained hyperuricaemia with MSU crystal deposition); (3) inter-critical gout (the period between acute attacks) and (4) chronic tophaceous gout (longstanding gout associated with tophus deposition and bone/joint damage) (51).

Acute gouty arthritis presents with a rapid onset of severe monoarticular arthritis, severe pain, erythema and swelling, with maximal intensity of pain over a 8-12 hour period to the affected joint (9). The majority of attacks affect the 1st metatarsophalangeal (1MTP) joint of the foot, but there may also be involvement of the midfoot, ankle, heel, knee, wrist or fingers (10, 52). Episodes of untreated gout flares can span 3 to 10 days (53, 54). Brixner and Ho (55) reported that 60% of individuals with an initial gout flare experience a second flare within 1 year and 78% within 2 years.

Inter-critical gout is the asymptomatic phase between acute attacks (2). Despite the absence of symptoms, MSU crystals remain within the joint and continue to accumulate. Further disease progression results in shorter inter-critical periods, with more frequent, more protracted and increasingly debilitating flares. The inter-critical period between attacks

may range from months to years, with a reported likelihood of a patient experiencing a second attack within a year ranging between 54 and 60% (56).

Tophaceous gout is the most progressed phase of the disease and results from the longstanding effects of hyperuricaemia combined with delayed or ineffective treatment (11). Tophaceous gout is characterised by destructive polyarticular involvement with low grade joint inflammation, joint deformity, bone erosion and tophus formation (8). The time course duration from asymptomatic hyperuricaemia to tophaceous gout has been shown to vary widely from 3 to 42 years (2, 45, 57). Tophaceous gout develops within 5 years of onset of gout in 30% of people, occurs in 12 % of people with gout after 5 years and 55% after 20 years of untreated disease (2, 45, 57).

Tophi represent a complex and organised chronic inflammatory response to MSU crystals (15). Tophi typically occur within both subcutaneous tissues and within affected joints and may cause pain, cosmetic problems, obstruction of joint movement, joint destruction and musculoskeletal disability (12, 58). Microscopically, tophi appear as chronic granulomatous lesions comprising of mononucleated and multinucleated macrophages surrounding a core of MSU crystals and encased by dense connective tissue (15). Previous studies suggest that the development of gouty tophus is a dynamic process with a low level continuous recruitment, pro-inflammatory activation, maturation and turnover of monocyte-macrophages (59). The reason why some individuals are susceptible to formation of tophi is unknown, it is postulated that crystals may form at a rate that exceeds the handling capacity of tissue macrophages, or the possibility that macrophages fail to demonstrate a pro-inflammatory response to crystal uptake (59). Several zones have been characterised within tophi. These include the central crystalline zone, the cellular corona zone surrounding the central zone and an outer fibrovascular zone (60). Mononcytes and macrophages within the tophi have been identified to produce the enzymes gelatinase A and gelatinase B. These enzymes are capable of degrading type IV and V-collagen, elastin and gelatin (61).

Recently a new clinical staging system for hyperuricaemia and gout has been proposed (62). The new proposed staging system (Figure 1.1) provides a clear focus on gout as a chronic disease of MSU crystal deposition, as opposed to the traditionally held concept that gout is a condition of recurrent flares.

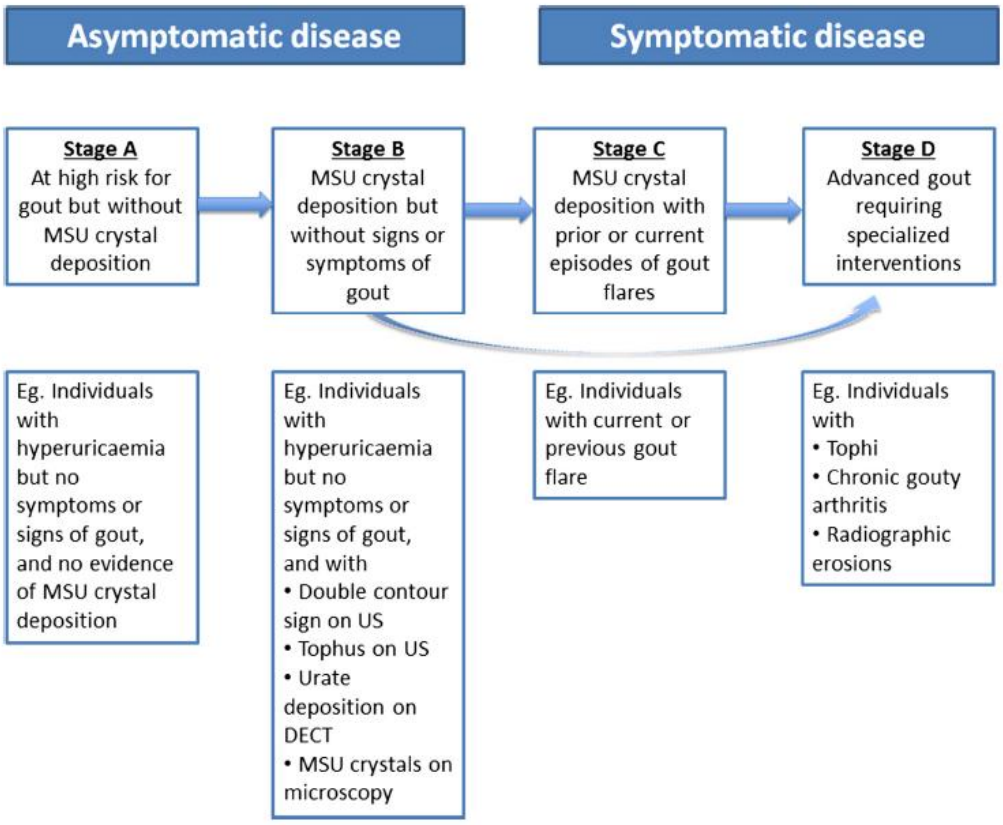


Figure 1.1. Proposed staging system for hyperuricaemia and gout. From Hyperuricaemia and gout: time for a new staging system? Dalbeth & Stamp (62), Reprinted with permission.

1.8. Comorbid conditions associated with gout

Patients with gout often have multiple comorbid conditions such as hypertension, cardiovascular disease (CVD), renal impairment, diabetes, obesity, hyperlipidemia and in combination known as the metabolic (63). The relationships between these comorbidities and gout are complex. The presence of these comorbidities contributes to the overall excessive cardiovascular mortality and morbidity due to myocardial infarction and peripheral arterial disease (64-66).

Complex interactions between comorbidities has been implicated in a cycle whereby comorbidities may both cause and affect elevation of serum urate levels (67). The fundamental strategy in pharmacological management is long term urate lowering therapy to achieve MSU crystal dissolution (68). A recent study reported in participants with gout, 74% with hypertension, 71% with $\geq$stage 2 chronic kidney disease, 53% with obesity, 26% with diabetes and 11% with heart failure (69).

Gout is associated with increased risk of CVD and death, particularly in those with a high cardiovascular risk (64, 70). Hyperuricaemia is an independent risk factor for CVD (71), with associations between hyperuricaemia/gout and stroke (72) and peripheral vascular disease (73) reported. Relationships between renal function, serum urate and gout are well established, with renal impairment associated with hyperuricaemia (74). The relationship between blood glucose, serum urate and between diabetes and gout is complex. Research suggests that those with moderately increased HbA1c (pre-diabetes) may be at increased risk of hyperuricaemia and gout, whereas those with established diabetes or significantly increased HbA1c may be at lower risk (74).

1.9. Pharmacological management approaches to gout

Recent research has provided the first consensus-based pharmacological and non-pharmacological recommendations for gout (68). The fundamental strategy in effective gout management is long term urate lowering therapy to achieve MSU crystal dissolution (68). The American College of Rheumatology (ACR) guidelines recommend that for most people with gout, the target serum urate concentration is < 0.33 mmol/L, however, a lower target serum urate of < 0.27 mmol/L has been proposed for people with tophi. The ACR guidelines recommend single-agent xanthine oxidase inhibitors (Allopurinol or Febuxostat) to maximum dose as first-line urate-lowering therapy, followed by the addition of a uricosuric agent. Probenecid is recommended as an alternative first-line therapy if either Allopurinol or Febuxostat are contraindicated or not tolerated. Pegloticase (a form of uricase, not available in New Zealand) is recommended as a third-line agent in distinct cases for those not achieving target serum urate concentration and continuing disease activity (68). In conjunction with intensive urate-lowering therapy, effective anti-inflammatory medications to both prevent and treat gout flares are required in people with tophaceous gout. The 2012 ACR guidelines recommend that low-dose colchicine or Non-steroidal anti-inflammatory drugs (NSAIDs) are most appropriate for first-line anti-inflammatory prophylaxis and that in the presence of gouty tophi, a longer duration of anti-inflammatory prophylaxis is indicated than for those without tophi (68).

Non-pharmacological recommendations centre on providing patient education surrounding the role of uric acid in gout, long term urate treatment targets, dietary and lifestyle factors (68). Dietary recommendations include avoidance or high purine containing meats, high

fructose beverages or foods and excessive alcohol. People with gout are encouraged to limit serving sizes of meats and seafood, table sugar, salt and alcohol. People with gout are encouraged to low-fat or non-fat dairy foods and vegetables (68). Recommendations also include that all people with gout have a clinical examination to evaluate disease activity and burden, with attention to modifiable secondary causes of hyperuricaemia such as comorbidities, and medications (68). Recent research suggests that walking shoes with good cushioning and motion control may reduce foot pain and disability (75).

1.10. Gout and the foot

The most commonly affected joints in a gouty attack are the 1MTP joint, the midfoot and the ankle (76). The first attack of gout affects the 1MTP joint in 56-78% of patients, with 90% having an attack in the hallux at some point in their disease course (77-80). Midfoot and ankle involvement occurs in 25-50% and 18-60% of patients, respectively (10, 78, 81). A community based observational study also found hallux valgus present in 41% of participants compared to 25% of controls (82). Recent research has highlighted the significance of MSU crystal deposition in the tendons and bones of the foot (17). Dalbeth (17) assessed multiple joint in 92 feet of patients with tophaceous gout using dual energy computerised tomography. Thirty eight percent of cases showed MSU deposition in the 1MTP joint, 22% in the 5^{th} metatarsophalangeal (5MTP) joint and 11% in the 2^{nd} metatarsophalangeal (2MTP) joints. The study also reported MSU deposition through multiple midfoot joints.

1.11. Gout and the Achilles tendon

Limited research has been conducted describing structural, functional and biomechanical changes in the AT resulting from tophaceous gout. Naredo (83) using grey-scale US in 92 men with gout, reported the AT abnormalities (hyperechoic areas) to be present in 34% of AT examined and 7% of control participants. Dalbeth (84) reported in 92 people with tophaceous gout, 39% displayed MSU crystal deposition within the AT using dual-energy computerised tomography imaging. In the 72 AT that were affected, 38% had only non-entheseal involvement, 40% had both entheseal and non-entheseal involvement and 22% had only entheseal involvement. The authors postulated that the deposition of MSU crystals in the AT may be as a result of increased biomechanical strain within the AT. Case reports

have associated rupture of the AT with gout (85, 86). Mahoney (85) reported a case of AT rupture in a patient with tophaceous gout, postulating rupture was associated with MSU crystal deposition, reducing the tensile strength of the tendon. However, no data was provided or statistical analysis performed to link MSU crystal deposition and tendon rupture. Dodds & Barry (87) investigated the association between serum urate level and rupture of the AT. The serum urate levels were compared in 30 patients who presented with an AT rupture, and compared to age and sex matched controls with no history of AT rupture. Results demonstrated people with an AT rupture had a higher average serum urate level when compared to controls. The authors postulated that a raised serum urate level may affect tendon nutrition through alteration of proteoglycan metabolism. In a review of 60 people with crystal related arthropathies using US imaging, Grassi (35) reported the normal fibrillar echotexture of tendons can be completely deranged by the presence of intratendinous tophus deposits.

1.12. Structure, function and biomechanics of the Achilles tendon

The AT is a confluence of the gastrocnemius and soleus muscles. As the tendon fibres of the gastrocnemius and soleus descend in the lower leg they converge and rotate in a spiraling fashion (approximately 90º) with full incorporation typically occurring 8 to 10 cm superior to the calcaneal insertion (88). The rotation is more evident in the lower 5 to 6 cm of the tendon and is thought to aid its elastic recoil (20).

The tendinous fibres from the gastrocnemius insert into the posterolateral calcaneus, while those of the soleus insert into the posteromedial aspect of the calcaneus (89). The zone where the AT inserts into the calcaneus has been named the enthesis organ in recognition of the functional and dynamic events that occur at this anatomical site (90). The enthesis itself, the sesamoid and periosteal fibrocartilages, the retrocalcaneal bursa and its associated fat pad (Kager's fat pad) are the components of the enthesis organ as originally defined by Benjamin and McGonagle (90, 91). The AT attaches into the middle third of the posterior surface of the calcaneus, allowing the upper third (the superior tuberosity) to act as a pulley mechanism for the AT, reducing the stress concentration on the enthesis. The retrocalcaneal bursae and fat pad further aid stress dissipation in this zone by minimizing frictional forces between the AT and superior tuberosity (92).

The AT is the thickest and strongest tendon in the human body (19). The basic structural elements of the AT consist of collagen fibres synthesised by tenocytes contained within an extracellular matrix. The major fibrillar component of the AT is closely packed Type I collagen, which account for 60% dry weight of the tendon and 95% of the total collagen fibres (93). Type I collagen is responsible for the tendon's mechanical strength and its ability to withstand tensile stress (94). Type III and V collagen represent approximately 5% of the tendon composition, the size and orientation of these fibrils, along with the overall physiological composition, determine the mechanical properties of the tendon (94). The extracellular matrix is composed of water (approximately 55% of the weight of tendon), elastin fibres and several glycoproteins that provide functional stability to the collagen fibres (94, 95). The collagen fibre structural units are bound into bundles by the endotenon to give higher structural units called fascicles, which in turn are bound together by epitenon and paratenon to form the tendon (Figure 1.2) (20). The endotenon contains the vascular, lymphatic, and neural transmission routes to maintain tendon fibroblasts, and the epitenon binds the fascicles together and supplies blood. The paratenon permits tendon sliding relative to adjacent structures (20). The AT receives blood supply from the musculo-tendinous junction, along the length of the tendon (via the paratenon) and junction with the calcaneus (96). The blood supply consists mainly of longitudinal arteries that course the length of the tendon, derived from either the peroneal and posterior tibial arteries (97). An area of low vascularity approximately 2 to 6 cm superior to the insertion is described in literature (95).

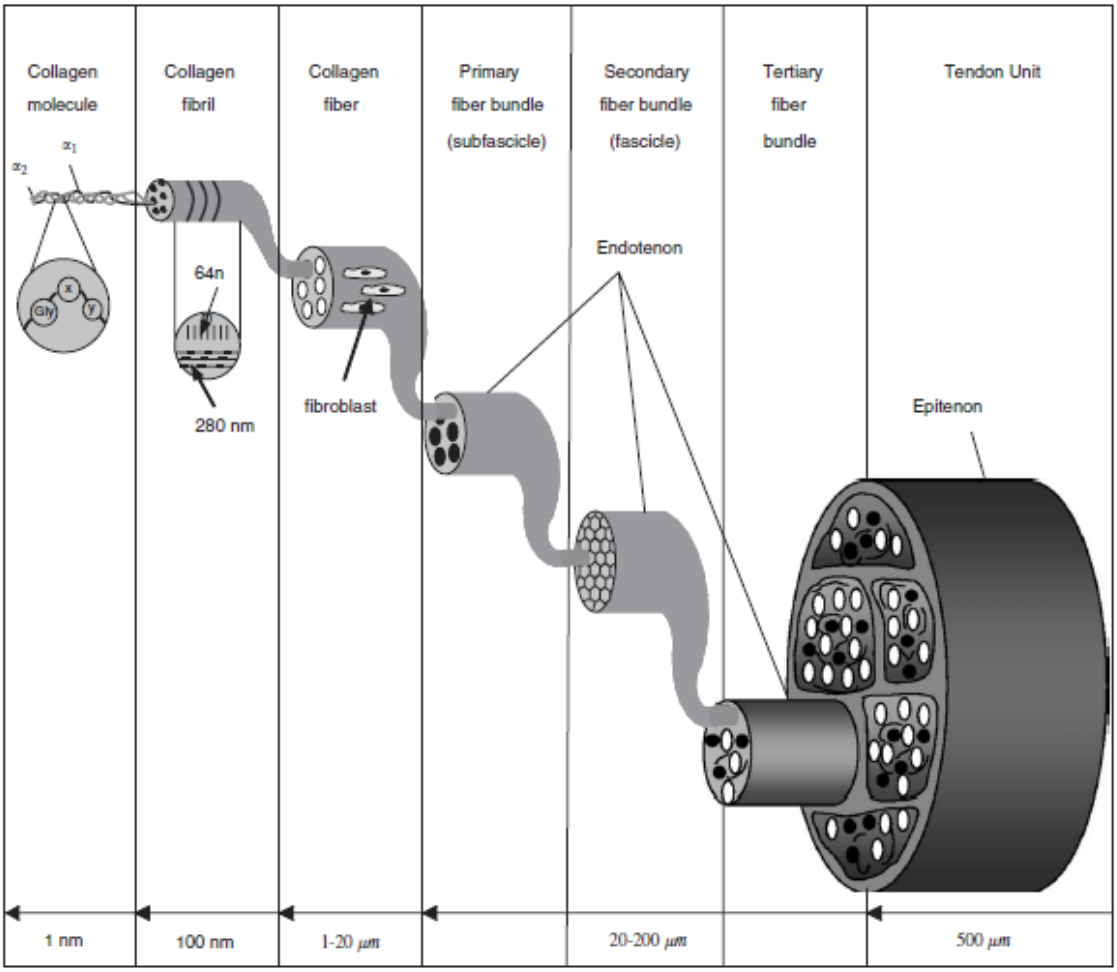


Figure 1.2. The multi-unit hierarchical structure of the human tendon. From Mechanobiology of tendon, Wang (94), Reprinted with permission.

The gastro-soleus complex primarily provide a plantarflexion moment at the talocrural joint that accounts for 93% of the plantar flexor torque (98). The range of motion of the ankle joint during a normal gait cycle is plantarflexion to about 7 degrees (0 to 12% of gait cycle) and dorsiflexion to approximately 10 degrees (between 12% to 48% of gait cycle) and plantarflexion to 20 degrees (48% to 62% of the gait cycle) (22). The gastro-soleus complex is active in the stance phase, with activity beginning at approximately 10% of the gait cycle; maximal activity occurs at 40% and activity ceases at 50% of the gait cycle (22). The main function of the gastro-soleus complex is to restrain the forward movement of the tibia over the stance foot (22).

The arrangement of the AT within this muscle tendon complex supplements passive force transmission with energy storage and recycling (99). These mechanisms enhance joint

performance and efficient power production (100). The AT, like other tendons, is a viscoelastic tissue that displays stress relaxation and creep (101). The mechanical behavior of the AT can be depicted by a stress strain curve (Figure 1.3). The tendon then deforms in a linear fashion indicative of collagen sliding with fibres becoming more parallel. The tendon will behave in an elastic fashion and return to original length when unloaded at strains under 4%. Microscopic failure occurs when the strain exceeds 4%, and, beyond 8-10% strain, macroscopic failure occurs from intrafibril damage by molecular slippage (102).

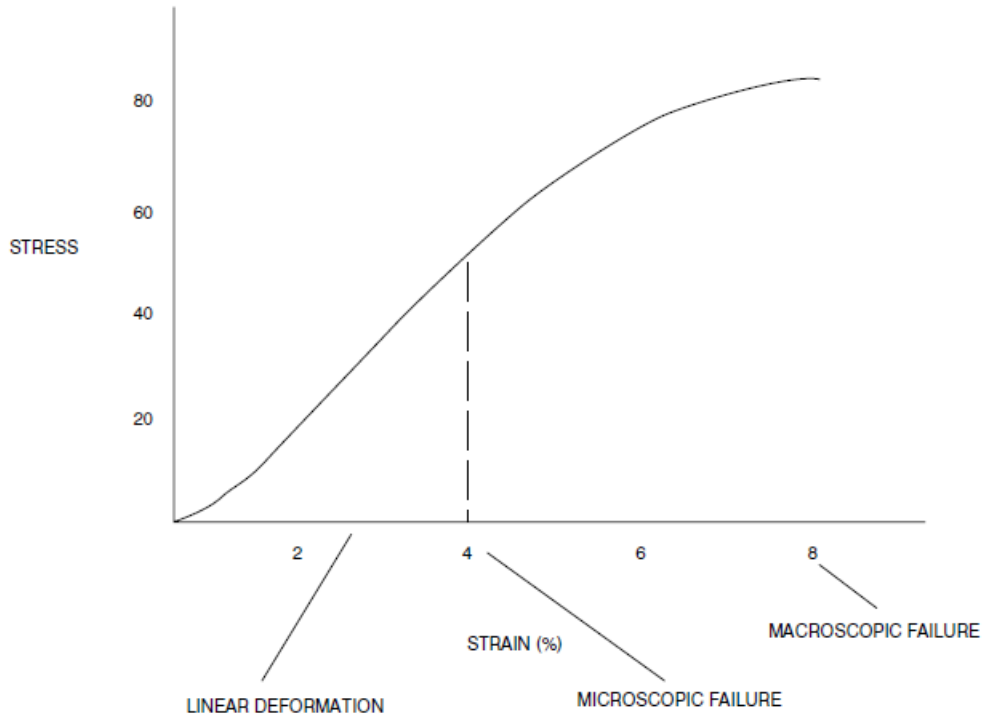


Figure 1.3. Stress strain curve demonstrating mechanical behavior of normal tendon. From Biology of tendon injury: healing, modelling and remodelling, Sharma and Maffulli (101). Reprinted with permission.

The mechanical traits of the AT are primarily responsible for its ability to withstand large muscular forces with minimal deformation (100). Stiffness, an important constituent of tendon mechanical properties, is the ratio of force applied to the tendon and its elongation in response to the force. It has a significant influence on force transmission, muscle power, and energy absorption and release during locomotion (103). An optimal level of tendon stiffness is critical for effective muscle-tendon interactions and for minimizing the

energetic costs of locomotion (100). Tendon stiffness may be influenced by tendon length and cross sectional area (CSA). A shorter tendon with larger CSA is expected to have greater stiffness (100). Young's modulus (stiffness normalized to tendon CSA and length) provides a measure of tendon material properties irrespective of its geometric characteristics. This is especially important in the case of pathological tendons, as pathological tendons usually present with greater CSA (100).

Acute tendon injuries heal in a standard triphasic response: inflammation, proliferation and maturation and return slowly to a normal tendon structure (101). Tendons affected by overuse injury (tendinopathy) do not follow this same healing pathway, the result being long term disruption to the internal structure of the tendon (26). Tendon pathology is characterised by four main structural changes: a change in cell function, an increase in ground substance, a breakdown of collagen bundles and neurovascular proliferation (neovascularisation) (104). Previous studies have shown that type III collagen is synthesized during the healing process at the repair site by cells that once produced type I collagen (102). A disruption to this structure and arrangement, accompanied by an increase in mechanically weaker type III collagen fibres may weaken the tendons' mechanical (stiffness) and material properties (Young' modulus) (34, 100).

1.13. Three-dimensional gait analysis of the foot

Human movement analysis using stereophotogrammetric measurements and rigid body modelling requires the identification of appropriate body segments and axes (105). The systems of axes is defined by the positioning skin mounted markers (105). The understanding of foot and ankle motion during gait has grown substantially in the past decade with the developments in 3D multi-segment foot models. Prior to the development of multi-segment foot models the understanding of foot function was based on a single segment foot model. These models were unable to demonstrate the complex interactions of joint articulations distal to the ankle (106). Over fifteen foot models based on skin mounted markers have now been developed to explain joint kinematics in the foot (107). All 3D multi-segment foot models vary with regard to marker placement and the number of foot segments modelled. The number of segments modelled varying between 3 to 9 foot segments (107-109). Foot segments commonly modelled include the hindfoot, forefoot and hallux, with recent models separating the midfoot into a medial and lateral component

(109). Although there is no consensus regarding the most appropriate number of foot segments to model, there is consensus that modelling the foot by multi-segment methodologies is more appropriate than viewing the foot as a single segment (107, 110, 111).

The most commonly applied 3D multi-segment foot models include the Milwaukee Foot model (112), the Oxford Foot Model (113) and the Heidelberg Foot Model (114). The most commonly applied model in inflammatory arthritis is the Oxford Foot Model. Chapter 3 provides a detailed review of the spatiotemporal, kinematic, kinetic and plantar pressure gait parameters that have been assessed in people with inflammatory arthritis. The chapter also details the 3D multi-segment foot models used to acquire kinematic gait data in inflammatory arthritis.

1.14. Assessment of gait in gout

Limited research has been conducted using 3D analysis methodologies to assess kinematic or kinetic gait parameters in tophaceous gout. Rome (18) assessed the impact of tophaceous gout on foot function, plantar pressure and the spatial and temporal gait parameters in 25 people with tophaceous gout, compared to age and sex matched controls. The spatial and temporal gait parameters investigated included: step and stride length, single and double leg support, velocity and cadence. Results indicated that patients with tophaceous gout had foot related pain and disability, reduced step length, stride length, velocity and cadence when compared to controls. Plantar pressure results demonstrated a reduction in peak plantar pressure under the hallux. The authors postulated that people with tophaceous gout alter their gait pattern to reduce pressure to the 1MTP joint as a pain-avoidance strategy.

1.15. Ultrasound Imaging

US waves projected into the tissue are either reflected back or penetrate into the tissue. By timing the period elapsed between the US production and echo reception the distance can be calculated and an image formed (115). US images produced are described in terms of their echogenicity. The common US terminology related to description of the echogenicity is presented in Table 1.4.

Table 1.4: Ultrasound lesion terminology

Ultrasound lesion	Definition
Anechoic	No internal echoes, appears dark or black
Isoechoic	Similar appearance to surrounding tissue
Hypoechoic	Less echoic or darker than surrounding tissue
Hyperechoic	More echoic or whiter than surrounding tissue

Note. From Ultrasound Physics and Instrumentation, Case (115). Reprinted with permission.

US imaging is an ideal modality to assess pathological changes to the AT and is considered the first choice imaging technique when assessing tendon pathology (116-119). US imaging can assess the internal structural organisation of the tendon as well as the peritendinous structures (sheath, bursae, enthesis). US imaging has been used extensively in the assessment of AT pathology, with the technique assessing both chronic degenerative and acute inflammatory tendon pathology (116, 120). Additional US imaging techniques such as power Doppler (PD) has allowed for assessment of vascularisation in the AT (121, 122). In the last decade, PD, imaging has been used to quantify the degree of inflammatory change in numerous forms of inflammatory arthritis (123).

When examined in a longitudinal orientation by US imaging, the AT appears as a homogenous ribbon-like structure with a parallel fibrillar pattern of tendon fibres outlined by a straight hypoechoic border representing the paratenon (124). Hypoechoic lines within the tendon represent acoustic borders between the fibrils and intervening connective tissue. In transverse orientation these lines are represented by a honeycomb pattern (124). The normal appearance of the AT when examined by US imaging is displayed in Figure 1.4.

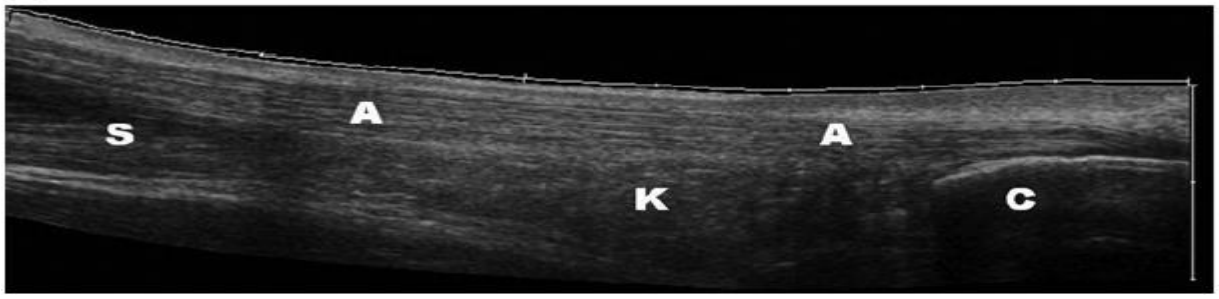


Figure 1.4. Longitudinal ultrasound image of normal Achilles tendon (A), calcaneus (B), fat pad (K), soleus muscle (S). From The role of ultrasound imaging in acute rupture of the Achilles tendon, Elias & McKinnon (124). Reprinted with permission.

1.16. Ultrasound imaging and tophaceous gout

US imaging is being increasingly used to investigate gout due to its low cost, the lack of ionising radiation, its multi-planar imaging capability, its high resolution, and the ability to perform a dynamic assessment (125). The physics of US imaging make it an ideal tool to detect crystalline material in soft tissues. Crystalline material found in gouty joints reflects US waves more strongly than surrounding tissues such as unmineralised hyaline cartilage or synovial fluid, and can thus be readily distinguished (125).

Although the gold standard for diagnosis of gout remains positive identification of MSU crystals via arthrocentesis (joint aspiration), US imaging provides a non-invasive technique to aid diagnosis, monitor disease progression and provide insights into pathological changes (24). US imaging is able to detect various specific and non-specific US lesions in gout. Non-specific features include those findings that may be common among other forms of inflammatory arthritis such as: joint effusion, synovitis, hypervascularisation, bony erosion and proliferative new bone formation (25).

Detection of MSU crystals by US imaging allows for non-invasive assessment and a potential method of monitoring disease progression. Under US imaging MSU crystals may appear within synovial fluid as a snowstorm appearance. The snowstorm appearance is determined by the presence of multiple foci with different echogenicity or within articular cartilage as the double contour sign (35). The double contour sign is US lesion specific to gout and refers to a hyperechoic irregular band over the superficial margin of the anechoic cartilage and is produced by deposition of MSU crystals on the surface of hyaline cartilage

(126, 127). Thiele & Schlesinger (127) retrospectively compared US images of gout patients to images of controls with rheumatic diseases. The results demonstrated the double contour was a specific finding occurring in 92% of gouty joints. Wright (126) demonstrated that the double contour sign was present in 22% of gout patients when investigating bony erosions at the 1MTP joint. Figure 1.5 demonstrates the typical appearance of the double contour sign in the 1MTP joint.

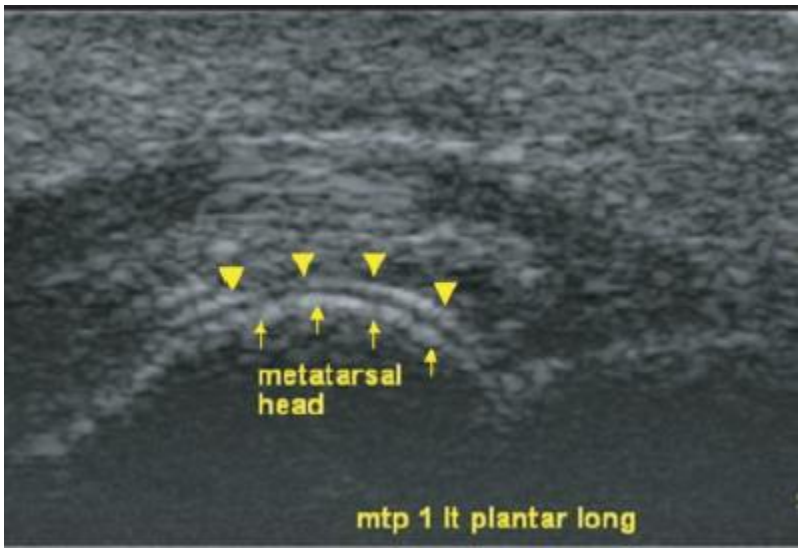


Figure 1.5. The double contour sign. From Diagnosis of gout by ultrasound, Thiele & Schlesinger (127). Reprinted with permission.

US imaging has been used to assess and characterise tophi. Under US imaging tophi present as hypoechoic or hyperechoic non-homogenous mass surrounded by an anechoic rim (128). de Ávila Fernandes (129), using an observational cross-sectional methodology, described the US features of tophi in 138 affected areas in 31 patients with tophaceous gout. Results indicated that tophi were largely hyperechoic (brighter than surrounding tissue), displayed heterogeneous echotexture (stippled areas of intensity within tophi), and had poorly defined borders. Although this study defined the characteristics of tophi, enabling the differentiation of tophi from other soft tissue structures, the tophi examined were from various locations in the participants including the hand, forearm, knee, leg ankle and foot. The authors provided no detail specific to the anatomical locations of the tophi. Puig (130) assessed 35 hyperuricaemia patients and found tophi were present in 34% of soft tissue. The authors did report tophi to be located in the knees, ankle and patellar tendon, but did not define the specific anatomical locations of the tophi.

US imaging has also been used to quantify tophus size, with reduction in tophus size considered important for studies of patients with tophaceous gout (131, 132). US imaging has also a reported ability to detect 90% of tophi detected by magnetic resonance imaging (MRI) and the ability of being able to assess subcutaneous and intra-articular tophi (131). Figure 1.6 displays the typical US appearance of a hyperechoic tophus (dotted lines surrounded by Xs) surrounded by a partial anechoic halo (arrow) in the elbow. The posterior aspect of the tophus has an imprecise contour (arrowheads).

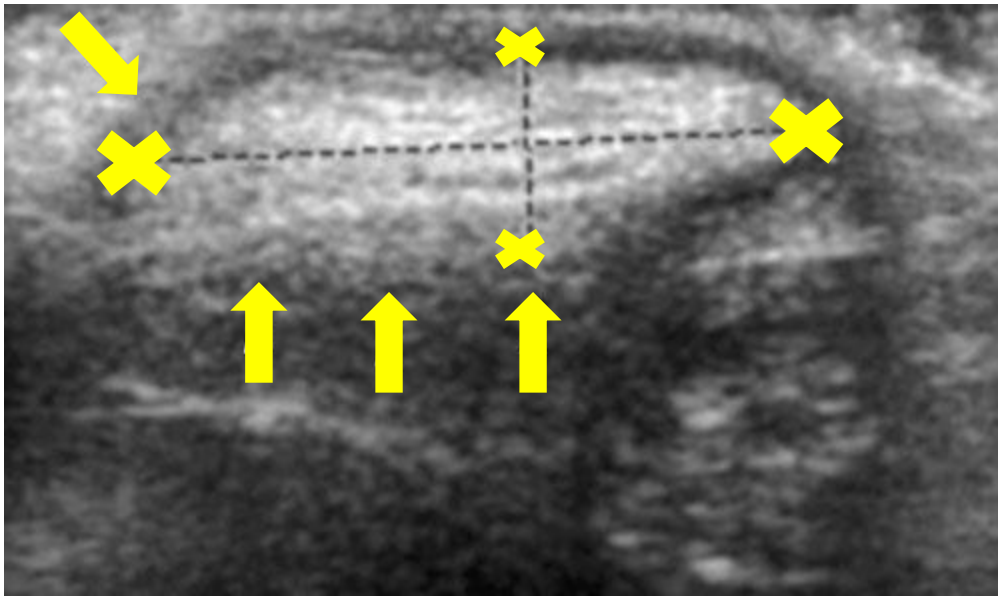


Figure 1.6. The appearance of a tophi under ultrasound imaging. From Ultrasound features of tophi in chronic tophaceous gout, de Ávila Fernandes (129). Reprinted with permission.

Tophi are frequently observed by US imaging to be in contact with bone and joint structures (129). Wright (126) was the first to demonstrate US imaging was able to detect significantly more erosions than x-rays at the 1MTP joint in gout.

The development of new blood vessels within an articular or periarticular structure due to active inflammation can be assessed using PD (133). PD assessment of Achilles tendinopathy has demonstrated vascularisation, even when vessels are too small to be visualised by MRI (133). Normal tendons do not exhibit PD signal but in tendinopathy tendon vascularisation has been demonstrated to be present within the small vessels and has been associated with pain and poor function (133-135). PD has also been used to investigate inflammatory arthropathies, most notably RA (136-138). In RA, PD has been

used to grade inflammatory change (synovitis) with semi-quantitative grading systems developed to score PD signal (139). In spondyloarthropathy (SpA) PD has been used to demonstrate vascularisation in the mid-portion and insertion of the AT (140). The use of PD in the study of gout is limited. Puig (130) investigated 35 people with asymptomatic hyperuricaemia and found increased vascularity within or around tophi in 23% of patients. This study was limited by the lack of comparison to control participants. Though the research identified tophi location within periarticular structures, specific anatomical locations of the tophi were not provided.

Although the radiographic appearance of gout is well recognised and is included in the ACR preliminary clinical classification criteria for gout (49), US imaging is reported to have various advantages over conventional radiography (141). US imaging has demonstrated increased sensitivity to detect early signs of small bone changes in gout can be detected when compared to conventional radiography (141, 142). Howard (143) reported high agreement between rheumatologists in reading of ultrasonography images obtained by a single operator, for the features of MSU crystal deposition. In this study, ultrasonography features of MSU crystal deposition (defined as tophus or the double-contour sign) were present in 50% of people with gout, 29% of people with asymptomatic hyperuricaemia, and 5% of controls.

CHAPTER 2

The assessment of inflammatory and structural lesions of the Achilles tendon by ultrasound imaging in inflammatory arthritis: a systematic review and meta-analysis

2.0. Purpose of the systematic review

The systematic review was undertaken for the following purposes:

1. To determine what US lesions have been used to quantify structural change in the AT of people with inflammatory arthritis.
2. To guide research design, specifically:
    a. To determine how US lesions have been scored by previous research in inflammatory arthritis.
    b. To determine appropriate definitions for US lesions of the AT in the context of inflammatory arthritis.
3. To conduct meta-analysis to demonstrate what AT lesions significantly differ and the degree to which these lesions differ across different forms of inflammatory arthritis.

2.1. Introduction

US imaging is a highly sensitive, reliable and non-invasive tool which allows for the assessment of lesions of tendons and entheseal sites and is considered the gold standard for imaging tendons in rheumatology (144-147). US has greater sensitivity than conventional radiography in the detection of erosions, synovitis (142, 148) and urate deposition in gout (141). Compared to magnetic resonance imaging, US has demonstrated higher sensitivity in the detection of enthesitis (149) and higher specificity and sensitivity than clinical examination. Subsequently, the use of US imaging to assess lesions in the AT and calcaneal enthesis has increased (150).

In clinical practice, the identification of inflammatory and structural lesions in the AT and enthesis are important to establish the extent of pathology, to monitor disease activity and to determine treatment efficacy in inflammatory arthritis. However, Gandjbakhch (151) reported that poor quality exists in defining US lesions. In order to standardise US lesion definitions the Outcome Measures in Rheumatology Clinical Trials (OMERACT) US task force provided consensus-derived definitions of bone erosion, synovial fluid, synovial hypertrophy, tenosynovitis and enthesopathy related to RA (152). With the increased use of US imaging the OMERACT US task force further defined B-mode US lesions in SpA, providing definitions encompassing entheseal thickening, calcification and Doppler signal (153). Furthermore, the OMERACT US task force proposed separation of US lesions into those reflective of inflammation and structural damage. US lesions indicative of inflammation (acute/active US enthesitis) include hypoechogenicity, tendon thickening and Doppler signal. US lesions representative of structural damage (chronic/inactive US enthesitis) include erosions, enthesophytes, calcification and cortical irregularities (153). However, there was poor consensus agreement for differentiation between acute and chronic US lesions (153).

Previous systematic reviews have reported the level of homogeneity in the ultrasound definitions for the principal lesions of enthesitis, evaluated the metric properties of ultrasound for detecting enthesitis in spondyloarthropathy (SpA) and RA (151, 154). They have also examined the prevalence of US abnormalities and assessed the diagnostic accuracy and the sensitivity of US evaluation of the enthesis in SpA (151, 154). US lesions reflective of calcaneal enthesitis and structural damage are a typical clinical aspect of SpA (14), but have not been evaluated in other forms of inflammatory arthritis. The aim of this

systematic review and meta-analysis was to identify differences in US lesions of the AT between people with inflammatory arthritis and healthy controls. This is the first systematic review to examine the prevalence of US lesions specific to the AT across different forms of inflammatory arthritis.

2.2. Methods

2.2.1. Identification of studies

Four electronic databases were searched (Medline, CINAHL, SportDiscus and The Cochrane Library). The search was conducted between June and July, 2014 and the search strategy combined terms appropriate to: RA, SpA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), gout, and calcium pyrophosphate deposition (CPPD); AT pathology and US imaging (Table 2.1). The term SpA encompasses a heterogeneous group of conditions, characterised by vertebral involvement, peripheral oligoarthritis or polyarthritis, enthesitis, AS, PsA and undifferentiated spondyloenthesoarthritis (14, 15). The review included SpA but also reported on AS and PsA as separate diseases.

Table 2.1: Search strategies**:** (a) search terms for rheumatic disease (b) search terms for Achilles tendon pathology (c) search terms for ultrasonography, and (d) combination of search terms

a	1	Subject term	exp. Rheumatic Disease
	2	Keywords	Rheumatoid or Rheumatic or Rheumatology or Inflammatory rheumat* or Rheumatic disease or Rheumatoid arthritis or Gout or Psoriatic arthritis or Ankylosing spondylitis or Spondyloarth* or Calcium pyrophosphate deposition or CPPD
b	3	Keywords	Achilles tend* or Achilles paratendin* or Achilles paratendon* or Achilles enthesis* or Achilles insertion or Achilles Burs* or Calcaneal burs* or Achilles thicken* or Bone spur or Entheso* or Calcaneal erosion or Erosion or Vascularisation or Neovascularisation or hypoecho*
	4	Subject term	exp. Pathology
c	5	Subject term	exp. Ultrasonography
	6	Keywords	Ultrasonograph* or Sonograph* or Ultrasound or US or MSUS or Doppler or Power Doppler or PDUS or Colour Doppler
d	7	Combine	1 or 2
	8	Combine	3 or 4
	9	Combine	5 or 6
	10	Combine	7 [and] 8 [and] 9

2.2.2. Inclusion/exclusion criteria

The selection of titles, abstracts and articles was undertaken by one reviewer. All titles were screened, subsequently selected abstracts retrieved and full-text articles reviewed. Studies were included if they: reported people with inflammatory arthritis; assessed adults aged >18 years old; reported US lesions of the AT or enthesis; included a healthy comparison control participants; were articles published in English. Surgical and pharmacological intervention studies were excluded. No limitation was placed on the date of publication.

2.2.3. Assessment of methodological quality and diversity

The quality of studies was assessed independently by two reviewers, who were blinded to author and publication details. Study quality was rated using a modified version of the quality index tool originally described by Downs and Black (155). The quality index tool consists of 27 items, which allows for assessment of internal and external validity, quality of reporting and study power. A total of 14 questions were considered not applicable to the study designs included in this review, resulting in the retention of 13 questions (Table 2.2). Each question was scored “0” or “1” (0 = no/unable to determine, or 1 = yes). The total percentage score for each paper was determined. In the absence of validated cut-off scores and following a review of past articles that have applied the Downs and Black criteria, studies that scored: ≥11 (85%) were deemed high quality; 8-11 (61%-84%) moderate quality; and <8 (61%) poor quality (156, 157).

Table 2.2: Questions included from the Quality Index checklist (155)

1	Is the hypothesis/aim/objective of the study clearly described?
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3	Are the characteristics of the patients included in the study clearly described?
6	Are the main findings of the study clearly described?
7	Does the study provide estimates of the random variability in the data for the main outcomes?
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
16	If any of the results of the study were based on "data dredging", was this made clear?
18	Were the statistical tests used to assess the main outcomes appropriate?
20	Were the main outcome measures used accurate (valid and reliable)?
21	Were the patients in the cases and controls (case-control studies) recruited from the same population?
22	Were study subjects in the cases and controls (case-control studies) recruited over the same period of time?

2.2.4. Data extraction

A standardised form was used by one a reviewer to extract publication details (authors and year), sample characteristics (sample size) and participant characteristics (age, sex and type of inflammatory arthritis). Frequencies and measurements of the US lesions indicative of inflammation and structural damage were also extracted. The OMERACT US lesion definitions were used to group and define lesions (153). Lesions relating to inflammation included hypoechogenicity, tendon thickening and Doppler signal (153). Lesions of structural damage included erosions, enthesophyte formation, calcification and cortical irregularities (153). The scoring methods for the inflammatory and structural lesions were also recorded.

2.2.5. Data analysis and synthesis

The clinical and methodological diversity among the studies was assessed to determine the appropriateness of data pooling for meta-analysis. Two reviewers reached consensus regarding the appropriateness of conducting meta-analysis. The criteria for pooling included: (a) participants exhibited the same type of inflammatory arthritis, (b) US lesions were clearly defined in text and/or supported by in-text citations and (c) direct measurement of an US lesion occurred, and the same methodology was used to score the lesion. Odds ratios (OR) with 95% CI (confidence intervals) were calculated, where data pooling was considered appropriate. OR were considered significant if the 95% CI did not contain zero. An OR = 1 indicated exposure does not affect the odds of the outcome; OR > 1 indicated exposure associated higher odds of the outcome and OR < 1 indicated exposure associated with a lower outcome (158). The difference in means and 95% CI was calculated for studies that directly measured US lesions.

Meta-analysis was performed using the Comprehensive Meta-analysis, versions 2 (159). Heterogeneity was considered low if the I^2 value was 25% or less, moderate if the value was between 25% and 50%, high if between 50% and 75% and very high if greater than 75% (160). A fixed-effect model was applied where the I^2 statistic was less than 50% and the Chi^2 test indicated a non-significant degree of heterogeneity ($P > 0.1$). The random-effect model was used where the I^2 statistic was greater than 50% and the Chi^2 test indicated statistically significant heterogeneity ($P < 0.1$) (161).

2.3. Results

2.3.1. Selection and inclusion of studies

All items were reported using the PRISMA statement (162). A total of 469 references were initially identified for screening (Figure 2.1). Detailed review of abstracts and full-text reviews resulted in 445 records being excluded and thirteen articles being included in the final analysis (163-175).

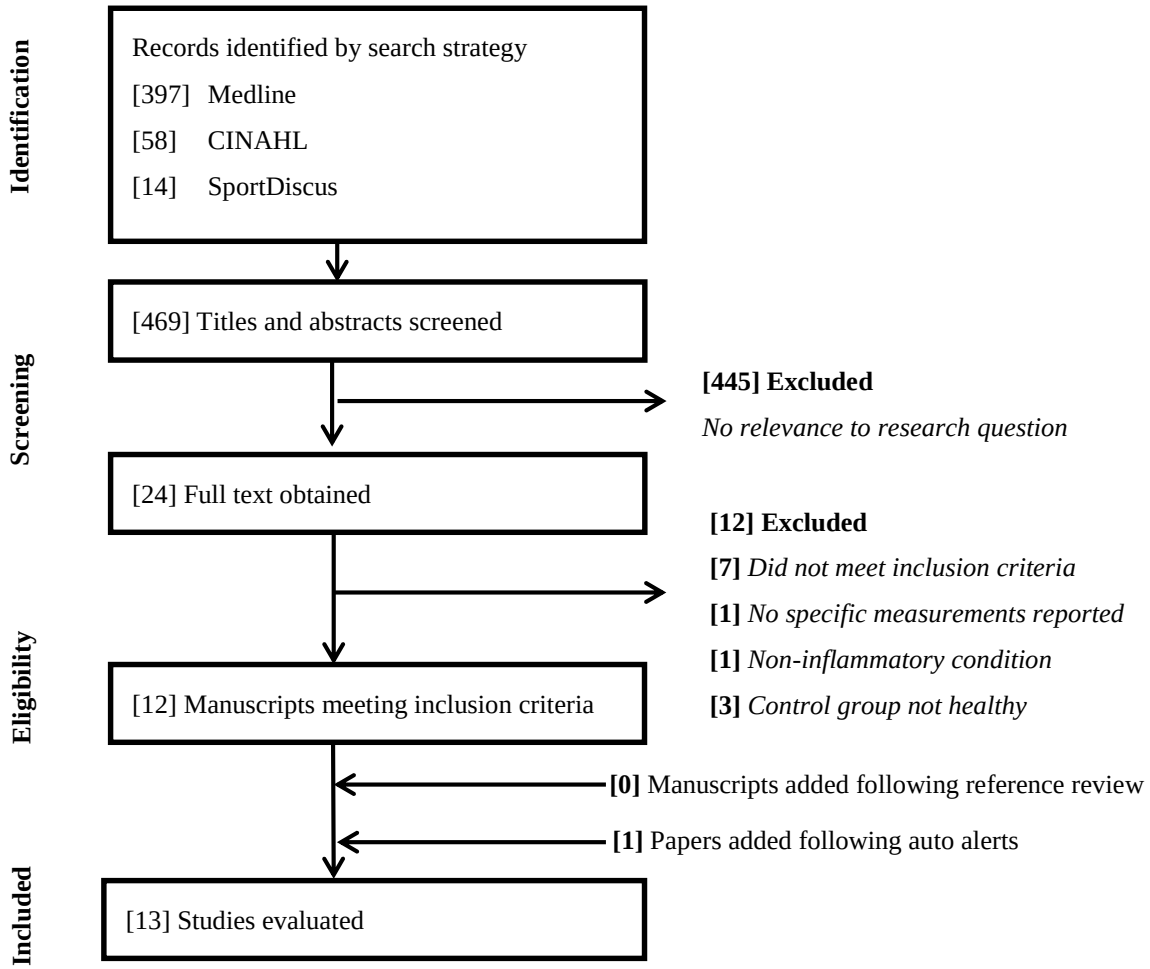


Figure 2.1. PRISMA flow diagram

2.3.2. Methodological quality of studies

Two reviewers independently scored 169 items and agreed on 162 items (96%), with an inter-rater agreement kappa of 0.85 ($p < 0.001$). The seven disagreements were resolved following discussion, whereupon consensus was reached. Twelve studies (163-168, 170-175) were considered of high quality and one (169) of moderate quality. None of the included studies described the time period for the recruitment for both case and control populations (QI criteria 22). The numerical (%) quality scores ranged from 10-12 (76-93%), with a median (%) score of 12 (93%), suggesting the majority of studies were of high quality (Table 2.3).

Table 2.3: Quality Index scores for included articles

Author	**1**	**2**	**3**	**6**	**7**	**10**	**11**	**12**	**16**	**18**	**20**	**21**	**22**	**QI score n, (%)**
Falsetti (163)	1	1	1	1	1	1	1	1	1	1	1	1	0	12/13 (93%)
Falsetti (164)	1	1	1	1	1	1	1	1	1	1	1	1	0	12/13 (93%)
Genc (165)	1	1	1	1	1	1	1	1	1	1	1	0	0	11/13 (84%)
McGonagle (166)	1	1	1	1	1	1	1	1	1	1	1	0	0	11/13 (84%)
Li (167)	1	1	1	1	1	1	1	1	1	1	1	0	0	11/13 (84%)
Feydy (168)	1	1	1	1	1	1	1	1	1	1	1	0	0	11/13 (84%)
Freeston (169)	1	1	1	1	1	0	1	1	1	1	1	0	0	10/13 (76%)
Bandinelli (170)	1	1	1	1	1	1	1	1	1	1	1	0	0	11/13 (84%)
Falcao (171)	1	1	1	1	1	1	1	1	1	1	1	1	0	12/13 (93%)
Turan (172)	1	1	1	1	1	1	1	1	1	1	1	1	0	12/13 (93%)
Wiell (173)	1	1	1	1	1	1	1	1	1	1	1	1	0	12/13 (93%)
Woodburn, (174)	1	1	1	1	1	1	1	1	1	1	1	1	0	12/13 (93%)
Aydin (175)	1	1	1	1	1	1	1	1	1	1	1	0	0	11/13 (84%)
										Median				12 (93%)

2.3.3. Study characteristics

The characteristics of the 13 studies are displayed in Table 2.4 and include SpA, AS, PsA, RA and CPPD. A total of 1287 participants were reported, 928 with inflammatory arthritis and 359 controls. Of the 928 cases, 467 were females and 381 males. The 359 control participants included 174 females and 152 males. The mean (SD) age of the cases and controls was 45.3 (8.9) and 44.8 (9.2) years, respectively.

Table 2.4: Population characteristics of included studies

Study	Case demographics				Control demographics		
	Condition	**N**	**Sex (F:M)**	**Mean Age (years)**	**N**	**Sex (F:M)**	**Mean Age (years)**
Falsetti (163)	RA	158	111:47	58.9	50	26:24	56.3
	PsA	125	35:30	54.4			
Falsetti (164)	CPPD	57	27:30	69.4	50	25:25	66.3
Genc (165)	RA	24	22:2	44.4	20	15:5	42.6
	AS	18	4:14	41.4			
McGonagle (166)	Early SpA	20	8:12	43.0	10	4:6	44.0
	Established SpA	17	8:9	52.8			
Li (167)	AS	50	12:38	33.0	15	10:5	34.0
	RA	10	7:3	34.0			
	PsA	5	2:3	50.0			
	SpA	5	2:3	32.0			
Feydy (168)	SpA: no heel pain	25	13:12	45.0	24	12:12	50.0
	SpA: history of heel pain	13	9:4	50.0			
	SpA: heel pain	13	10:3	43.0			
Freeston (169)	PsA	42	23:19	46.1	10	6:4	43.9
Bandinelli (170)	PsA	92	54:41	51.6	40	22:18	49.6
Falcao (171)	SpA	66	34:32	32.5	23	NR	NR
	RA	23	NR	NR			
Turan (172)	AS	41	14:27	38.4	32	11:21	33.1
Wiell (173)	SpA	12	9:3	38.5	10	6:4	41.5
	Non-specific SpA	15	5:10	47.0			
Woodburn (174)	PsA	42	25:17	45.0	29	18:11	40.0
Aydin (175)	SpA	55	33:22	40.2	46	19:17	36.4

RA, rheumatoid arthritis; PsA, psoriatic arthritis; CPPD, calcium pyrophosphate deposition disease; AS, ankylosing spondylitis; PsA, psoriatic arthritis; N, number; F, female; M, male; NR, not reported.

2.3.4. Definition of US lesions

US lesions of inflammation and hypoechogenicity were not assessed or defined as a separate entity. AT thickening (cross-sectional diameter at the enthesis) was assessed in seven studies (165, 168, 170, 172-175) and was most commonly defined by the cut-off value of >5.29 mm (9). Eight studies assessed the presence of Doppler signal (164, 167-169, 171-174). One study (169) provided a definition of positive Doppler signal (Table 2.5).

The US lesions of bone-spurs, enthesophytosis and enthesophyte were synonymous. Ten studies (163-166, 168-170, 172-174) investigated enthesophyte formation, four provided definitions referenced to previous literature (163, 164, 166, 170). Eleven studies assessed erosions (163-170, 172-174), with five studies (163-166, 170) providing a referenced definition proposed by either OMERACT (152) or Balint (150). Four studies investigated tendon calcification (164, 168, 169, 173), with Falsetti (164) and Wiell (173) providing definitions, but not referenced to previous work. Cortical bone irregularities were investigated by one study (167), but no definition of the lesion was provided (Table 2.5).

Table 2.5: Definitions of inflammatory and structural ultrasound lesions

Study	Condition	US Lesion	Definition of US lesion with reference
Falsetti (163)	RA PsA	Posterior erosions	Interruption of the cortical bone profile (117, 176, 177)
		Enthesophytosis	Hyperechoic bony spur that interrupts the cortical profile, determining the characteristic shadowing (117, 176, 177)
Falsetti (164)	CPPD	Vascular signal	Presence of flow in orthogonal scans, presence of pulsatility of flow, permanence of flow at increase of pulse repetition frequency (no reference)
		Posterior erosions	Interruption of the cortical bone profile (163, 178, 179)
		Enthesophytosis	Hyperechoic bony spur interrupting the cortical profile, determining the characteristic shadowing (163, 178)
		AT calcification	Hyperechoic deposits with acoustic shadowing generally not in continuity with the bone profile observed within the fibrillar tendon structure (no reference)
Genc (165)	RA AS	Tendon thickened Bone erosion Enthesophyte	No specific in-text definitions were provided but references were provided to Balint (150) and Lehtinen (180)
McGonagle (166)	SpA	Bony spurs	Cortical protrusions seen in at least 2 perpendicular planes (152)
		Entheseal erosions	Cortical break visible in at least 2 perpendicular planes (152)
Li (167)	AS ReA PsA SpA	Abnormal Vascularisation Cortical bone erosion Achilles enthesitis Cortical bone irregularity	No in-text definitions of lesions or reference provided
Feydy (168)	SpA	Tendon thickening Vascularisation Bone erosion Enthesophyte Calcification	No in-text definitions of lesions or reference provided
Freeston (169)	PsA	Power Doppler signal	Presence of PD signal was considered positive if found within the tendon 2 mm proximal to the bony insertion, but not in the body of the tendon or any associated bursa (no reference)
		Erosion Bony spur Calcification	No in-text definitions of lesions were provided. The OMERACT (152) recommendations were discussed in text but no references were stated

Bandinelli (170)	PsA	AT thickness	Defined using Balint cut-off values (150)
		Power Doppler signal	No definition or reference as to what was considered presence of PD signal
		Erosions	A cortical break with a step down defect of bone contour (visible in the longitudinal and transversal axis) (150)
		Enthesophytes	Irregularity of cortical bone insertion (150)
Falcao (171)	PsA RA	Power Doppler signal	No definition or reference as to what was considered presence of PD signal
Turan (172)	AS	Tendon enlargement	No definitions of lesions or reference provided
		Erosions	
		Enthesophytes	
Wiell (173)	SpA Non-specific SpA	Tendon enlargement	Subjective estimation of focal or diffuse increased thickness (also considering the thickness of the opposite tendon). No reference
		Intratendinous vascularisation	PD signal inside the tendon (no reference)
		Entheseal vascularisation	PD signal at the tendon insertion adjacent to the cortical bone (no reference)
		Erosions	Bone cortex discontinuation in the insertional area, visualised in two planes (no reference)
		Enthesophytes	Bone cortex proliferation in the insertional area (no reference)
		Calcifications	Hyperechoic band or structure not adjacent to bone with or without acoustic shadow (no reference)
Woodburn (174)	PsA	Tendon thickening	No in-text definitions of lesions. Reference was made to GUESS (150) in the definition of US lesions
		Erosion	
		Enthesophyte	
Aydin (175)	SpA	Tendon thickness	Referred to Balint (150) cut off value to define thickness

2.3.5. Scoring of US lesions

The scoring of US lesions is presented in Table 2.6. AT thickening was scored in eight studies (165, 166, 168, 170, 172-175). The cut-off value of AT thickness > 5.29mm (150) was applied in five studies (165, 168, 170, 174, 175). AT thickness was directly measured in five studies (165, 168, 170, 174, 175), with AT thickness measured proximal to the enthesis in two studies (172, 175) (Table 7). Of the eight studies that scored Doppler signal (164, 167-173), two used a semi-quantitative system (169, 170). Six studies (164, 167, 168, 171-173) scored the Doppler signal using a binary system (present absent or normal/abnormal). Erosions, enthesophytes, calcifications and cortical irregularities were scored using a binary (present/absent) system with the exception of McGonagle (166), who used a semi-quantitative system to quantify enthesophyte size (Table 2.6).

Table 2.6: Ultrasound lesions and scoring of lesions in the Achilles tendon

Author	US Mode	US AT Lesion	Condition	Frequency (%)		Scoring of US AT Lesions
				Cases	Control	
Falsetti (163)	Grey-scale	Posterior erosions	RA	12	0	Inflammatory alteration graded according to a semiquantitative scale: Grade 1 (mild) Grade 2 (moderate) Grade 3 (considerable) Other lesions graded as present/absent expressed as a percentage.
			PsA	5		
		Posteroinferior enthesophytosis	RA	34	22	
			PsA	49		
Falsetti (164)	Grey-scale Power Doppler	Vascular signal in AT insertional on PDS		11	0	All US lesions graded as present/absent expressed as a percentage.
		Posterior erosions		0	0	
		Posterior inferior enthesophytosis		30	12	
		AT calcification	CPPD	51	0	
Genc (165)	Grey-scale	Tendon thickened	RA	42	5	In the systematic analysis of the tendon insertions, presence or absence of thickening in the tendon insertions (tendinitis), intratendinous focal changes (focal tendinitis), bony erosions and enthesophytes were recorded at each site Cut off values and measurement locations were defined by GUESS (150)
			AS	67		
		Bone erosion	RA	6	0	
			AS	11		
		Enthesophyte	RA	10	0	
			AS	28		

McGonagle (166)	Grey-scale	Tendon thickening	Early SpA	80	NR	The presence or absence of erosions and spurs was recorded in 3 separate regions within the enthesis organ complex: 1) the fibrous distal half of the insertion, 2) the fibrocartilaginous proximal half of the insertion, 3) the fibrocartilage-covered superior tuberosity. The sizes of the spurs were documented using a 0–3-point scale, where 1 = minimal, 2 = moderate, and 3 = large.
			Established SpA	NR		
		Entheseal erosions	Early SpA	55	0	
			Established SpA	41		
			Non-specific SpA	27		
		Bony spurs	Early SpA	40	80	
			Established SpA	100		
Li (167)	Grey-scale Colour Doppler	Abnormal vascularisation	AS	56	0	All US lesions graded as present/absent expressed as a percentage
			ReA	65		
			PsA	80		
			uSpA	20		
		Cortical bone erosion	AS	11	0	
			ReA	15		
			PsA	30		
			uSpA	10		
		Cortical bone irregularity	AS	46	0	
			ReA	45		
			PsA	80		
			uSpA	40		

Feydy (168)	Grey-scale Power Doppler	Tendon thickening (1cm from enthesis) Entheseal thickening	SpA: no heel pain SpA: history of heel pain SpA: heel pain	Refer to table 2.7		The following lesions were classified as signs of early injury: tendon and aponeurosis echostructure abnormalities, retrocalcaneal bursitis, thickening of the tendon at enthesis insertion and at 1 cm from enthesis, power Doppler signal in retrocalcaneal bursa, tendon or aponeurosis. The following lesions were classified as signs of chronic injury: calcifications, erosions and enthesophytes. Tendon thickness graded using Balint cut-off (150). Doppler signal assess by binary system (% present).
		Vascularisation Tendon	SpA: no heel pain	0	0	
			SpA: history of heel pain	2		
			SpA: heel pain	2		
		Vascularisation Bone enthesis junction	SpA: no heel pain	2	0	
			SpA: history of heel pain	1		
			SpA: heel pain	3		
		Bone erosion	SpA: no heel pain	2	0	
			SpA: history of heel pain	1		
			SpA: heel pain	3		
		Enthesophyte	SpA: no heel pain	8	10	
			SpA: history of heel pain	2		
			SpA: heel pain	2		
		Calcification	SpA: no heel pain	3	1	
			SpA: history of heel pain	0		
			SpA: heel pain	0		
		Cortical Bone	SpA: no heel pain	0	0	
			SpA: history of heel pain	0		

Freeston (169)	Grey-scale Power Doppler	Power Doppler	PsA		Not specific to AT	Not specific to AT	US abnormalities were divided into "active inflammation" and "structural Change" GS and PD were scored separately on a semiquantitative (SQ) scale (range 0–3) for each enthesis imaged. The GS score was a composite score of tendon/aponeurosis thickening and hypoechogenicity (loss of fibrillar pattern), using the highest score for either parameter as the final GS score. Presence of PD signal was considered positive if found within the tendon 2 mm proximal to the bony insertion, but not in the body of the tendon or any associated bursa. A score of GS > 1 and/or a PD score > 0 was arbitrarily used to describe US entheseal abnormality, as low-level GS changes can be seen in normal subjects (13). Markers of structural change at the enthesis, such as erosion, bony spur, and intratendinous calcification, were recorded as present or absent. Erosions were only scored if identified in 2 planes and located within the area into which the tendon or aponeurosis typically inserts.
		Erosion			5	0	
		Bony spur @ calcaneus			49	50	
		Intratendinous calcification @ Achilles			0	0	
Bandinelli (170)	Grey-scale	AT thickness	PsA	R	38	0	Enthesis thickness was expressed in millimetres (mm) and was also scored by Balint cut-off (150). Vascularity, studied at insertion of enthesis at the cortical bone, was scored as a binary item (positive if any signal was present and negative if absent) and was also semi-quantitatively graded (no flow (grade 0); only one spot detected (mild or grade 1); 2 spots (moderate or grade 2); >3 spots (severe or grade 3), a total PD was calculated by summing semi quantitative PD scores of each tendon.
				L	29		
		Power Doppler signal		R	14	0	
				L	19		
		Erosions		R	2	0	
				L	1		
		Enthesophytes		R	52	0	
				L	55		
Falcao (171)	Grey-scale Colour Doppler	Doppler signal	SpA: heel pain		1	0	The maximal diameter obtained on longitudinal and transversal scan was collected. The presence or absence of Doppler signal in the cortical bone profile was also recorded The average of three consecutive measurements of the maximal thickness obtained in longitudinal and transverse axes was scored.
			PsA		6		
			RA		NR		

GUESS, Glasgow Ultrasound Enthesis Scoring System

Table 2.7: Scoring of Achilles tendon thickness by direct measurement

Study	Condition	Cases mean thickness, mm (SD)	Controls mean thickness, mm (SD)
Genc (165)	RA	R - 5.1 (1.0)	4.5 (0.4)
		L - 5.2 (0.8)	
	AS	R - 4.9 (0.8)	
		L - 5.4 (1.2)	
Feydy (168)	SpA no heel pain	4.1 (0.6)[a]	4.4 (0.6)
	SpA history heel pain	4.5 (1.2)	
	SpA with heel pain	4.3 (1.2)	
Bandinelli (170)	PsA	R - 5.0 (1.1)[b]	R - 3.7 (0.4)
		L - 4.9 (1.0)	L - 3.8 (0.5)
Woodburn (174)	PsA with enthesitis	4.6 (1.3)	3.8 (0.7)
	PsA no enthesitis	3.9 (0.6)	3.6 (0.6)
Aydin (175)	SpA	4.4 (0.8)[c]	4.0 (0.8)
		4.3 (0.6)	4.1 (0.5)

[a] Left and right AT combined in heel pain group. In all other groups, only data from the AT was reported

[b] The AT of the most symptomatic limb measured in PsA groups. Not clear in controls if data was unilateral or combined.

[c] Combined data of left and right AT

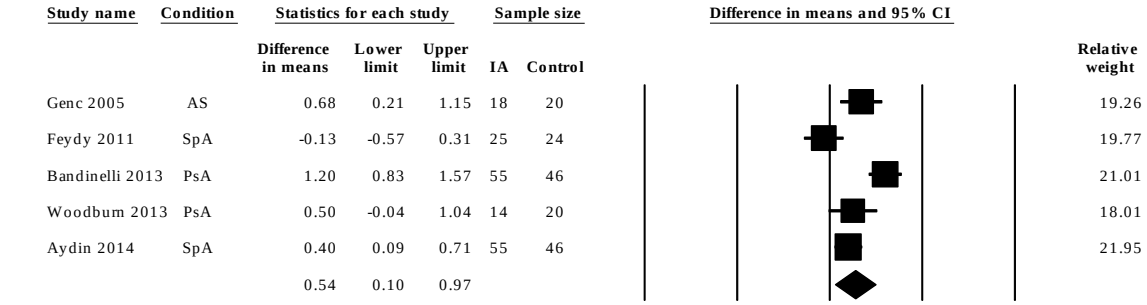
2.3.6. Pooled results

In studies with SpA participants, the lesions of tendon thickness, enthesophyte formation and erosion were considered for meta-analysis. Doppler signal was not viewed as appropriate for data pooling due to inconsistencies in the definition of what constituted a positive Doppler signal. Similarly, the US lesions of tendon calcifications, cortical irregularities and hypoechogenicity were not adequately defined so were not considered for meta-analysis. Three studies (163, 165, 171) included a RA participants used as a comparison group. Only one AT lesion (erosion) was reported in more than one RA study and was considered appropriate for meta-analysis. One study involving participants with CPPD (164) and that met the inclusion criteria, was not included for data pooling.

2.3.7. Tendon thickening at the Achilles tendon enthesis

Eight studies assessed AT thickness by direct quantitative measurement or comparison to cut-off values, or a combination of both methods (165, 166, 168, 170, 172-175). Five studies (165, 168, 170, 174, 175), all of which included participants with SpA, quantified

AT thickness in relation to established cut-off values (150) and were considered appropriate for meta-analysis. The mean thickness at the enthesis in SpA participants was 0.54mm thicker than control participants (95% CI = 0.10 to 0.97mm) (Figure 2.2). Three studies (166, 172, 173) were excluded from meta-analysis as assessment of the AT thickness was not referenced to a cut-off value or directly measured.

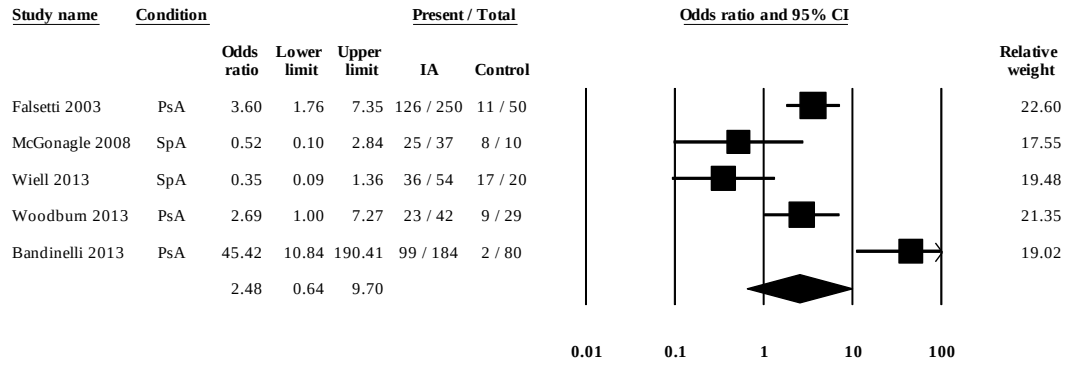


Test for heterogeneity: $\chi^2 = 22.23$, df = 4 (P < 0.001); $I^2 = 82\%$
Test for overall effect: z = 2.40 (P = 0.016)

Figure 2.2. Forest-plot of studies reporting direct measurement of Achilles tendon entheseal thickness in SpA

2.3.8. Enthesophyte formation

Ten studies reported enthesophyte formation at the posterior calcaneus (163-166, 168-170, 172-174). Five studies (163, 166, 170, 173, 174) defined enthesophyte and were considered appropriate for meta-analysis, Five studies were excluded from the meta-analysis; four studies provided no definition of an enthesophyte (165, 168, 169, 172) and one study was in participants with CPPD (164). In the meta-analysis, there was no significant increase in enthesophytes in the participants with SpA, compared with the control participants (OR = 2.48, 95%CI = 0.64 to 9.70, P = 0.19, Figure 2.3).



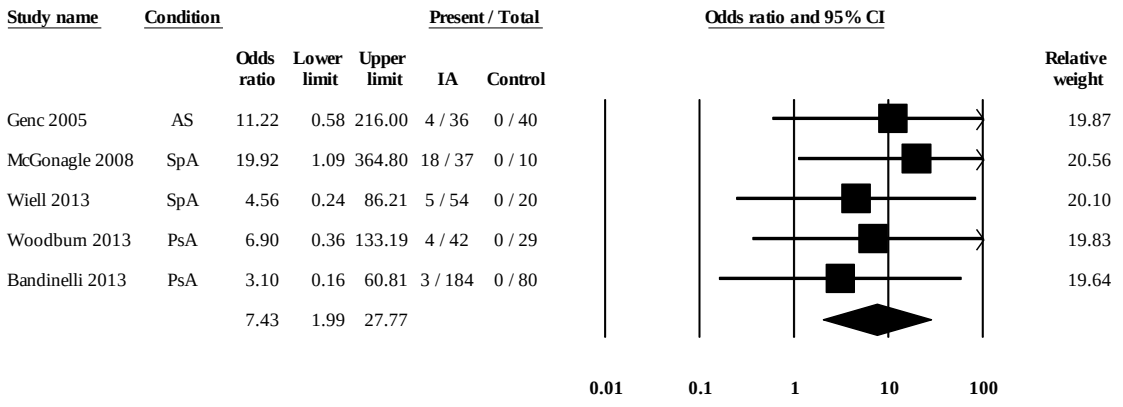
Test for heterogeneity: $\chi^2 = 27.80$, df = 4 ($P < 0.001$); $I^2 = 86\%$

Test for overall effect: z = 1.31 (P = 0.19)

Figure 2.3. Forest-plot of studies reporting enthesophyte formation at the Achilles enthesis in SpA

2.3.9. Erosions

Ten SpA studies reported evidence of calcaneal erosions (163-170, 172-174). Five studies were excluded from meta-analysis as they did not provide definitions of calcaneal erosion or data reporting was incomplete (23, 27, 28, 30, 33). The five remaining SpA studies (165, 166, 170, 173, 174) defined erosions and were considered appropriate for meta-analysis. The meta-analysis demonstrated that calcaneal erosions were observed significantly more frequently in participants with SpA compared with healthy controls (OR = 7.43, 95%CI = 1.99 to 27.77, P = 0.003, Figure 2.4).



Test for heterogeneity: $\chi^2 = 0.96$, df = 4 ($P = 0.92$); $I^2 = 0\%$

Test for overall effect: z = 2.98 (P = 0.003)

Figure 2.4. Forest-plot of studies reporting calcaneal erosion in SpA

Two RA studies also reported calcaneal erosions (163, 165) and were considered appropriate for meta-analysis. The meta-analysis demonstrated that calcaneal erosions were present significantly more frequently in participants with RA compared with healthy control participants (OR = 9.60, 95%CI = 1.23 to 74.94, p = 0.03, Figure 2.5).

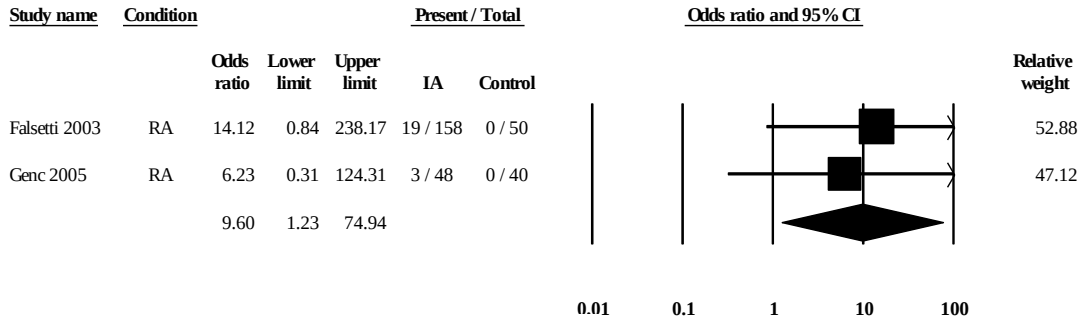


Figure 2.5. Forest-plot of studies reporting calcaneal erosion in RA

2.4. Discussion

This review identified evidence for differences in US lesions of the AT that distinguished between people with inflammatory arthritis and healthy controls by reviewing case-control studies. The studies were of high quality with the majority involving participants with SpA, the main focus pertaining to entheseal lesions of the AT. Limited evidence was found comparing US lesions of the AT in RA and CPPD. No studies assessed US lesions of the AT in gout. In SpA, pooled estimates suggest increased entheseal thickening, and in both SpA and RA, increased frequency of calcaneal erosions compared to controls. There was no evidence to indicate that enthesophyte formation was more frequent in SpA compared to controls.

To define and score tendon thickness in inflammatory arthritis, the scoring system and cut-off score proposed by Balint (150) was the most frequently applied method. Although AT thickness was defined, this review found limited information (two studies) relating to the assessment of AT thickness at sites proximal to the AT enthesis (172, 175). Quantifying thickness proximal to the enthesis has become significant as the recent OMERACT definition of entheseal tendon thickness references the body of the tendon as a point of comparison (153).

Although the presence of Doppler signal has been used to discriminate between inflammatory and mechanical change at the AT enthesis in SpA, Doppler signal may be associated with degenerative change at the AT sites proximal to the enthesis. In CPPD, the presence of Doppler signal was not associated with inflammation but linked to tendon degeneration (164). No similarities were found in the definition of Doppler signal, with only one study (164) providing a definition of a positive Doppler signal. However, the definition of Doppler signal has only recently been described by OMERACT (153).

The majority of studies used a simple binary method (present/absent) to score Doppler signal. The scoring method is unable to demonstrate the degree of inflammatory activity or display sensitivity to change. The two studies that used a semi-quantitative approach to score Doppler signal differed (169, 170). Freeston (169) scored the Doppler signal as mild, moderate or severe, whereas Bandinelli (170) reported on the quantity of Doppler signal detected.

Although the pooled analysis did not demonstrate increased frequency of enthesophyte formation in SpA, consideration must be given to the size and location of the enthesophyte and relationship to the disease type and stage. McGonagle (166), Bandinelli (170) and Freeston (169) investigated enthesophyte formation in the early stages of SpA, with McGonagle (166) comparing early and established SpA. McGonagle (166) also quantified enthesophyte size, reporting large enthesophytes in established SpA, suggesting that enthesophyte formation may be controlled by the inflammatory processes in the early stages of the disease and proliferate when inflammation diminishes.

Only one study was found describing the location of the enthesophyte formation (26). McGonagle (166) reported the enthesophyte formation in the distal enthesis in both early and established SpA. Enthesophyte formation was also a feature in CPPD, but, as with the majority of SpA studies, the anatomical location of the enthesophyte at the enthesis organ and size was not reported. Enthesophytes were quantified by one of three methods; (i) binary (present/absent); (ii) non-validated scoring or (iii) as a component of the Glasgow Ultrasound Enthesis Scoring System (GUESS), using the pole of the calcaneus AT enthesis subscale (150). Of note, the GUESS has no method for the quantification of enthesophyte size or location.

Erosions were a feature at the AT enthesis in SpA and RA. Presentation of bone erosions across studies differed between SpA and RA in size, location and associated bone formation. Li (167) reported cortical bone erosions to have shorter disease duration in SpA, than in participants without erosion and cortical bone erosions to occur at areas of the periosteal and the enthesis fibrocartilage. McGonagle (166) further reported that erosions were observed in fibrocartilaginous areas, either the proximal part of the insertion and the superior tuberosity but did not occur in the distal part of the AT enthesis in people with early SpA. Falcao (171) demonstrated that erosions typically occur in the bursal proximal portion of the enthesis in people with SpA, possibly establishing a link between erosions and adjacent anatomical structures.

This systematic review has some limitations. The OMERACT US lesion definitions were applied (153) in the review: however all studies included in this review were published prior to the release of the OMERACT definitions. A number of studies were excluded from data pooling due to inconsistencies in data reporting, and these studies may have added significant weighting to the pooled data. The review was restricted to case-control studies and did not consider findings from other study designs.

Further work should distinguish between US lesions that are reflective of inflammatory and structural damage in the AT and calcaneal enthesis. This may enable the differentiation of US lesions of the AT and enthesis in other forms of inflammatory arthritis, for example, RA, gout or differentiating between early and established SpA. Investigation into the size, specific zones, calcaneal erosions and associated enthesophyte formation will give further insights into the differentiation between mechanical and disease-driven enthesophyte formation. Future studies should consider the revised OMERACT definition (153) of AT thickness in describing lesions at the AT.

2.5. Conclusion

The systematic review identified that the majority of studies reported US lesions in SpA, but limited evidence relating to other forms of inflammatory arthritis. Analysis revealed significant differences in the presentation of tendon thickness and erosions in participants with SpA. US lesions were not consistently defined with regard to OMERACT definitions and numerous scoring systems were used across the majority of studies. Consistent application of the OMERACT US definitions and the scoring of US lesions is required in future studies of AT disease in inflammatory arthritis. Further work should distinguish between US lesions reflective of inflammation and structural damage in the AT and calcaneal enthesis.

CHAPTER 3:

Gait characteristics associated with the foot and ankle in inflammatory arthritis: a systematic review and meta-analysis

3.0. Purpose of systematic review

The systematic review was undertaken for the following reasons:

1. To highlight the limited data that exists describing gait adaptations in people with tophaceous gout.
2. To compare and contrast if the gait strategy in people with gout to other forms of inflammatory arthritis. As gout has a different pathological process to other forms of inflammatory arthritis it was important to articulate that gait adaptation in gout should not be considered a similar process to other forms of inflammatory arthritis.
3. To establish what gait parameters are frequently assessed in inflammatory arthritis to explain adaptations in gait strategy.
4. To inform research design. Specifically, information surrounding what gait parameters were frequently assessed in inflammatory arthritis guided the gait parameters assessed in the thesis.
5. To evaluate the differing methodologies used to quantify gait strategy in inflammatory arthritis. This was important and guided the decision to use the multi-segmented foot model detailed in chapter 4.
6. Where appropriate, to conduct meta-analysis to determine the extent to which gait parameters differed between people with inflammatory arthritis and healthy controls.
7. No previous reviews have systematically assessed gait parameters across different forms of inflammatory arthritis.

3.1. Introduction

The term inflammatory arthritis has been used to describe a number of inflammatory joint diseases including: RA, AS, PsA, gout (181). Inflammatory arthritis can cause lower limb and foot pain and impairment, functional disability, reduced mobility, joint deformity and altered gait strategies (110, 182-185).

Foot pain is considered an important factor in the development of antalgic gait in inflammatory arthritis, specifically in RA and gout (18, 182, 186). In RA, foot pain is derived from structural and functional alterations associated with inflammatory and structural change (182, 187). With the development of an antalgic gait, adaptations occur based upon a pain avoidance strategy. Previous studies have reported gait adaptations in RA which include: a decrease in walking velocity and subsequent alterations to velocity-related spatiotemporal parameters including, reduced cadence, increased double limb support time and decreased step length (188-192). Changes to kinematic parameters including reduced sagittal plane ankle ROM and increased peak rearfoot eversion have also been reported (183, 188, 191, 192). Furthermore, previous studies have reported alteration to kinetic parameters including reduced peak ankle plantarflexor power associated with reduced walking velocity, reduced ankle joint ROM, reduced ankle joint angular velocity, reduced ankle plantarflexor moments and decreased strength of the ankle plantarflexor muscles (190, 191, 193). An increase in peak forefoot plantar pressure parameters has also been reported in RA (190).

Gait analysis provides information about spatial-temporal parameters, kinetics, kinematics and muscle activity to further delineate the relationship between joint disease, joint impairments and compensatory gait strategies adopted to overcome painful and disabling deformities (189, 194). Gait analysis has been reported as a useful clinical tool to quantify foot function in both early and established RA (110, 183, 188, 189). RA commonly affects the lower limb and foot in relation to pain, activity limitation and disability, thereby affecting people's quality of life (188, 195). However, less commonly described inflammatory arthritic conditions from a lower limb biomechanical perspective, such as AS, PsA, gout, polymyalgia rheumatica (PMR), SS and systemic lupus erythematous (SLE), also have various consequences for the lower limb such as changes in foot function, and extra articular complications involving the skin and vascular integrity (18, 174, 184, 185, 196-198).

In a recent systematic review of studies investigating walking abnormalities associated with RA, Baan (199) demonstrated changes in gait such as a slower walking, longer double support time, and avoidance of extreme positions. These changes were in relation to the frequently found foot deformities in RA, for instance, hallux valgus, pes planovalgus and forefoot abnormalities. However, Baan (199) reported only gait parameters in RA and did not consider other inflammatory arthritic conditions. Recently there has been an interest in evaluating gait patterns in other inflammatory arthritic conditions that includes gout (18), PsA (174) and AS (185). No previous systematic review has conducted meta-analysis of gait parameters in inflammatory arthritis compared to healthy control population. The aim of the systematic review was to evaluate spatiotemporal, foot and ankle kinematic, kinetic, peak plantar pressure and muscle activity parameters in people with inflammatory arthritis and healthy controls.

3.2. Methods

3.2.1. Identification of studies

Four electronic databases were searched (Medline, CINAHL, SportsDiscus and The Cochrane Library). The search was completed in March 2015. The search strategy combined terms appropriate to the anatomical location; the type of gait analysis and inflammatory arthritic condition (Table 3.1). An initial review was undertaken of all titles and abstracts. All articles considered appropriate were read in full to establish if they met the eligibility criteria.

Table 3.1: Search strategy

a	1	Subject term	exp. Gait analysis
	2	Keywords	Lower extremi* [or] Lower limb* [or] Foot [or] Feet [or] Ankle* [or] Leg* [or] Rear foot [or] Hind foot [or] Knee [or] Hip
	3	Keywords	Kinematic* [or] Kinetic* [or] Spatial [or] Temporal [or] Spatio-temporal [or] electromy* [or] EMG [or] plantar pressure [or] pressure [or] force [or] pedobarogr*
	4	Combine	2 [and] 3
	5	Combine	1 [or] 4
b	6	Subject term	exp. Rheumatic disease
	7	Subject term	exp. Rheumatoid arthritis
	8	Subject term	exp. Gout
	9	Subject term	exp. Systemic sclerosis
	10	Subject term	exp. Polymyalgia rheumatica
	11	Subject term	exp. Psoriatic arthritis
	12	Subject term	exp. Lupus erythematosus
	13	Subject term	exp. Ankylosing spondylitis
	14	Keywords	Rheumat* [or] Spondyl*
c	15	Combine	6 [or] 7 [or] 8 [or] 9 [or] 10 [or] 11 [or] 12 [or] 13 [or] 14
	16	Combine	5 [and] 15

Search strategy: Gait characteristics associated with the foot and ankle in inflammatory arthritis. (a) Search terms for gait analysis (b) search terms for inflammatory rheumatic disease (c) Combination of search terms

3.2.2. Inclusion and exclusion criteria

Studies were included if they: reported people with inflammatory arthritis that included RA, AS, PsA, gout, PMR, systemic sclerosis (SSc) and SLE; assessed adults aged >18 years old; reported spatiotemporal, kinematic, kinetic, peak plantar pressure or muscle activity data during gait; were articles that included a healthy group as means of comparison; and were published in English. Surgical and pharmacological intervention studies were excluded. No limitation was placed on the date of the publication.

3.2.3. Data extraction

All titles and abstracts identified through database searches were downloaded into Endnote X4 (Thomson, Reuters, Carlsbad, CA). Each title and abstract was evaluated for potential inclusion by two independent reviewers. If there was insufficient information contained in

the title to determine suitability the full text was obtained. Any discrepancies between the two reviewers were resolved at a consensus meeting.

3.2.4. Assessment of methodological quality and diversity

The quality of studies was evaluated independently by two reviewers, who were blinded to author and publication details. Study quality was rated using a modified version of the quality index tool originally described by Downs and Black (155). The quality index tool consists of 27 items which allow for assessment of internal and external validity, reporting and power. The tool was modified to exclude thirteen questions that were not relevant to the articles assessed in this review, resulting in the retention of 14 questions (Table 3.2). The scoring system grades each of the 14 questions either a (0 = no/unable to determine, or 1 = yes) with the exception of question five (0 = no, 1 = partially, 2 = yes). The summed score for each study, the maximum achievable being 15, was calculated. No cut off scores have been described to categorise study quality for the Downs and Black quality Index (157). In the absence of validated cut-off scores and following review of past articles that have applied the Downs and Black criteria the following cut-off values were applied: ≥ 12 high quality, greater than 7, but less than 12 moderate quality, < 6 poor quality (156, 157).

Table 3.2: Questions included from the Quality Index checklist to rate study quality

1	Is the hypothesis/aim/objective of the study clearly described?
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3	Are the characteristics of the patients included in the study clearly described?
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6	Are the main findings of the study clearly described?
7	Does the study provide estimates of the random variability in the data for the main outcomes?
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
16	If any of the results of the study were based on "data dredging", was this made clear?
18	Were the statistical tests used to assess the main outcomes appropriate?
20	Were the main outcome measures used accurate (valid and reliable)?
21	Were the patients in the cases and controls (case-control studies) recruited from the same population?
22	Were study subjects in the cases and controls (case-control studies) recruited over the same period of time?

3.2.5. Data analysis and synthesis

Relevant gait parameters and information regarding overall study design, subject characteristics and gait analysis parameters were extracted from each paper by one reviewer from those studies meeting the inclusion criteria. Data was tabulated according to the specific inflammatory arthritic condition and gait parameters.

The clinical and methodological diversity among the studies was assessed to determine the appropriateness of data pooling for meta-analysis. Factors considered important for comparison included: mean age, sex distribution, case and comparison group size, data acquisition methodology and instrumentation. Two authors reviewed the included studies and reached consensus on the appropriateness of conducting meta-analysis. Heterogeneity was considered low if the I^2 value was 25% or less, moderate if the value was between 25% and 50%, high if between 50% and 75% and very high if greater than 75% (160). A fixed-

effect model was applied where the I^2 statistic was less than 50% and the Chi^2 test indicated a non-significant degree of heterogeneity ($P > 0.1$). The random-effect model was used where the I^2 statistic was greater than 50% and the Chi^2 test indicated statistically significant heterogeneity ($P < 0.1$) (161).

Where data was available from each paper a standardised mean difference (SMD) (Hedges's g) and 95% CI were calculated (200). This was calculated as the difference between cases and control participant means divided by the pooled SD. Interpretation of SMDs was based on previous effect size (ES) guidelines: small effect ≥ 0.2, medium effect ≥ 0.5, large effect ≥ 0.8 (201). Effect sizes were considered statistically significant if the 95% CI did not contain zero for the SMD. All data were analysed using the Comprehensive Meta-analysis, version 2 (159). Studies that met the inclusion criteria but did not report SD, or where the SD could not be obtained were excluded from meta-analysis.

3.3. Results

3.3.1. Selection and characteristics of studies

All items were reported using the PRISMA statement (162). 3134 citations were identified for screening with 36 articles being included for further analysis (Figure 3.1). Thirty-one studies evaluated gait parameters in RA (110, 183, 186-192, 202-223), three in AS (185, 224, 225) one in PsA (174) and one in gout (18). Twenty-four studies examined spatiotemporal gait parameters, with 19 in RA, two in AS, one PsA and gout (Table 3.3). Twenty-one studies assessed kinematic parameters, with 17 in RA, three AS and one in PsA (Table 3.4). Ten studies examined kinetic parameters with eight in RA, one AS and one in PsA (Table 3.5). Sixteen studies evaluated plantar pressure parameters, with 15 in RA and one in gout (Table 3.6). Three studies assessed all gait parameters (spatiotemporal, kinematic, kinetic and plantar pressures) in the population (186, 188, 189). No studies reported gait characteristics in SSc, PMR or SLE. The total number of participants was 2275; 1321 with inflammatory arthritis and 954 controls. Case participants included 863 females and 312 males. The mean (SD) age of the cases and controls was 52.6 (9.3) and 47.8 (9.2) years, respectively (Table 3.7).

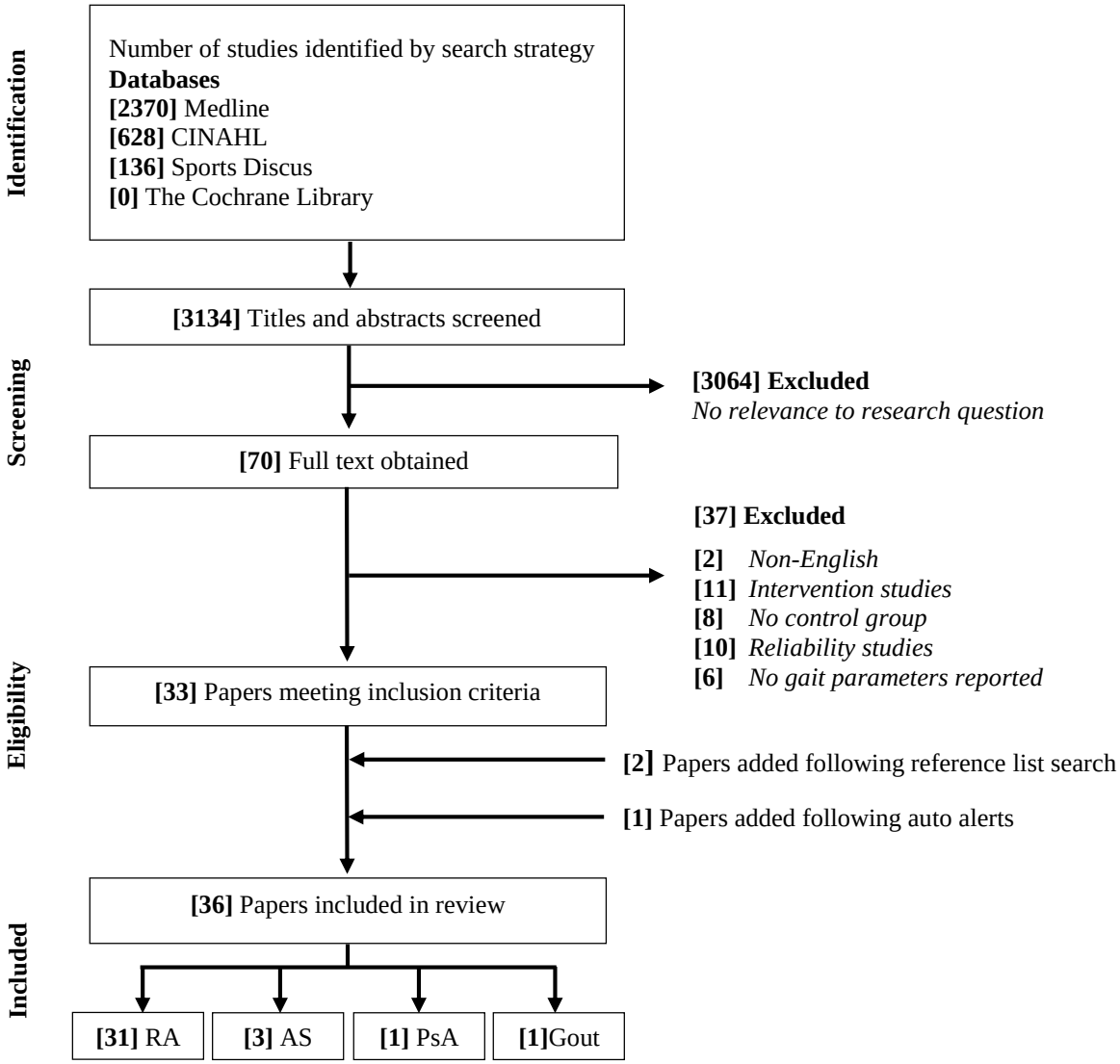


Figure 3.1. PRISMA flow chart

Table 3.3: Spatiotemporal gait parameters measured and methods of data acquisition.

Author & reference		IA	Data acquisition method	Parameters measured
Dubbeldam	(205)	RA	3D gait analysis	Walking velocity, cadence, stride time, double stance percentage, stride length, stride width, step length
Rome	(207)	RA	Electronic Walkway	Walking velocity, cadence, gait cycle time, single support time, double limb support time, base of support
Eppeland	(208)	RA	Electronic Walkway	Walking velocity, cadence, step length, stance phase duration, step width
Turner	(188)	RA	Electronic Walkway	Walking velocity, double support time
Turner	(189)	RA	Electronic Walkway	Walking velocity, double support time
Weiss	(191)	RA	3D gait analysis	Walking velocity, cadence, stride length, step length, single support, double support
Turner	(190)	RA	Electronic Walkway	Walking velocity, double support percentage
Turner	(183)	RA	Electronic Walkway	Walking velocity, cadence, gait cycle time, stride length, double support time
Laroche	(211)	RA	3D gait analysis	Walking velocity, stride length, walking frequency, stance phase duration, double stance phase duration
Khazzam	(192)	RA	3D gait analysis	Walking velocity, stride length, cadence, stance duration
Semple	(213)	RA	Electronic Walkway	Walking velocity
Laroche	(212)	RA	3D gait analysis	Walking velocity, walking frequency, stride length, stance duration, double support phase duration
Woodburn	(110)	RA	3D gait analysis	Walking velocity
O'Connell	(186)	RA	Electronic Walkway	Walking velocity, cadence, stride length
Fransen	(219)	RA	Electronic Walkway	Walking velocity, stride length, percentage double support time, stance phase percentage
Zebouni	(225)	AS	Electronic Walkway	Contact time, stride length & stride frequency
Isacson	(226)	RA	Electronic Walkway	Walking velocity, stride length, duration of gait cycle
Minns	(221)	RA	Force sandals	Walking velocity, cadence, stride length, stride width
Simkin	(222)	RA	Force plate	Walking velocity, stride frequency, stride length, stance time, swing time, double support period
Stauffer	(223)	RA	Electronic Walkway	Walking velocity, cadence, stance phase percentage
Del Din	(185)	AS	3D gait analysis	Walking velocity, stride period, stride length, stance period
Mangone	(224)	AS	3D gait analysis	Walking velocity, cadence, stride length
Woodburn	(174)	PsA	Electronic Walkway	Walking velocity
Rome	(18)	Gout	Electronic Walkway	Walking velocity, cadence, step length, stride length, single leg support, double leg support, stance phase duration, swing phase duration

IA, inflammatory arthritis

Table 3.4: Kinematic gait parameters measured and methods of data acquisition.

	IA	Parameters measured	Kinematic Assessment Method & model	Biomechanical Model
Barn (203)	RA	Peak rearfoot eversion, peak rearfoot plantarflexion, lowest navicular height, peak midfoot inversion, peak forefoot abduction, peak forefoot dorsiflexion	3D analysis	Hyslop (109)
Dubbeldam (205)	RA	Tibio-talar dorsiflexion, medial arch collapse, hallux dorsiflexion, subtalar eversion, mid-/hindfoot supination, fore-/midfoot supination, leg/hindfoot external rotation, forefoot/ankle abduction metatarsal 1-5 angle, hallux abduction	3D analysis	(Heidelberg) Simon (114)
Turner (188)	RA	Rearfoot terminal stance plantarflexion, rearfoot midstance eversion, forefoot midstance inversion, forefoot peak abduction, lowest navicular height, peak hallux dorsiflexion	3D analysis	Carson (113)
Turner (189)	RA	Initial foot contact angle, terminal stance heel rise, minimum navicular height in stance, maximum rearfoot eversion in stance,	3D analysis	Carson (113)
Turner (190)	RA	Initial foot contact angle, terminal stance heel rise, minimum arch height, peak eversion	3D analysis	Carson (113)
Weiss (191)	RA	Trunk tilt range, trunk lateral sway range, hip flexion extension range, hip abduction, knee flexion extension range, ankle plantarflexion, ankle dorsiflexion	3D analysis	Newington (227)
Khazzam (192)	RA	Sagittal, coronal and transverse motion of the hindfoot, forefoot and hallux at load response, midstance, terminal stance, pre-swing, initial swing, mid-swing and terminal swing	3D analysis	Milwaukee (228)
Laroche (211)	RA	Range of motion of MTP joints, foot angle at toe-off	3D analysis	Courtine (229) & Borghese (230)
Laroche (212)	RA	Mean articular amplitudes of MTP joints, mean plantar/dorsi flexion ROM of MTP joints	3D analysis	Courtine (229) & Borghese (230)
Woodburn (110)	RA	Peak dorsiflexion & plantarflexion & ROM, Peak inversion & eversion & ROM, peak adduction, abduction & ROM for the rearfoot & forefoot, minimum & maximum height & displacement of the navicular, peak extension, flexion & ROM of the hallux	3D analysis	Carson (113)
Turner (183)	RA	Max ankle joint dorsi/plantarflexion, maximum inversion/eversion, maximum internal/external rotation, range of ankle joint motion in sagittal, frontal and transvers plane, toe off angle, time to maximum eversion motion time integral of sagittal, frontal and transverse ankle motion	Electromagnetic tracking	N/A
Woodburn (187)	RA	Dorsi/plantarflexion, inversion/eversion & internal/external rotation of ankle joint during stance phase of gait	Electromagnetic tracking	N/A
Woodburn (202)	RA	Dorsi/plantarflexion, inversion/eversion & internal/external rotation of ankle joint during stance phase of gait	Electromagnetic tracking	N/A
O'Connell (221)	RA	Ankle motion during stance, mean heel rise during stance phase of gait	3D analysis	Siegel (218)
Siegel (218)	RA	Foot to floor contact angle, degree of heel rise at toe off, foot out toe angle, plantar/dorsiflexion/inversion/eversion/abduction/adduction of the foot	3D analysis	Siegel (218)
Isacson (220)	RA	Hip, knee & ankle joint flexion/extension, abduction/adduction, rotation	Electrogoniometry	N/A
Stauffer (223)	RA	Standing knee flexion, sagittal, coronal & transverse knee motion, stance phase knee flexion	Electrogoniometry	N/A

Del Din (185)	AS	Flexion/extension, abduction/adduction and internal/external rotation of the trunk, pelvis, hip and ankle. Only flexion/extension reported at the knee	3D analysis	Leardini (231) & Sawacha (232)
Mangone (224)	AS	Pelvis ROM, pelvic tilt, pelvic rotation, shoulder rotation, hip flexion	3D analysis	Davis (233)
Zebouni (225)	AS	Hip flexion & extension, knee flexion & extension	Electrogoniometry	
Woodburn (174)	PsA	Peak ankle/rearfoot dorsiflexion, peak ankle/rearfoot eversion, peak ankle/rearfoot internal rotation, navicular height	3D analysis	Hyslop (109)

IA, inflammatory arthritis; ROM, range of motion; 3D, three-dimensional; N/A, not applicable

Table 3.5: Kinetic gait parameters measured and methods of data acquisition.

Author	Condition	Parameters measured
Barn (203)	RA	Peak ankle power, peak ankle moment
Turner (189)	RA	Peak ankle plantarflexion moment, peak ankle power
Weiss (191)	RA	Joint moments at ankle joint
Turner (190)	RA	Ground reaction forces; peak plantarflexion moment, peak ankle joint power
O'Connell (221)	RA	Ground reaction forces, mean ankle plantarflexion net muscular moment
Siegel (218)	RA	Muscular moment at ankle joint, ground reaction forces
Simkin (222)	RA	Peak force on heel, peak force on midfoot, peak force on 1, 2 metatarsal heads, peak force on 3, 4, 5 metatarsal heads, peak force on toes
Stauffer (223)	RA	Ground reaction forces
Del Din (185)	AS	Flexion-extension, abduction-adduction & internal-external rotation moments at ankle joint
Woodburn (174)	PsA	Peak ankle joint moment, peak ankle joint power, peak AT force

Table 3.6: Plantar pressure gait parameters measured and methods of data acquisition.

Author	Condition	Acquisition system	Parameters measured
Bowen (204)	RA	In-shoe pressure system	Peak plantar pressure forefoot
Yavuz (206)	RA	Custom device	Peak plantar pressure (1st metatarsal head, hallux, lesser digits); Pressure Time Integral (1st metatarsal head, hallux)
Schmiegel (210)	RA	Plantar pressure plate	Peak plantar pressure (hindfoot, midfoot, metatarsal 1, 2, 3-5, hallux, 2nd toe, toes 3-5)
Schmiegel (209)	RA	Plantar pressure plate	Peak plantar pressure (hindfoot, midfoot, metatarsal 1, 2, 3-5, hallux, 2nd toe, toes 3-5)
Turner (188)	RA	Plantar pressure plate	Centre of pressure at 50% of foot length, lesser toe contact area, midfoot contact area, forefoot peak pressure
Turner (189)	RA	Plantar pressure plate	Centre of pressure at 50% of foot length, lesser toe contact area, midfoot contact area, forefoot peak pressure
Semple (213)	RA	Plantar pressure plate	Velocity and duration centre of pressure
Rosenbaum (214)	RA	Plantar pressure plate	Peak plantar pressure (hindfoot, midfoot, metatarsal 1, 2, 3-5, hallux, 2nd toe, toes 3-5)
Turner (190)	RA	Plantar pressure plate	Centre of pressure at 50% of foot length, lesser toe contact area, midfoot contact area, forefoot peak pressure
Tuna (215)	RA	Plantar pressure plate	Peak plantar pressure (hindfoot, midfoot, forefoot phalanx)
Otter (216)	RA	Plantar pressure plate	Peak plantar pressure (forefoot), force time integral (forefoot)
Turner (183)	RA	Plantar pressure plate	Peak plantar pressure and force, PTI & FTI, total contact area for hindfoot, midfoot forefoot, hallux & digits
O'Connell (186)	RA	Force plate system	Centre of pressure at 50% of foot length
Woodburn (217)	RA	In-shoe pressure system	Peak plantar pressure (metatarsal heads 1-5)
Minns (221)	RA	Plantar pressure plate	NR
Rome (18)	Gout	In-shoe pressure system	Peak plantar pressure (hindfoot, midfoot, 1st , 2nd , 3rd, 4th & 5th metatarsal heads, hallux, toes 2-5

PTI, pressure time integral; FTI, force time integral; NR, not reported

Table 3.7: Characteristics of included studies.

Author, year (ref)	IA	Case demographics			Control demographics		
		Number	Gender (F:M)	Age mean (SD)	Number	Gender (F:M)	Age mean (SD)
Barn, 2013, (203)	RA	10	6:4	50.0 (9.0)	5	3:2	47.0 (6.0)
Woodburn, 2013, (174)	PsA	42	25:17	45.3 (12.7)	29	18:11	40.0 (10.5)
Bowen, 2011, (204)	RA	114	93:21	59.6 (12.0)	49	37:12	33.2*
Del Din, 2011, (185)	AS	12	4:8	49.4 (10.5)	12	4:8	55.75 (3.2)
Mangone, 2011, (224)	AS	17	2:15	47.0 (21.9)	10	1:9	38.7 (14.5)
Rome, 2011, (18)	GT	25	6:19	61.2 (11.7)	25	6:19	57.3 (12.2)
Dubbeldam, 2011, (205)	RA	21	17:4	46.6 (12.8)	14	11:3	41.6 (8.5)
Yavuz, 2010, (206)	RA	9	8:1	53.2 (12.3)	14	9:5	53.6 (18.7)
Rome, 2009, (207)	RA	19	15:4	56.1 (11.1)	21	12:9	51.0 (8.9)
Eppeland, 200, (208)	RA	17	7:10	51.1 (6.2)	20	8:12	50.4 (5.3)
Turner, 2008, (188)	RA	12 (FF) 10 (RF) 6(COMB)	9:3 8:2 4:2	7.9 (9.3) 53.8 (13.2) 64.7 (6.9)	53	33:20	55.2 (11.7)
Turner, 2008, (189)	RA	74	58:16	56.4 (12.0)			
Weiss, 2008, (191)	RA	50	43:7	55.0 (14.0)			
Schmiegel, 2008, (210)	RA	112	NR	55.0 (11.0)	53	33:20	55.2 (11.7)
Schmiegel, 2008, (209)	RA	21	NR	57.1 (10.2)	37	22:15	51.0 (14.0)
Khazzam, 2007, (192)	RA	22	20:2	54.0*	20	NR	53.2 (12.3)
Laroche, 2007, (211)	RA	9	6:3	60.0 (7.0)	16	NR	50.8 (9.4)
Semple, 2007, (213)	RA	74	58:16	54.6 (12.0)	25	12:13	41.0*
Laroche, 2006, (212)	RA	9	6:3	60.6 (6.8)	9	7:2	60.0 (7.0)
Rosenbaum, 2006, (214)	RA	25	23:2	55.0 (9.9)	53	33:20	55.2 (11.7)
Turner, 2006, (190)	RA	12	12:0	46.0*	7	5:2	58.5 (7.4)
Tuna, 2005, (215)	RA	50	38:12	50.0 (9.0)	21	20:1	50.8 (9.3)
Otter, 2004, (216)	RA	25	21:4	45.3 (12.7)	12	12:0	47.0*
Woodburn, 2004, (110)	RA	11	9:2	59.6 (12.0)	50	39:11	49.8 (7.6)
Turner, 2003, (183)	RA	23	14:9	49.4 (10.5)	25	22:3	48.0 (8.6)
Woodburn, 2002, (187)	RA	50	34:16	54.0 (11.8)	5	NR	NR
Woodburn, 1999, (202)	RA	10	NR	52.3*	23	14:9	49.5 (13.6)
O'Connell, 1988, (221)	RA	10	8:2	54.0	45	29:16	51.8 (12.4)
Woodburn, 1996, (217)	RA	102	76:26	63.5*	10	NR	27.9*
Siegel, 1995, (218)	RA	4	3:1	56.5 (7.2)	7	5:2	34.0*
Fransen, 1994, (219)	RA	113	76:37	60.0 (5.5)	42	31:11	61.0*
Zebouni, 1992, (225)	AS	12	4:8	46.5*	2	2:0	28.0 (11.0)
Isacson, 1988, (220)	RA	17	17:0	40.0 (5.0)	102	67:35	58.7 (5.3)
Minns, 1984, (221)	RA	124	104:20	56.6*	11	NR	39.5*
Simkin, 1981, (222)	RA	18	11:7	58.0*	11	11:0	29.0 (7.0)
Stauffer, 1977, (223)	RA	30	18:12	NR	67	32:35	50.2 (10.2)

IA, inflammatory arthritis; *SD, SD not reported; NR, not reported; FF group, severe forefoot deformity group; RF group, severe rearfoot deformity group; COMB group, severe fore- and rearfoot deformity group

3.3.2. Methodological quality of studies

Two reviewers independently scored a total of 504 items and agreed on 480 items (95%) with an inter-rater agreement of $\kappa = 0.90$ ($p < 0.001$). Six of the 36 articles were of high quality (quality score ≥ 12). The median (%) quality score of all articles was 10 (67%), ranging between 20-87% (Table 3.8). There was limited reporting of study recruitment in the majority of studies, making it difficult to assess the generalisability of study results. The majority of studies investigating kinematic and kinetic parameters also reported small sample sizes.

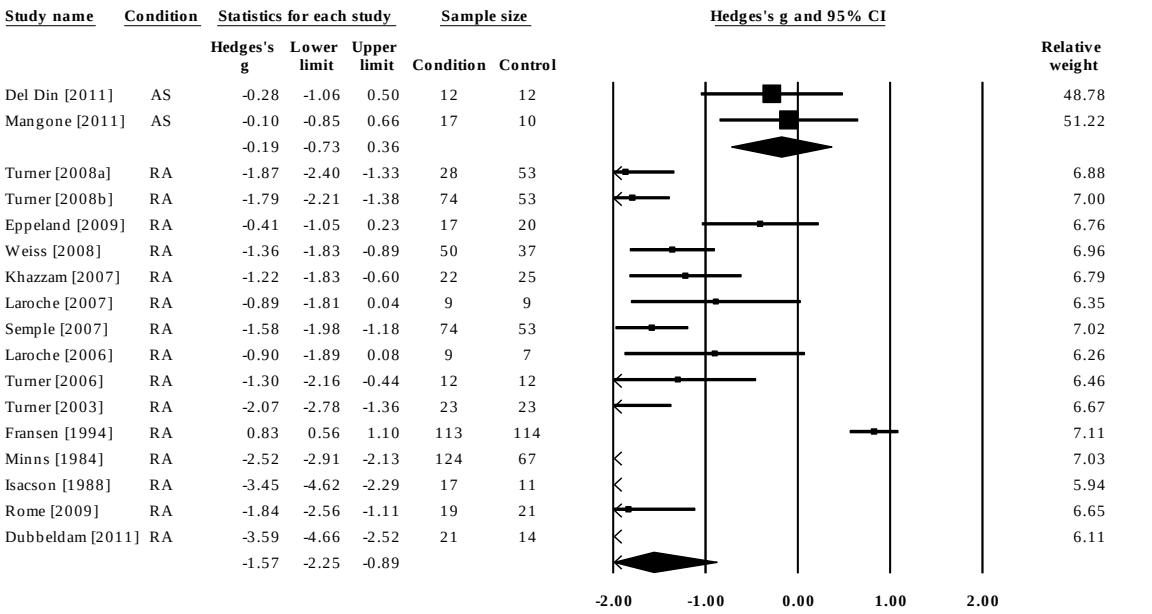
Table 3.8: Results of the quality index scores in alphabetical order

		Quality Index criteria														QI score total **(%)**	
Author, year (ref)		**1**	**2**	**3**	**5**	**6**	**7**	**10**	**11**	**12**	**16**	**18**	**20**	**21**	**22**		
Barn, 2013	(203)	1	1	1	2	1	1	1	0	0	1	1	0	0	1	**11**	***(73)***
Bowen, 2011	(204)	1	1	1	2	1	1	1	0	0	1	1	1	0	1	**12**	***(80)***
Del Din, 2011	(185)	1	1	1	2	1	1	1	1	0	1	1	1	1	0	**13**	***(87)***
Dubbeldam, 2011	(205)	1	1	1	1	0	1	1	0	0	1	1	1	0	0	**9**	***(60)***
Eppeland, 2009	(208)	1	1	1	2	1	1	1	1	1	1	1	0	1	0	**13**	***(87)***
Fransen, 1994	(219)	1	1	1	2	1	1	1	0	1	1	1	0	1	0	**12**	***(80)***
Isacson, 1988	(220)	1	0	1	0	1	0	0	0	0	1	1	0	1	0	**6**	***(40)***
Khazzam, 2007	(192)	1	1	0	0	1	1	1	1	0	1	1	1	1	1	**11**	***(73)***
Laroche, 2007	(211)	1	1	1	0	1	0	1	0	0	1	0	0	0	0	**6**	***(40)***
Laroche, 2006	(212)	1	1	0	0	0	0	0	0	0	1	0	0	0	0	**3**	***(20)***
Mangone, 2011	(224)	1	1	1	0	0	1	1	0	0	1	1	0	0	0	**7**	***(47)***
Minns, 1984	(221)	0	0	1	1	1	0	0	0	0	1	0	0	0	0	**4**	***(27)***
O'Connell, 1988	(186)	1	1	0	0	1	0	0	0	0	1	0	0	0	0	**4**	***(27)***
Otter, 2004	(216)	1	0	1	0	1	1	1	0	0	1	1	0	1	0	**8**	***(53)***
Rome, 2009	(207)	1	1	1	1	1	1	1	0	0	1	1	0	0	0	**9**	***(60)***
Rome, 2011	(18)	1	1	1	1	1	1	1	0	0	1	1	1	1	0	**11**	***(73)***
Rosenbaum, 2006	(214)	1	1	1	1	1	1	1	0	0	1	1	1	0	0	**10**	***(67)***
Schmiegel, 2008	(210)	1	1	1	2	1	1	0	1	1	1	1	0	1	0	**12**	***(80)***
Schmiegel, 2008	(209)	1	1	1	2	1	1	0	0	0	1	1	1	0	0	**10**	***(67)***
Semple, 2007	(213)	1	1	1	0	1	1	1	1	1	1	1	1	0	0	**11**	***(73)***
Siegel, 1995	(218)	1	1	0	0	0	0	0	0	0	1	0	0	0	0	**3**	***(20)***
Simkin, 1981	(222)	1	1	0	0	0	0	0	0	0	1	0	0	0	0	**3**	***(20)***
Stauffer, 1977	(223)	1	1	1	1	1	0	0	0	0	1	0	1	0	1	**8**	***(53)***
Tuna, 2005	(215)	1	1	1	1	1	1	0	0	0	1	1	0	0	0	**8**	***(53)***
Turner, 2003	(183)	1	1	1	1	1	1	0	0	0	1	1	0	0	0	**8**	***(53)***
Turner, 2006	(190)	1	1	1	1	1	0	0	1	1	1	0	1	1	0	**10**	***(67)***
Turner, 2008	(188)	1	1	1	2	1	1	0	0	0	1	1	1	0	0	**10**	***(67)***
Turner, 2008	(189)	1	1	1	2	1	1	1	0	0	1	1	1	1	0	**12**	***(80)***
Weiss, 2008	(191)	1	1	0	1	1	1	1	0	0	1	1	1	1	0	**10**	***(67)***
Woodburn, 1996	(217)	1	1	1	2	1	1	1	0	0	1	1	1	0	0	**11**	***(73)***
Woodburn, 1999	(202)	1	1	1	2	1	0	0	1	0	1	1	1	1	0	**11**	***(73)***
Woodburn, 2002	(187)	1	1	1	2	1	1	1	0	0	1	1	1	0	0	**11**	***(73)***
Woodburn, 2004	(110)	1	1	0	0	0	1	0	0	0	1	0	1	0	0	**5**	***(33)***
Woodburn, 2013	(174)	1	1	1	2	1	1	1	0	0	1	1	0	0	0	**10**	***(67)***
Yavuz, 2010	(206)	1	1	0	0	0	1	0	0	0	1	1	0	0	0	**5**	***(33)***
Zebouni, 1992	(225)	1	1	0	0	0	0	0	0	0	1	1	0	0	0	**4**	***(27)***
													Median			**10 (67)**	

3.3.3. Spatiotemporal gait parameters

Fifteen RA (183, 188-192, 205, 207, 208, 212, 213, 219-222), one PsA (174) and one gout study (18) reported significant decreases in walking velocity. No significant differences in walking velocity were reported for AS (185, 224). Overall, pooled data (SMD, 95% CI) (Figure 3.2) for walking velocity, demonstrated a significant decreased large effect size for RA (SMD -1.55, -2.27 to -0.83) and a non-significant decrease for AS (SMD -0.19, -0.73 to 0.36).

Five RA studies (183, 191, 205, 207, 221) and one gout (52) reported significant decreases in cadence. Cadence was not significantly decreased in AS (225). Overall, pooled data for cadence in RA (Figure 3.3) showed a decreased but significant large effect size (SMD -0.97, -1.49 to -0.45). Nine RA studies (183, 191, 192, 205, 212, 219-222), one AS (225) and one gout (18) reported significant decreases in stride length. Pooled data for stride length in RA (SMD -1.66, -1.84 to -1.49) and AS (SMD -0.62, -1.08 to -0.27) were significantly decreased with a large effect size (Figure 3.4). Eight RA studies (183, 188-191, 205, 207, 219) and one gout study (18) reported significant increases in double support. Pooled data for double support in RA showed (Figure 3.5) a significantly increased large effect size (SMD 1.01, 0.66 to 1.36).

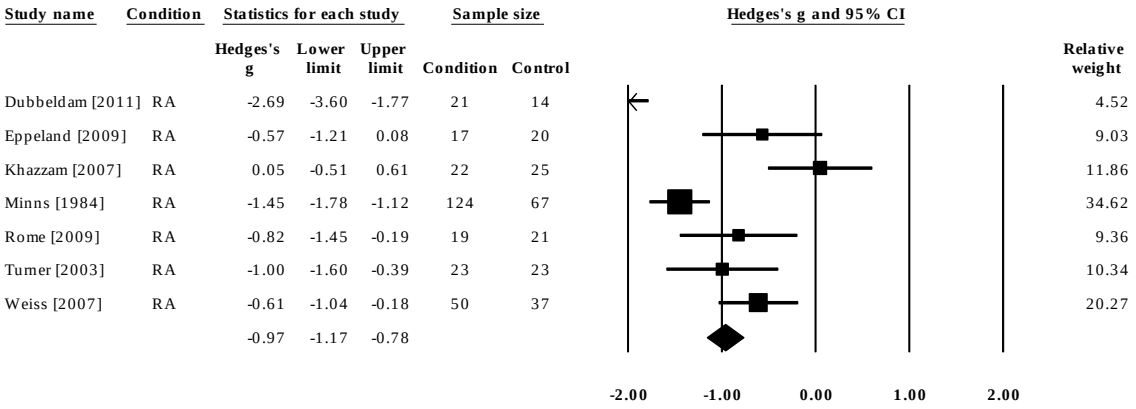


AS: Test for heterogeneity: $\chi^2 = 0$, df = 1 (P = 0.74); $I^2 = 0\%$

Test for overall effect: z = -0.68 (P = 0.74)

RA: Test for heterogeneity: $\chi^2 = 324.66$, df = 14 (P < 0.001); $I^2 = 96\%$
Test for overall effect: z = -4.51 (P < 0.001)

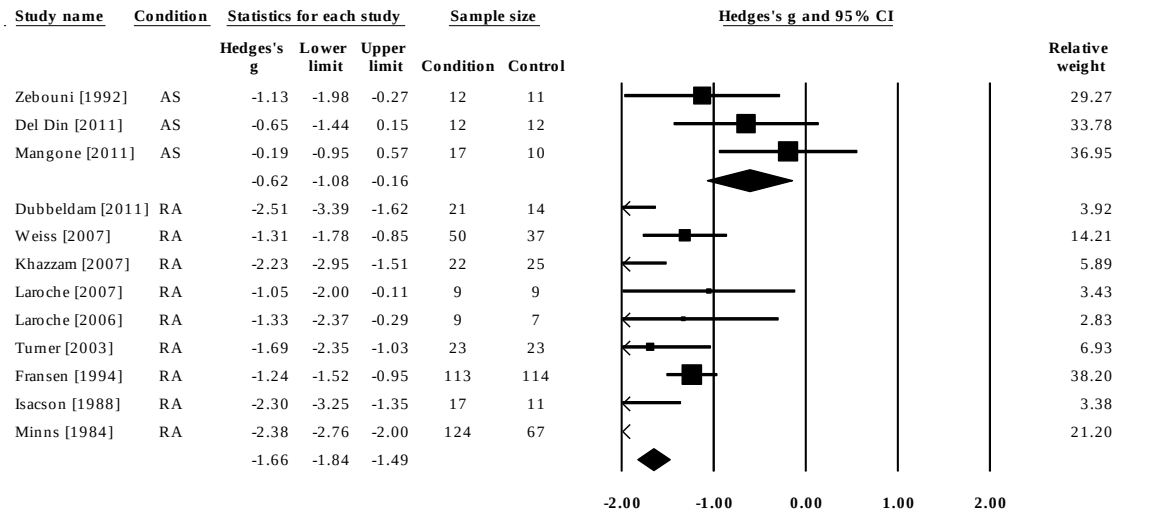
Figure 3.2. Forest plot of studies reporting walking velocity. AS, ankylosing spondylitis; RA, rheumatoid arthritis; CI, confidence interval



RA: Test for heterogeneity: $\chi^2 = 38.65$, df = 6 (P < 0.001); $I^2 = 85\%$

Test for overall effect: z = -3.69 (P < 0.001)

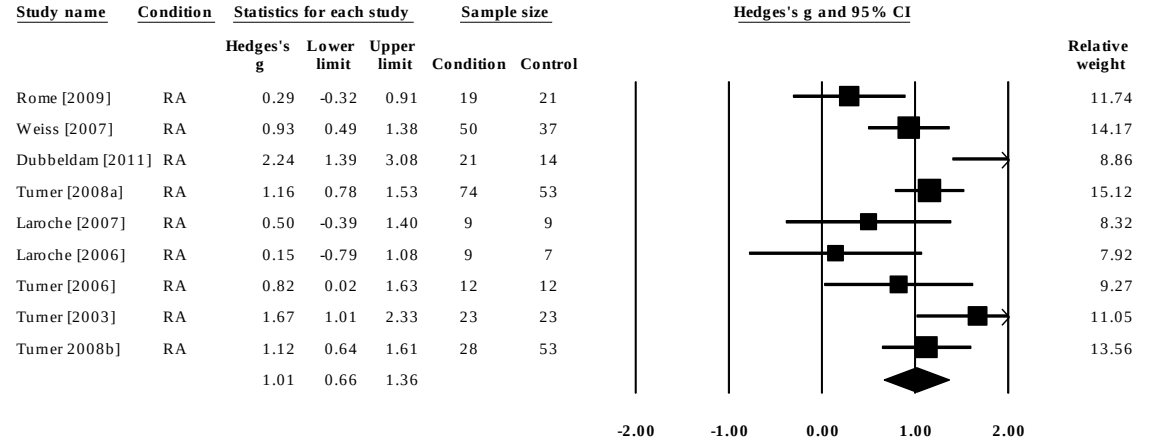
Figure 3.3. Forest plot of studies reporting cadence. RA, rheumatoid arthritis; CI, confidence interval



AS: Test for heterogeneity: $\chi^2 = 2.58$, df = 2 (P = 0.27); $I^2 = 22\%$
Test for overall effect: z = -2.63 (P = 0.009)

RA: Test for heterogeneity: $\chi^2 = 34.08$, df = 8 (P < 0.001); $I^2 = 77\%$
Test for overall effect: z = -8.47 (P < 0.001)

Figure 3.4. Forest plot of studies reporting stride length.



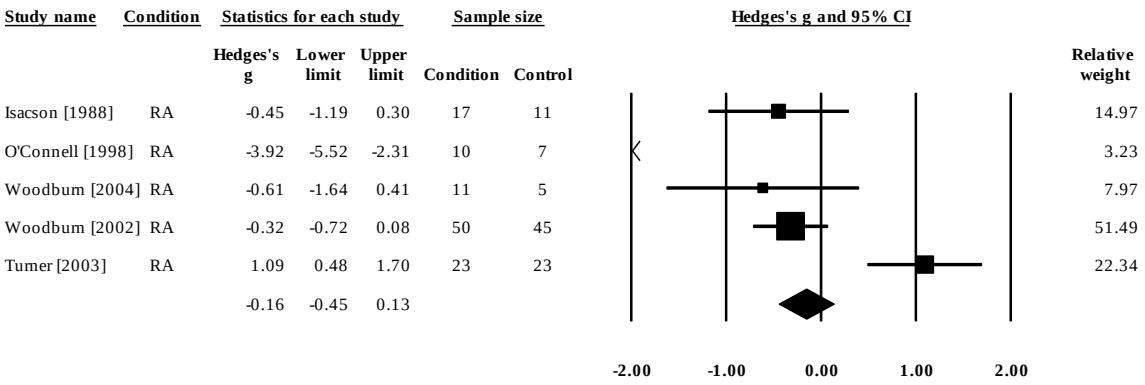
RA: Test for heterogeneity: $\chi^2 = 22.81$, df = 8 (P = 0.004); $I^2 = 65\%$
Test for overall effect: z = 5.65 (P < 0.001)

Figure 3.5. Forest plot of studies reporting double support time.

3.3.4. Kinematic and kinetic gait parameters

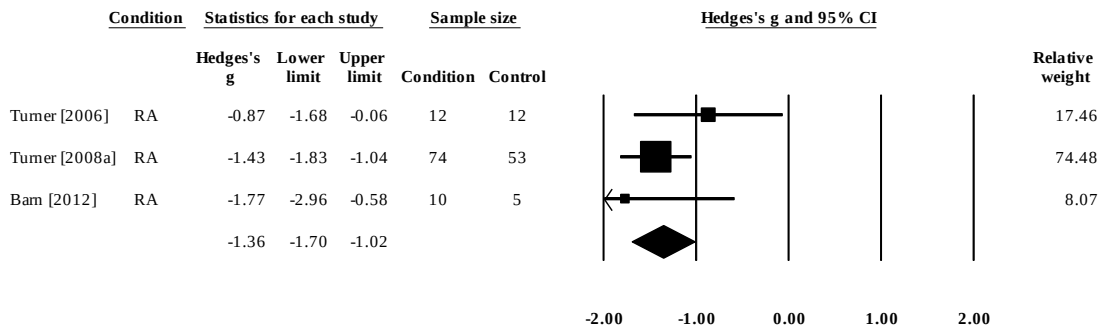
Five RA studies reported on the total ankle range of motion (110, 183, 186, 187, 220). Three studies reported no significant differences (110, 187, 220), with one study reporting a significant increase (183) and one study reporting a significant decrease in the total ankle

range of motion (186). Results of the meta-analysis (Figure 3.6) demonstrated that the overall effect size for total ankle range of motion was non-significant (SMD –0.64, -1.66 to 0.39). Ankle power was reported in three RA (189, 190, 203) and one PsA study (174). All four studies reported significant reductions in ankle power. The overall effect size for ankle power in RA (Figure 3.7) was significantly large (SMD -1.36, -1.70 to -1.02).



RA: Test for heterogeneity: $\chi^2 = 39.21$, df = 4 ($P < 0.001$); $I^2 = 90\%$
Test for overall effect: z = -1.29 (P = 0.23)

Figure 3.6. Forest plot of studies reporting ankle range of motion.

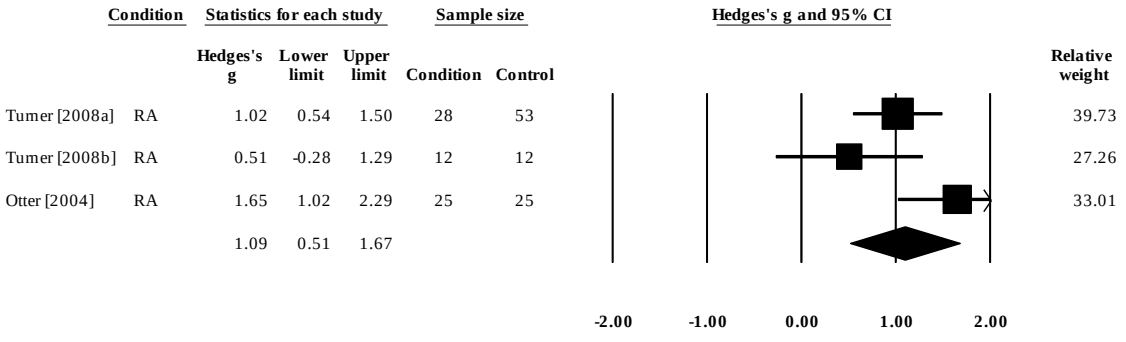


RA: Test for heterogeneity: $\chi^2 = 2.01$, df = 2 (P =0.37); $I^2 = 35\%$
Test for overall effect: z = -7.85 (P < 0.001)

Figure 3.7. Forest plot of studies reporting ankle power.

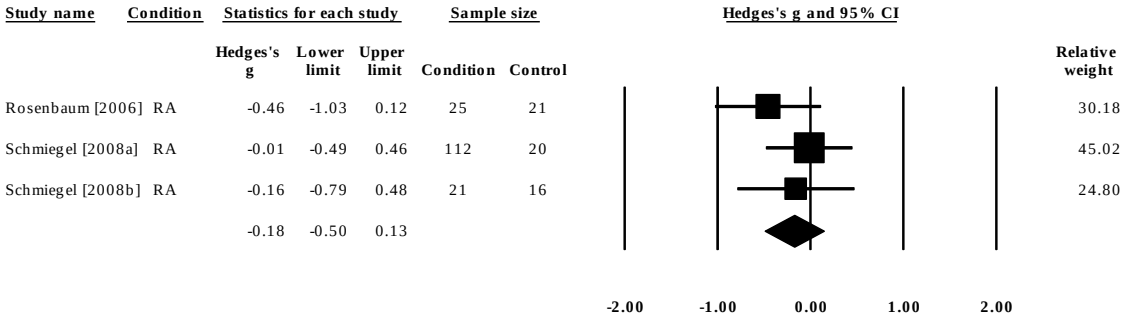
3.3.5. Peak plantar pressure gait parameters

Three RA studies (188, 190, 215, 216) reported significantly higher forefoot peak plantar pressures in RA. Results from the meta-analysis (Figure 3.8) showed that the overall effect size for peak plantar pressure to the forefoot was significantly large (SMD 1.09, 0.51 to 1.67). Pooled results in the RA studies demonstrated no significant difference in peak plantar pressure for the rearfoot (Figure 3.9), midfoot (Figure 3.10), first metatarsal (Figure 3.11), 2nd metatarsal (Figure 3.12) and the 3-5th metatarsal heads (Figure 3.13). Hallux peak plantar pressure (Figure 3.14) was reported to be significantly lower in gout (18).



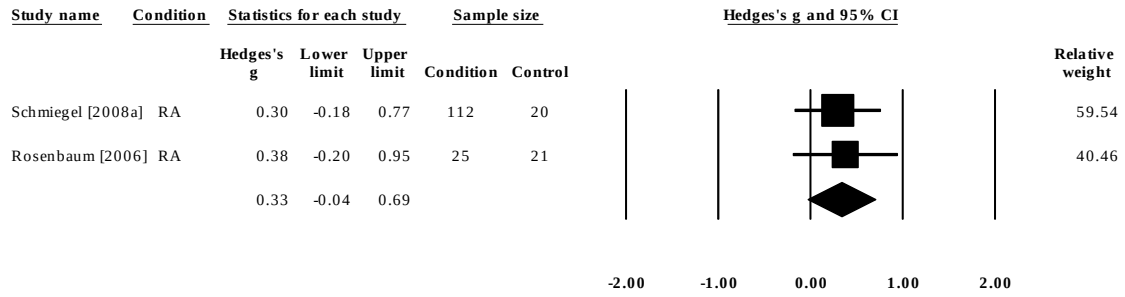
RA: Test for heterogeneity: $\chi^2 = 5.19$, df = 2 (P =0.075); $I^2 = 61\%$
Test for overall effect: z = 3.68 (P < 0.001)

Figure 3.8. Forest plot of studies reporting forefoot peak plantar pressure.



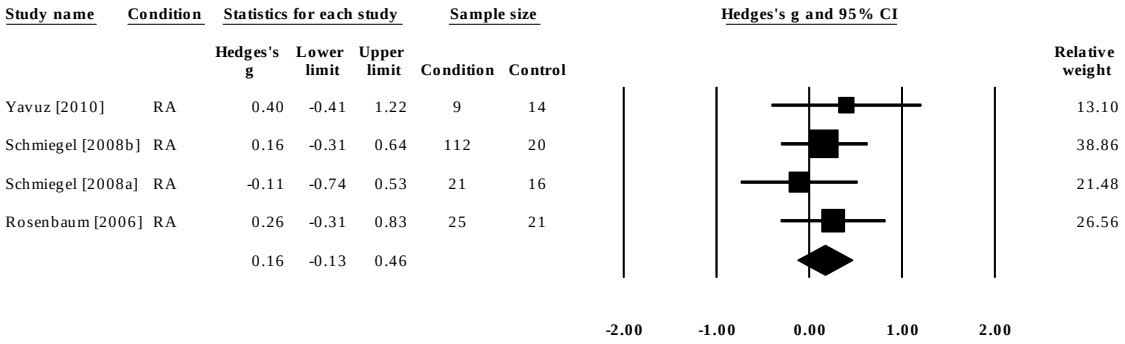
RA: Test for heterogeneity: $\chi^2 = 1.36$, df = 2 (P =0.51); $I^2 = 0\%$
Test for overall effect: z = -1.23 (P = 0.26)

Figure 3.9. Forest plot of studies reporting rearfoot peak plantar pressure.



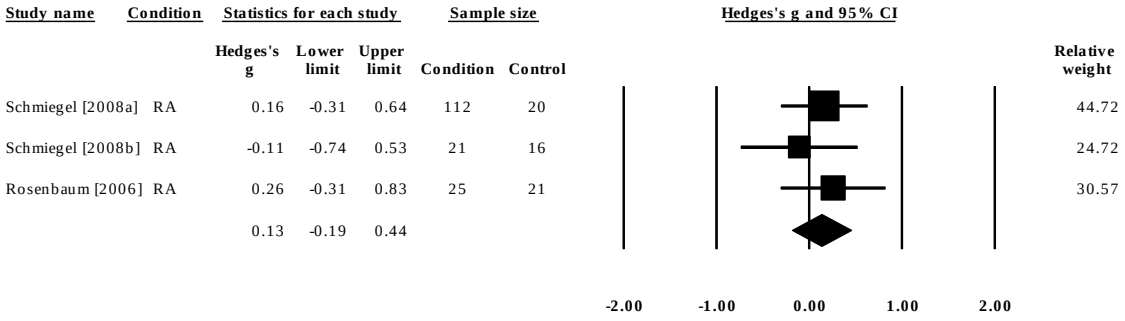
RA: Test for heterogeneity: $\chi^2 = 0.97$, df = 2 (P =0.62); $I^2 = 0\%$
Test for overall effect: z = 1.48 (P = 0.14)

Figure 3.10. Forest plot of studies reporting midfoot peak plantar pressure.



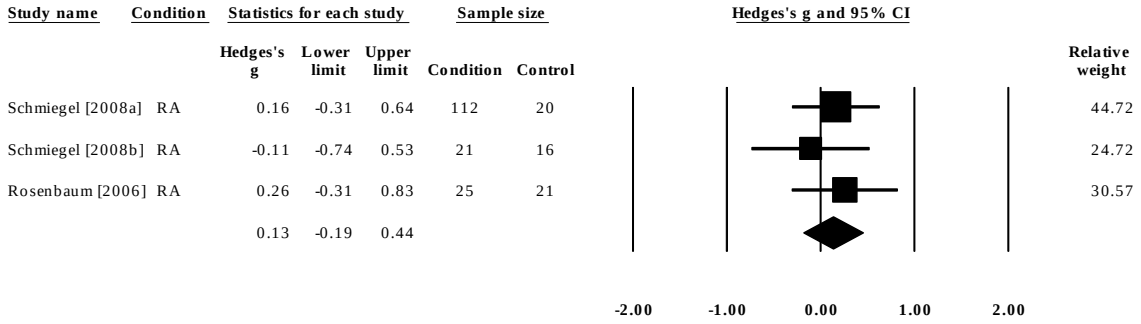
RA: Test for heterogeneity: $\chi^2 = 1.12$, df = 3 (P =0.77); $I^2 = 0\%$
Test for overall effect: z = 1.07 (P = 0.28)

Figure 3.11. Forest plot of studies reporting 1st metatarsophalangeal joint peak plantar pressure.



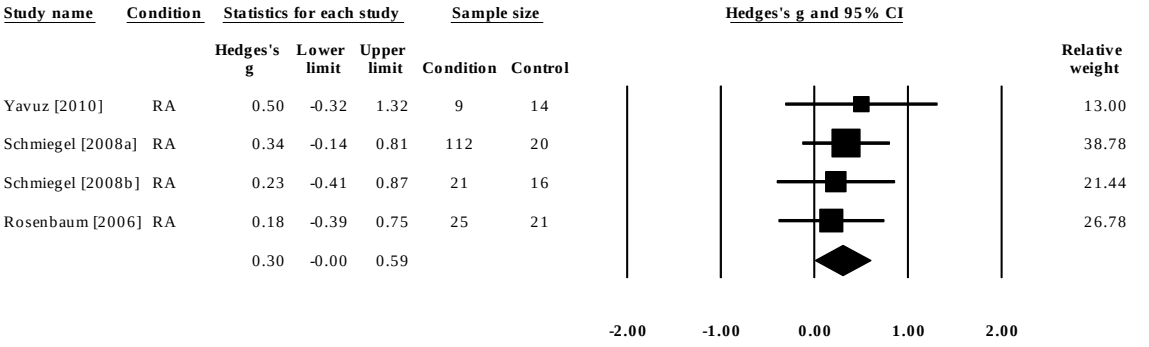
RA: Test for heterogeneity: $\chi^2 = 0.87$, df = 3 (P =0.83); $I^2 = 0\%$
Test for overall effect: z = 1.11 (P = 0.27)

Figure 3.12. Forest plot of studies reporting 2nd metatarsophalangeal joint peak plantar pressure.



RA: Test for heterogeneity: $\chi^2 = 0.74$, df = 2 (P =0.69); $I^2 = 0\%$
Test for overall effect: z = 0.78 (P = 0.44)

Figure 3.13. Forest plot of studies reporting 3rd to 5th metatarsophalangeal joint peak plantar pressure.



RA: Test for heterogeneity: $\chi^2 = 0.47$, df = 3 (P =0.97); $I^2 = 0\%$
Test for overall effect: z = 1.96 (P = 0.05)

Figure 3.14. Forest plot of studies reporting hallux peak plantar pressure.

3.3.6. Muscle activity

One RA study investigated muscle activity of the tibialis posterior muscle and reported increased muscle activity during the single support phase of gait (203).

3.4. Discussion

The systematic review highlights significant differences in gait variables between people with inflammatory arthritis and controls. The review found the majority of studies report on RA with a limited number of studies on other inflammatory arthritic conditions. The results reinforced the premise of adoption of a pain avoidance strategy reported in previous RA studies, specifically that, people with RA adopt an antalgic gait due to a decrease in walking velocity, cadence, increased double limb support time, and decreased ankle power with increased peak plantar pressures to the forefoot (186, 189, 191, 192). Antalgic gait was also found in gout and AS suggesting that adaptation may occur due to the disease or a compensatory mechanism to accommodate for localised foot pain and deformity (188). Gait adaptation in PsA may relate to entheseal foot pathologies and foot pain (109, 184). Woodburn (174) postulated a stress shielding mechanism may be the driver of gait adaptation with walking velocities decreased in attempt to lower stress at the AT. An altered gait adaptation in gout illustrates a similar mechanism. The review found a reduction in peak plantar pressure under the first metatarsal head, suggesting that people with gout use a pain-avoidance strategy to reduce the pain associated with the structural joint damage of the first metatarsophalangeal joint.

The chief advantage of 3D motion analysis is that dynamic assessments of foot motion during functional activities, such as walking, can be performed (234). Recent advances in motion capture technology afford improved spatial resolution and allow the definition of relatively small segments in the foot (234). In the last decade there has been an exponential growth in the use of 3D models to explain gait strategies (107). The development of detailed foot models is beginning to quantify the kinematics and kinetics of the foot, however there are limitations for use in people with inflammatory arthritis. Issues related to soft tissue artefacts and the validity of skin markers to track underlying skeletal segments remains problematic. Inaccurate identification of anatomical landmarks due to the presence of foot deformity in inflammatory arthritis may affect the estimation, interpretation and reconstruction of joint axis and ultimately the calculation of joint kinematics and kinetics (235). The development of foot models has also increased the detail and variety of 3D motion analysis variables used to explain gait strategy in people with inflammatory arthritic conditions. In comparison to spatiotemporal gait parameters and plantar pressure variables,

there appears to be no consensus as to the most important gait variables to report and their relationship to overall functional status.

This review has some limitations. There was a large variation in the disease activity, disease duration and level of deformities across all studies. Many studies used relatively small samples that were underpowered and the heterogeneous nature of the inflammatory arthritic population makes interpretation of the data difficult. A number of studies were included in the review but excluded from data pooling due to a lack of data reporting of standard deviations and mean values of gait parameters. Previous studies have described a wide range of methodologies to acquire and define gait parameters and this complicates the synthesis of data across different studies. The review was restricted to case-control studies and did not consider findings from intervention studies. Analysis only included the foot and ankle characteristics in inflammatory arthritis, with no consideration given to data from the knee, hip and pelvis.

Two key pathways have been postulated to contribute to the development of foot pain and deformity in inflammatory arthritis: inflammatory and mechanical (234). However, limited objective evidence exists to comprehensively examine inflammatory and mechanical markers in the context of foot pain and deformity across inflammatory arthritic conditions. Given the limited data across all inflammatory arthritic conditions, future directions should include electromyographic variables that may provide information on the forces producing the movements and abnormal muscle activation patterns. Future research is required to understand the combined effects of spatiotemporal, kinematic, kinetic and plantar pressure that affect foot function. This will allow for relationships to be investigated across the differing gait parameters and may further define the mechanism of gait adaptation in inflammatory arthritic conditions.

3.5. Conclusion

The advancement of 3D gait analysis has given a clearer insight into the complex interaction between the underlying mechanisms of inflammation and mechanical pathways that influence the development of foot problems in people with inflammatory arthritis. The review identified 36 gait studies with the majority of studies reporting gait adaptations in RA, but limited evidence relating to other inflammatory arthritic conditions. Poor data

reporting, small sample sizes and heterogeneity across inflammatory arthritic conditions limit the interpretation of the findings. Future studies should consider a standardised analytical approach to gait analysis that will enable comparisons across studies and provide clinicians and researchers with objective evidence of foot function in people with inflammatory arthritis.

CHAPTER 4

Methodology

4.1. Introduction

As identified by the systematic reviews presented in Chapters 2 and 3, no studies have assessed US lesions in the AT or conducted 3D gait analysis in a population with tophaceous gout. Subsequently, two studies were conducted.

Study 1: A study investigating US lesions of the AT with US imaging in participants with tophaceous gout compared to control participants.

Study 2: A study investigating 3D gait analysis in participants with tophaceous gout compared to control participants.

This chapter will outline in detail an explanation of the methods used in Studies 1 and 2; specifically, the recruitment procedures, the clinical characteristics and patient-reported outcome measures (PROMs) obtained from the participants, and details of the methodological procedures surrounding both US imaging and gait analysis. Finally, the statistical techniques used to analyse the two studies will be detailed.

4.2. Participants

Twenty-four people with tophaceous gout were recruited from rheumatology outpatient clinics at the Auckland District Health Board (ADHB) rheumatology clinic. Twenty-four age and sex-matched participants were recruited from the AUT University and general population as control participants. The inclusion and exclusion criteria are displayed in Tables 4.1 and 4.2.

Table 4.1: Case inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients with a gout according to the 1977 preliminary ARA criteria (49)	Previous rupture of the AT
18 years or older	Current musculoskeletal injury to the lower limb
At least one subcutaneous tophus	Current history of peripheral neuropathy
Able to walk along a 10m walkway without gait aids	

Table 4.2: Control inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
No previous diagnosis of gout	Previous rupture of the AT
No previous diagnosis of IA	Current musculoskeletal injury to the lower limb
18 years or older	Current history of peripheral neuropathy
Able to walk along a 10m walkway without gait aids	

4.3. Case definition of tophaceous gout

A participant was considered to have tophaceous gout and to be eligible for inclusion if one of the following criteria A, B or C were met (Table 4.3):

Table 4.3: Criteria to define tophaceous gout patient (49)

A)	The presence of characteristic urate crystals in the joint fluid
B)	Tophus proven to contain urate crystals by chemical means or polarised light microscopy:
C)	Presence of 6 or more of the following 12 clinical and radiographic phenomena

1. More than one attack of acute arthritis
2. Maximum inflammation developed within one day
3. Monoarthritis attack
4. Redness observed over joint(s)
5. First metatarsophalangeal joint painful or swollen
6. Unilateral first metatarsophalangeal joint attack
7. Unilateral tarsal joint attack
8. Tophus (proven or suspected)
9. Hyperuricaemia
10. Asymmetric swelling within a joint on x-ray
11. Subcoritcal cysts without erosion on x-ray
12. Joint fluid culture negative for organisms during attack

4.4. Recruitment procedure

4.4.1. Case participant screening

A list of participants with tophaceous gout was compiled by the Department of Rheumatology from those attending the ADHB Greenlane Rheumatology Clinic between January 1st 2013 and July 1st 2013.

4.4.2. Control participant screening

Participant names were collected from the AUT Podiatry Clinic patient database who had attended the AUT podiatry clinic between July 1st 2012 and July 1st 2013. All participants who attend the podiatry clinic signed an informed consent form and provided an indication via a tick box if they were interested in participating in research. Recruitment posters were also placed around the AUT Akoranga campus.

4.4.3. Case and control participant enrolment

Participants identified as eligible were sent a letter informing them of the study. This included a patient information sheet inviting them to participate. For those who agreed to participate, the eligibility criteria were confirmed and a data collection appointment scheduled. All enrolled participants were either transported to AUT University via taxi (vouchers issued to cover the travel cost) or private transport (fuel vouchers to cover the cost of travel).

4.5. Sample size determination

The sample size was calculated to 22 participants per case and a control group relating to differences in estimates by a previous study on walking velocity in participants with tophaceous gout (18). This presupposes a mean (SD) walking velocity of 0.90 (0.3) m/s for participants with gout and 1.10 (0.3) m/s for control participants. Power was set to 90% with a significance level of 5%. Sample size was calculated using (PS Power & Sample size Calculations (version 3.0, 2009)). In addition to the sample size calculation, previous research using tophaceous gout populations (12, 17, 18) and previous gait research in inflammatory arthritis was considered.

4.6. Ethical approval

Ethical approval for the studies was approved by the Auckland University of Technology Ethics Committee, Auckland, New Zealand. The Auckland District Health Board Ethics Committee, Auckland New Zealand provided institutional approval for recruitment. The following is a list of the study approval numbers for the two studies undertaken in this thesis.

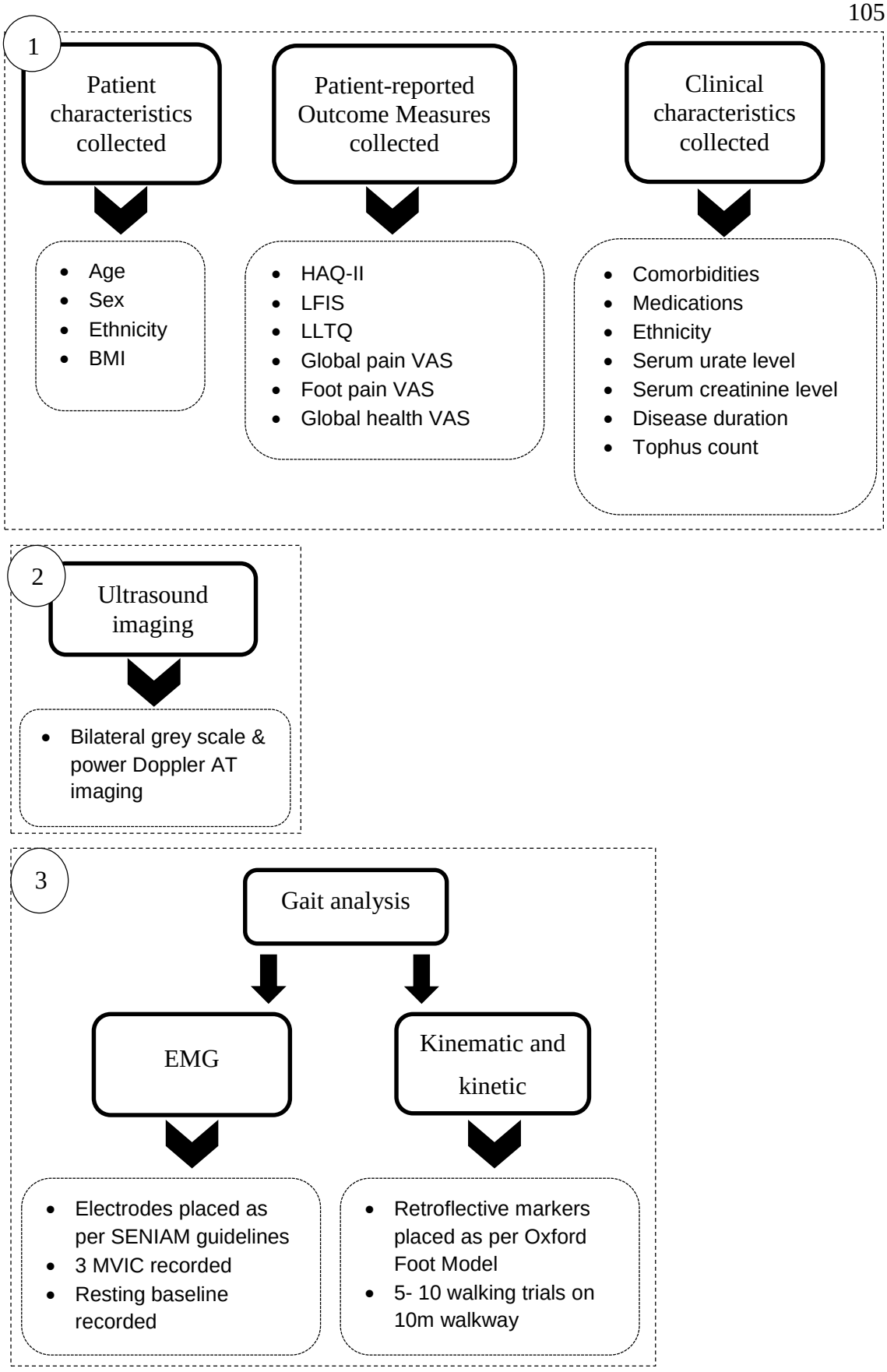
1. Auckland University of Technology Ethics Committee: 13/100 (please refer to page XVII of the thesis for evidence)
2. Auckland District Health Board Ethics Committee: A+5891 (please refer to page XVIII of the thesis for evidence)

4.6.1. Participant information and consent

All subjects read the Participant Information Sheet (Appendix 1) and signed a Consent Form (Appendix 2) prior to commencement of participation in the study.

4.7. Data collection

All participants demographic, patient reported outcome measures (PROM) and clinical characteristics were recorded. Participants initially underwent US analysis followed by gait analysis. The stages of data collection are displayed in Figure 4.1.



BMI, bodymass index; HAQ-II, health assessment quesionnaire; LFIS, leeds foot imapct scale; LLTQ lower limb task questionnaire; VAS, visual analogue scale; EMG, electromyography; SENIAM, surface electromyography for the non-invasive assessment of muscles; MVIC, maximum voluntary isometric contraction

Figure 4.1. Participant journey through data collection

4.7.1. Participant examination

The following information was obtained from each participant: demographic information including the participant's age, sex, height, weight, body mass index (BMI), and ethnicity. Clinical characteristics included age of first episode, disease duration, the presence of co-morbidities; hypertension, diabetes, cardiovascular disease and current medications. The latest serum urate and serum creatinine levels were obtained from the ADHB Department of Rheumatology. Following completion of the patient exam all participants completed the PROMs.

4.7.2. Rationale for use of outcomes measures

Pain and global function assessed by the VAS and activity limitation assessed by the HAQ-II were adopted based on the recommendations of OMERACT 10 pertaining to the reporting of PROMs in chronic gout studies (236). At the time of study there were no validated disease-specific instruments to quantify the impact of gout on the foot or the impact of gout related to lower extremity function. Subsequently, the LFIS and LLTQ were selected to assess the impact of tophaceous gout on the foot and the impact of tophaceous gout related to lower extremity function. While these PROMs are not validated in tophaceous gout both the LFIS and LLTQ have been used in previous studies in tophaceous and acute gout (18, 52, 237).

4.7.3. Patient-reported outcome measures

Pain: visual analogue scale (VAS) (238)

Pain was quantified using a pain VAS (Appendix 3). Pain severity was scored on a 100 mm horizontal line, the leftmost boundary representing 'no pain' and the rightmost boundary representing 'extreme pain'. The participants marked a cross at a point on the line which they felt best represented their current pain level. The distance from the cross to the leftmost boundary was measured in mm and scored out of 100.

Patient global assessment VAS (238)

A patient global VAS was used to determine the participant's overall well-being (Appendix 3). Well-being was scored by the patient marking a cross on a 100 mm horizontal line. The leftmost boundary represented 'completely well' and the rightmost boundary representing 'completely unwell'. Participants marked a cross on the line which they felt best represented their current status. The distance from the cross to the leftmost boundary was measured in mm, and scored out of 100.

Activity limitations: Health Assessment Questionnaire (HAQ-II) (239)

Functional status of the participants was assessed using the HAQ- II (Appendix 4). The HAQ-II contains 10 questions, 9 of which measure functional ability, with 1 question measuring disability. Each question can be answered by one of four answers, 'without any difficulty' (score = 0), 'with some difficulty' (score = 1), 'with much difficulty' (score = 2) and 'unable to' (score = 3). Scores were totalled and divided by the total number of questions answered. If less than 8 questions were answered the HAQ-II was not scored. A lower value was suggestive of a better functional status.

1. **Function in the lower limb: Lower Limb Tasks Questionnaire (LLTQ)** (240)

Function in the lower extremity was quantified by the LLTQ (Appendix 5) (240). The LLTQ scores the participants' account of their functional status in the previous 48 hours. The questionnaire is divided into two domains: activities of daily living and recreational activities, with each domain containing 10 questions. The questions are scored on a 5-point Likert scale (0 = unable, 1 = severe difficulty, 2 = moderate difficulty, 3 = mild difficulty, 4= no difficulty). The scores from the 10 questions were totalled, the maximum possible score being 40. Higher overall scores represented greater levels of lower extremity function. In addition, participants also scored the importance of each question on a 5-point Likert scale; (1 = not important, 2 = mildly important, 3 = moderately important, 4 = very important).

2. The Leeds Foot Impact Scale (LFIS) (241)

The LFIS consists of 51 questions, divided into two subcategories; impairment/footwear ($LFIS_{IF}$) and activity limitation/participation restriction ($LFIS_{AP}$) (Appendix 6). Questions 1-21 comprise the $LFIS_{IF}$ section and questions 22 to 51 the $LFIS_{AP}$ section. Each question is marked either 'true' or 'false' with a true response scored as one point and a false response as zero. Scores are totalled to provide an overall score for each subsection. The maximum overall score achievable is 51, with higher scores indicative of great levels of impairment (241). To interpret, the LFIS cut-off values proposed by Turner were applied (189). A $LFIS_{IF}$ score ≥ 7 points and an $LFIS_{AP}$ score ≥ 10 points indicating a high to severe level of foot impairment and disability.

4.8. Ultrasonography procedures

4.8.1. Grey-scale and power Doppler imaging equipment

US imaging was performed by one experienced radiologist at one location (Horizon Radiology, AUT University North Shore campus) who was blind to the clinical details of participants. US was performed using a Philips iU22 ™ unit equipped with a broadband 17-5 Megahertz (MHz) linear probe. Grey-scale machine settings were standardised prior to the study to optimise visualisation of superficial and deep structures. These settings were as follows: a dynamic range of 40-50dB; a grey-scale frequency of 12-14 MHz; and a gain of 60dB. PD settings were standardised with a pulse repetition frequency of 500 Hz, and a low wall filter of 42 Hz. The colour gain was increased to the highest value not generating PD signal and optimised for low flow.

4.8.2. Patient positioning

All participants assumed a prone position with the knee fully extended for visualisation of the AT (Figure 4.2). For all participants, bilateral systematic longitudinal and transverse imaging of the enthesis and body of the AT were conducted in grey-scale and subsequently with PD.

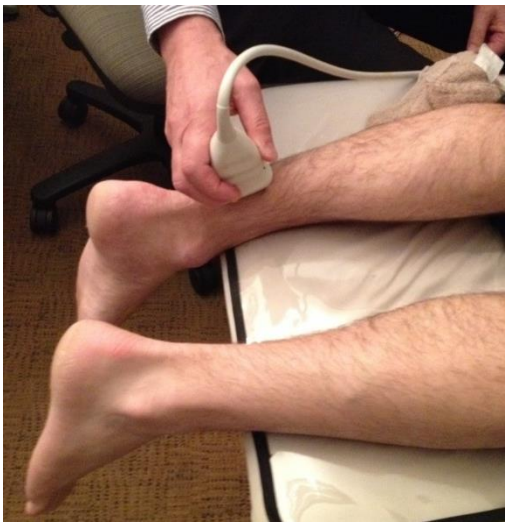


Figure 4.2. Patient positioning for ultrasound imaging

In order to investigate specific regions of the AT, the tendon was divided into 3 zones for analysis (Figure 4.3).

- Zone 1 (insertional zone): calcaneal enthesis to 2 cm proximal:
- Zone 2 (pre-insertional): 2 to 6 cm proximal to calcaneal enthesis:
- Zone 3 (proximal to mid-section): 6 cm proximal to enthesis to myotendinous junction of gastrocnemius

The zones for analysis were defined based on previous cross-sectional analysis of the AT which indicated a relative zone of hypovascularity within 2 to 6 cm proximal to the calcaneal insertion (242, 243).

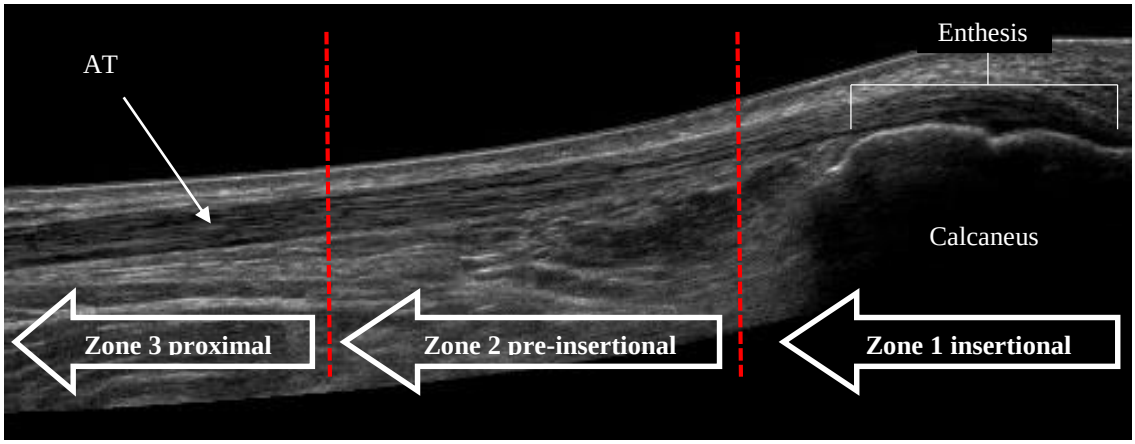


Figure 4.3. Longitudinal image of AT showing the zones in which lesions were scored.

4.8.3. Definitions of Achilles tendon lesions

The definitions used to diagnose the specific US lesions are presented in Table 4.4.

Table 4.4: Definitions of greyscale and power Doppler ultrasound lesions

US Lesion		Definition
Tophus characteristics		The presence of tophus in each zone was attributed a binary value (yes/no). The diameter of the longest tophus was measured in mm. A tophus was defined as hyperechoic heterogeneous or homogeneous lesions with poorly defined contours surrounded by an anechoic halo (129).
Tendon echogenicity	Focal hypoechoic areas	A lack of the homogeneous fibrillar pattern with loss of the tightly packed echogenic lines after correcting for anisotropy (153).
	Hyperechoic spots	Hyperechoic spots were defined as hyperechoic (bright) foci consistent with calcific deposits (relative to the tendon fibres), with or without acoustic shadow, seen in 2 perpendicular planes (153, 244).
Tendon vascularity	Intratendinous power Doppler signal	PD signal in the AT (140).
Tendon morphology	Partial tendon tear	Focal discontinuity visualized with the US beam exactly perpendicular to the tendon to avoid anisotropy (147).
	Complete rupture	Complete loss of tendon substance visualized with the US beam exactly perpendicular to the tendon to avoid anisotropy (245).
	Entheseal tendon thickness	Abnormal AT thickness was defined as $\geq$ 5.29 mm (150).
	Tendon length	Measured as the longitudinal length between the AT insertion into the Achilles notch and the soleus-Achilles musculotendinous junction Enthesis (MTJ). The soleus-Achilles MTJ was defined as the location where the AT divides into the soleus aponeurosis and gastrocnemius tendon (246).

Enthesis	Entheseal echogenicity	Circumscribed hypoechoic areas with loss of fibrillar echotexture (140).
	Entheseal echogenicity: calcifications	Calcifications appearing as intratendinous hyperechoic spots (140).
	Entheseal vascularity	Doppler activity approximately < 2 mm near the bony cortex. The Doppler signal must be at the enthesis, different from reflecting surface artefact or nutrition vessel signal, with or without cortical irregularities, erosions, or enthesophytes (153)
Bursal morphology	Retrocalcaneal bursitis	Bursa with well-defined compressible, anechoic or hypo echoic area inside with maximal diameter larger than 2mm as viewed in the longitudinal plane (247).
	Bursal size score	Diameter of the bursa scored (0: < 2 mm; 1: between 2–4 mm; 2: > 4 mm) (140).
	Bursal snowstorm appearance	Echogenic aggregates observed with the bursa (35).
	Tophus present in bursa	Aggregates located in bursa that were heterogeneous hyperechoic (relative to subdermal fat) aggregates with poorly defined margins with or without areas of acoustic shadowing (244).
	Bursal power Doppler signal	PD signal in the bursa (140).
Bone profile	Calcaneal bone cortex irregularities	A loss of the normal regular bone contour without any clear sign of enthesophyte and/or erosion (153).
	Calcaneal enthesophytes:	A step up of bony prominence at the end of the normal bone contour, seen in 2 perpendicular planes, with or without acoustic shadow (153).
	Calcaneal bone erosions:	A cortical breakage with a step down contour defect, seen in 2 perpendicular planes, at the insertion of the enthesis to the bone (152).

4.8.4. Scoring of grey-scale and power Doppler lesions

US lesions were scored using a semi-qualitative scoring system adapted from the work of Filippucci (140) conducted on the AT. The scoring system assessed the tophus characteristics, tendon echogenicity, tendon vascularity, tendon morphology, enthesis, bursal morphology and bone profile using binary, continuous measurement and semi-qualitative scale. The scoring system is summarised in Table 4.5 with the full scoring sheet located in Appendix 7, demonstrating the characteristics of the scoring system.

Table 4.5: Scoring system applied to grey scale and power Doppler ultrasound lesions at the Achilles tendon.

Tophus characteristics	Tophus present (yes/no)
	If tophus present, longest diameter (mm)
Tendon echogenicity	Focal hypoechoic areas with loss of fibrillar echotexture*
	Intratendinous hyperechoic spots*
Tendon vascularity	Intratendinous power Doppler signal*
Tendon morphology	Tendon tear: (0, absent; 1, partial tear; 2, complete rupture)
	Tendon thickness at the insertion of the deeper margin into the calcaneal bone (mm)
	Tendon thickness (mm)
	Tendon length (mm)
Enthesis	Entheseal echogenicity: focal hypoechoic areas*
	Entheseal echogenicity: calcifications*
	Entheseal vascularity*
Bursal morphology	Bursal size (mm)
	Bursal size score (0, < 2 mm; 1, between 2–4 mm; 2, > 4 mm)
	Bursal snowstorm appearance*
	Bursal power Doppler signal*
Bone profile	Calcaneal bone cortex irregularities*
	Calcaneal enthesophytes*
	Calcaneal bone erosions (0, no bone erosion; 1, between 0.1 and 2 mm; 2, > 2 mm)

*Scoring system ranging from 0 to 2 (0, none/absent; 1, mild–moderate; 2, severe); mm, millimetres.

4.9. Three-dimensional gait analysis

4.9.1. Gait analysis system

A nine-camera motion analysis system (Qualysis AB, Gothenburg, Sweden) was linked to a single desktop within the motion analysis laboratory and synchronised with a force plate and EMG system allowing simultaneous collection of kinematic, kinetic and EMG data. The cameras were positioned to provide the maximum field-of-view of the experimental area (Figure 4.4). Qualysis Track Manager (software) collected all kinematic and kinetic and EMG data. Two Advanced Mechanical Technology Inc., USA (AMTI) force plates outputted analogue signals which were amplified and then collected simultaneously with motion data. Force plate and EMG data were sent to a 64 channel analogue digital board, connected to the computer via a USB connector. Qualysis Track Manager software synchronised and stored the data with the motion data. Both AMTI force plate consisted of 2 piezoelectric transducers with dimensions of 508mm (length) x 463mm (width) x 82mm (depth). The plate was embedded into the walkway. EMG data were recorded using a Noraxon Desktop Direct Transmission System (DTS) enabling wireless surface EMG signal to be captured. The Noraxon system was synchronised within the Qualisys 3D motion analysis system to enable kinematic, kinetic and EMG data to be captured simultaneously.

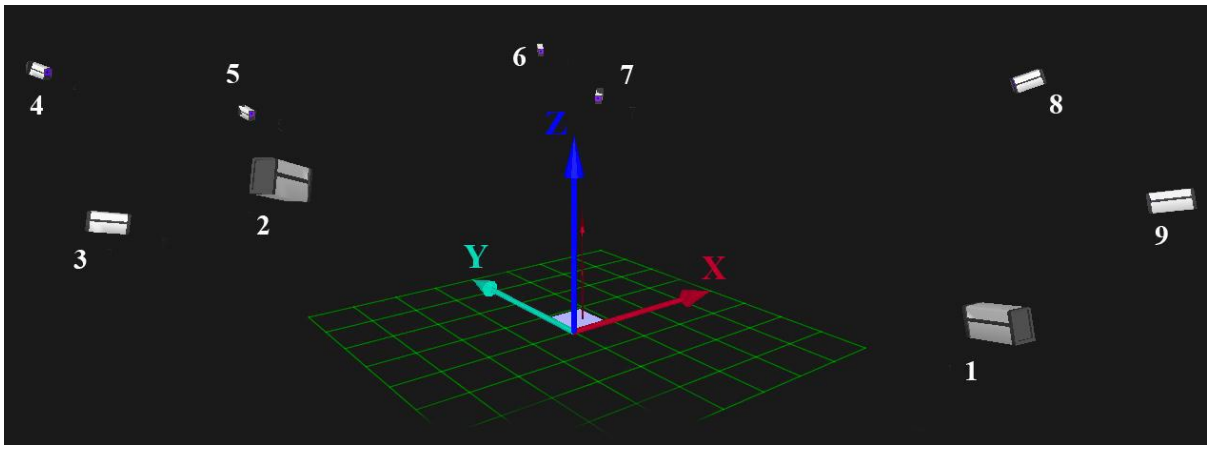


Figure 4.4. Camera placement of Qualysis system

4.9.2. System calibration

Prior to collection of kinematic, kinetic and EMG data the motion capture system was calibrated. Dynamic calibration was performed using a reference object, an 'L" shaped bar with 4 markers placed inside the force plate margins. The bar has 4 predefined reflective markers attached, one at each corner of the bar and one midway along the bar axis. The reference object defined the lab global coordinate system (x, y and z axis). The calibration procedure was performed by randomly moving a wand ('T' shaped wand with 2 reflective markers) through a circular motion in the volume to be calibrated (the region of interest). The system recorded a calibration file of 30 seconds at 100Hz. The residuals of each camera were expressed as the SD in millimetres (mm) of wand length. If the average resolution SD was less than 0.5mm calibration was deemed optimal. If the result was higher than this the camera position and resolution was checked and calibration repeated. As kinetic data was obtained the position of the two force plates required determination. Four markers were placed at the corners of each force plate to define their position and orientation with the global coordinate system.

4.9.3. Oxford Foot Model – rationale for use

The systematic review detailed in Chapter 3 explored the foot models that have been previously reported and the development of new models, for example the Salford foot model (248). Based on the findings from Chapter 3, the Oxford Foot Model was used to model the lower limbs (113). The Oxford Foot Model has been used by numerous research groups to quantify gait kinematics in paediatric, cerebral palsy, RA, healthy and flatfooted populations (110, 188, 249-253).

The decision to use the Oxford Foot Model to derive kinematic gait data was based on two principles. Firstly, as identified by Chapter 3, the Oxford Foot Model had been the applied in the most gait studies in participants with inflammatory arthritis to quantify kinematic joint motion (110, 188, 190). Secondly, reliability work had been conducted on the Oxford Foot Model in RA (110). Woodburn (110) investigated the within and between-day repeatability and compared foot motion between healthy adults and participants with RA. Inter-segment coefficient of multiple correlation values related to the within and between-day repeatability ranged between 0.83 and 0.98 for all foot segments assessed. Previous

research has demonstrated that coefficient of multiple correlation values > 0.8 indicate acceptable repeatability for motion assessed in the foot (110, 187). Through piloting work it was determined that skin-mounted markers based on the Oxford Foot Model were able to be tracked consistently.

4.9.4. The Oxford Foot Model – skin mounted marker placement

Nineteen Qualisys lightweight passive reflective markers (12 mm diameter) were attached to both limbs of each participant on specific anatomical bony landmarks. These defined relative segments of the foot and leg in accordance with the Modified Oxford Foot Model, described by Stebbins (249) (Figures 4.5 a & b). Marker locations were identified by palpation of the participant's feet and legs by an experienced musculoskeletal podiatrist and were marked with a non-toxic, washable marker pen. The reflective markers were adhered to the participant's skin using 3M® double sided tape. The segment marker name and anatomical location are displayed in Table 4.6.

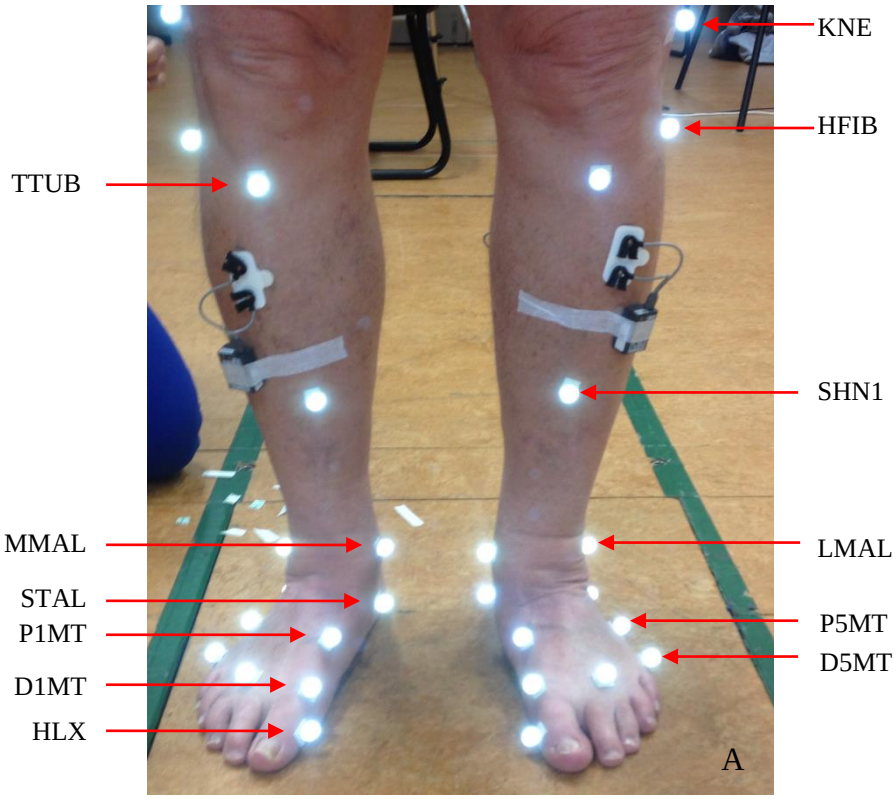


Figure 4.5a. Anterior view of marker positioning for Modified Oxford Foot Model

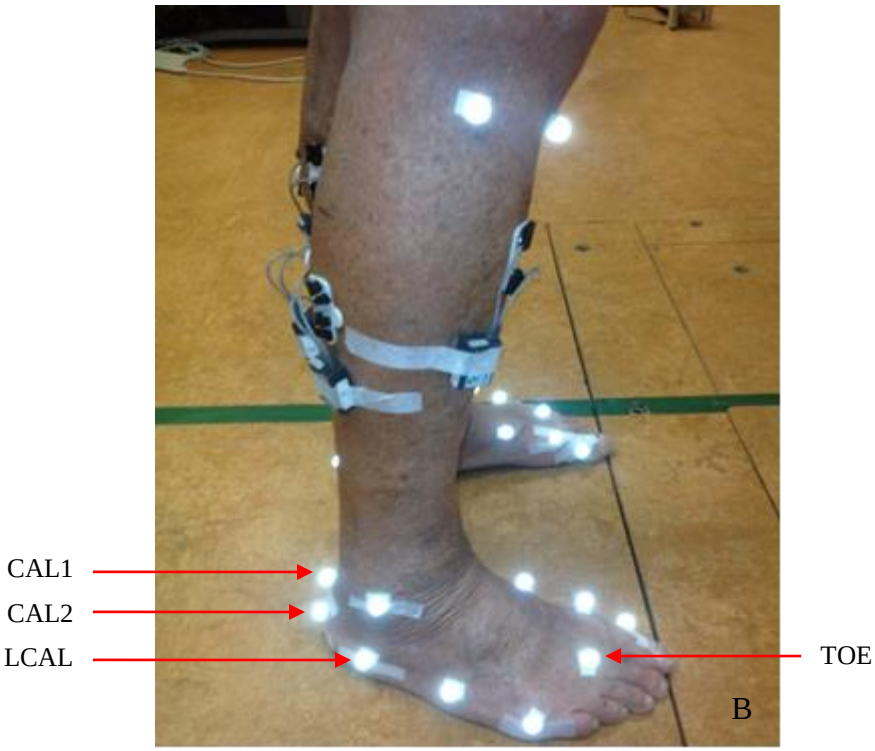


Figure 4.5b. Lateral view of marker positioning for Modified Oxford Foot Model

Table 4.6: Name and position of markers used for the Oxford Foot Model (249)

Marker name	Marker position	Segment
KNE	Femoral condyle	Femur
TTUB	Tibial tuberosity	Tibia
HFIB	Head of fibular	Tibia
LMAL	Lateral malleolus	Tibia
MMAL	Medial malleolus	Tibia
SHN1	Anterior aspect of shin	Tibia
CAL1	Posterior distal aspect of heel	Hindfoot
CAL2	Posterior medial aspect of heel	Hindfoot
LCAL	Lateral calcaneus	Hindfoot
STAL	Sustentaculum tali	Hindfoot
P1MT	Base of first metatarsal	Forefoot
P5MT	Base of fifth metatarsal	Forefoot
D1MT	Head of first metatarsal	Forefoot
D5MT	Head of fifth metatarsal	Forefoot
TOE	Between second and third metatarsal heads	Forefoot
HLX	Base of hallux	Hallux

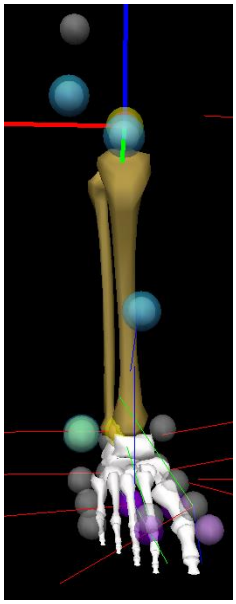
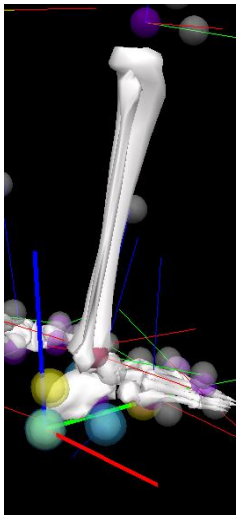
4.9.5. Oxford Foot Model - marker placement

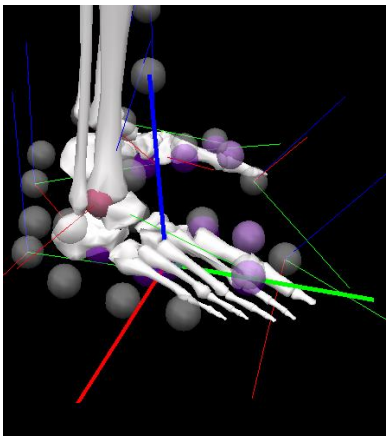
CAL1 and CAL2 were placed on posterior aspect of calcaneus such that they were on the distal and proximal ends of the midline in the sagittal plane, respectively. STAL was placed on the Sustentaculum tali. LCAL was placed on the lateral aspect of the calcaneus, at the same distance from the most posterior point as STAL. D1MT and D5MT were placed medially and laterally on the foot such that their centres lay along the line through the distal heads of the first and fifth metatarsal heads. P5MT was placed laterally over the proximal head of the fifth metatarsal in the plane containing the markers D1MT and D5MT. TOE was placed on the mid-point of the distal heads of the second and third metatarsals. P1MT was placed on proximal head of first metatarsal, just medial to the extensor halluces longus tendon (this structure was palpated by asking the subject to dorsiflex the hallux). HLX was placed on the medial side of the proximal phalanx of the hallux, mid-way between the superior and inferior surface (249).

4.9.6. Oxford Foot Model – segment definition

A four-segment, 3D rigid-link dynamic biomechanical model of the right and left lower legs representative of the Oxford Foot Model was constructed following the procedure outlined by C-Motion online tutorial (254). Segments were represented as geometric objects (cylinders) and scaled according to each individual (255). Segments and their relative axis were created defining the shank, the hindfoot, the forefoot and the hallux (Table 4.7).

Table 4.7: Anatomical reference frames for the Oxford Foot Model

Segment	Orthogonal Axis	Description	
Shank	X	Lateral and to the right in the frontal plane	
	Y	Anterior in the sagittal plane	
	Z	Vertical and perpendicular to X and Y axis	
Orthogonal axes were aligned according to the medial and lateral markers at the ends of each segment, with the longitudinal axis passing through the segment endpoints. The original land mark was at the proximal end of the tibia.			
Rearfoot	X	Lateral to the right in the frontal plane	
	Y	Anterior in the sagittal plane	
	Z	Vertical and perpendicular to X and Y axis	

Forefoot	X	Lateral to the right in the frontal plane	
	Y	Anterior in the sagittal plane	
	Z	Vertical and perpendicular to X and Y axis	
Hallux	X	Lateral to the right in the frontal plane	
	Y	Anterior in the sagittal plane	
	Z	Vertical and perpendicular to X and Y axis	
	Note: while the hallux is represented as a segment, only one marker was placed on the hallux. The hallux segment therefore "shares" the medio-lateral axis of the forefoot segment so that a coordinate system can be created for the hallux (254).		

4.9.7. Oxford Foot Model – joint rotation definitions

Angles of rotation for each segment were calculated according to the defined joint co-ordinate system. The sequence of rotation for the cardian angles was X (sagittal)–Y (frontal)–Z (transverse). Intersegment rotations were defined using the following terms: Ankle motion (rearfoot relative to the tibia), dorsiflexion (+) / plantarflexion (-) occurred about the x-axis, inversion (+) / eversion (-) occurred about the y-axis. Hallux motion (hallux relative to the forefoot), dorsiflexion (+) / plantarflexion (-) occurred about the x-axis.

4.9.8. Creation of the kinetic foot segment

Before Visual 3D was able to create force assignments (assigning segments to force platforms based on the estimated contact of a segment with the force platform) to permit calculation of ankle joint moments and power, it was necessary to create a kinetic foot segment. The one segment foot model was defined according to markers on the ankle and foot as described by C-Motion (254).

4.9.9. Kinematic and kinetic data collection procedure

Following application of the markers, a static trial was captured with the participant standing in upright double leg support in their natural base of gait. The static trial permitted calculation of off-set values for all joint rotations. These joint offset values were later subtracted from the appropriate joint rotations for the gait cycles of each participant (256). This process was conducted to account for variability in foot kinematics. Following completion of the static trial the two anatomical markers MMAL and CAL2 were removed. The dynamic trials were conducted with the remaining 34 markers (17 per limb). These markers acted as tracking markers during the dynamic trials.

Participants completed a familiarisation trial where they walked barefoot along a 10m walkway at their normal self-selected walking speed. Participants completed a minimum of 5 and a maximum of 10 dynamic walking trials barefoot on the walkway at their natural walking speed. At the conclusion of each trial all markers were checked in case of movement. During data collection participants were monitored visually and verbally and encouraged to rest if required.

4.10. EMG procedures

4.10.1. Rationale for selection of muscles for EMG analysis

As reported in Chapter 3, the quantification of muscle activity in inflammatory arthritis is limited and has not been reported in participants with tophaceous gout. Muscle activity in the medial and lateral gastrocnemius and the tibialis anterior was normalised to the MVIC. The medial and lateral gastrocnemius were selected on the basis that: the muscles are a confluence of the AT (the primary structure under investigation of this thesis); they are the primary plantarflexors of the foot during the stance phase of gait; and they control movement of the ankle joint. The tibialis anterior was selected as it is the primary dorsiflexor of the foot (antagonist to the gastrocnemius).

4.10.2. Measurement of muscle activity

EMG data were recorded using a Noraxon Desktop Direct Transmission System (DTS) enabling wireless surface EMG signal to be captured. The Noraxon system was synchronised within the Qualisys 3D motion analysis system to enable kinematic, kinetic and EMG data to be captured simultaneously. The Noraxon system comprises four components: (a) EMG electrodes; (b) EMG preamplifier leads; (c) EMG probes; and (d) the desktop receiver.

a) Noraxon dual surface electrodes (Noraxon USA Inc, Scottsdale, Az). The electrodes featured a self-adhesive Ag/AgCl contact material and an inter-electrode distance of 20 mm.

b) The preamplifier leads had no notch (50/60Hz) filters, 1st order high-pass filters set to 10Hz +/- 10% cut-off, a baseline noise: <1uV RMS, input impedance of > 100 Mohm, an input range of +/- 6.3mV, a base gain 200 and final gain of 500.

c) The EMG probes used were 3.4 x 2.4 x 1.4 cm and weighed approximately 14 grams.

d) The Desktop Direct Transmission System (DDTS) is a desktop receiver. This enables direct transmission of data from the EMG sensor site to the desktop receiver. The DDTS was connected to the computer via a USB cable and was able to detect signal from up to 20m from the EMG probe. The sensor acquisition system has 16 bit resolution, selectable low-pass cut-off at 500, 1000 or 1500Hz and a selectable sample rate of 1500 or 3000Hz. EMG signals were low-pass filter at 1000Hz and sampled at 1500Hz.

4.10.3. EMG experimental procedures

The location, preparation and application of the surface electrodes followed the Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) guidelines (257).

4.10.3.1. Tibialis anterior electrode location and placement procedure

Seated with hips and knee joint flexed at 90º, participants were asked to dorsiflex against resistance to determine the centre of the tibialis anterior muscle belly, an area approximately ⅓ of the distance between the head of the fibula and medial malleoli and orientated in the direction of the line between the tip of the fibula head and the tip of the medial malleolus (Figure 4.6a). A mark was made over the centre-most portion of the muscle belly where the electrode would be placed. The skin was prepared for electrode placement by shaving the site using a disposable safety razor, abrading the site with NuPREP® gel and gauze and cleaning the site with an isopropyl alcohol wipe. The electrode was placed in position and skin resistance assessed with a multimeter, if the skin resistance was greater than 5kΩ the electrode was removed and the preparation procedure repeated. If resistance levels were acceptable electrode position was verified and signal quality by visually inspecting the EMG signals while participants contracted each the muscle. This involved supporting the leg superior to the ankle joint with the ankle joint in dorsiflexion and the foot in inversion without extension of the hallux. Pressure was applied against the medial side, dorsal surface of the foot in the direction of plantarflexion of the ankle joint and eversion of the foot (258).

4.10.3.2. Lateral gastrocnemius electrode placement procedure

To determine electrode placement, subjects were asked to stand on both feet and perform a heel raise (rise up on to their toes) in order to locate the muscle belly. A mark was made to the central-most portion of the lateral gastrocnemius muscle belly to indicate electrode placement. The participant was moved to a plinth and placed in a prone position. The skin was prepared for electrode placement as for the tibialis anterior. The electrode was placed as displayed in Figure 4.6b. Skin resistance was assessed and electrode placement verified by manual muscle testing which involved the patient performing a standing heel raise (259).

4.10.3.3. Medial gastrocnemius electrode placement procedure

The procedure was replicated as for electrode placement on the lateral gastrocnemius (Figure 4.6b). Electrode placement was verified as for the lateral gastrocnemius (259).

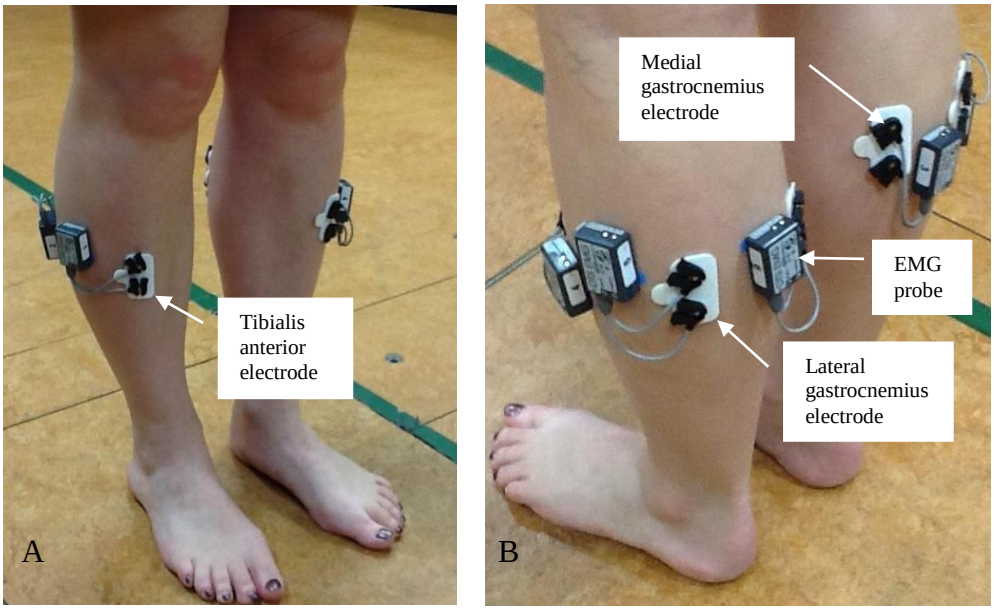


Figure 4.6. Electrode positioning for the tibialis anterior (A) and medial and lateral gastrocnemius muscles (B)

4.10.4. Maximum voluntary isometric contractions

4.10.4.1. Positioning

4.10.4.1.1. Medial and lateral gastrocnemius

MVICs were measured with the participants standing in their natural base and angle of gait. Participants were instructed to perform a bilateral heel raise to a position of maximum ankle plantarflexion standing with 0º knee flexion (259). The participants were encouraged to squeeze their gastrocnemius in this maximum position for a duration of 3 seconds. Following this, participants were instructed to relax into to a full weight-bearing position. This position was selected based on the previous research to acquire MVIC from the triceps surae muscle group (259).

4.10.4.1.2. Tibialis anterior

MVICs were measured in both tibialis anterior muscles independently. MVICs were generated with the participants seated with hips and knees flexed at 90º and foot resting on the ground. From this position the participants were asked to dorsiflex their foot, without extending their hallux or lifting their heel of the ground. Pressure was applied by the tester against the medial side, with the dorsal surface of the foot in the direction of plantarflexion of the ankle joint (258).

4.10.4.2. Protocol

Prior to recording MVIC trials, participants were familiarized with the testing procedure. A 10 second resting baseline was acquired, taken simultaneously from the medial and lateral gastrocnemius and tibialis anterior muscles, while the participants were seated, with hips and knees flexed at 90º and feet resting on the ground. Each participant completed three MVIC trials. During each maximum contraction the participant was given verbal encouragement to produce a maximum contraction. Each MVIC lasted approximately 6-8 seconds, which included a 2 second build-up followed by a maximum isometric 3 second effort contraction and a gradual 2 second decreased effort period. Maximum effort contractions were separated by a 2-minute recovery period.

4.11. Data processing

4.11.1. Kinematic data processing

Qualisys Track Manager (Version 2.8, build 1065, Qualysis AB, Gothenburg, Sweden) and Visual 3D Professional (Version 5.01.18, C-Motion Inc., Germantown, MD, USA) software programs were used for data processing. Marker coordinate data during the static and dynamic trials were captured using a Qualisys motion capture system (Qualisys Medical AB, Sweden) sampling at 240 Hz. 3D coordinate data were filtered at 6 Hz using a fourth order Butterworth filter. Following capture all dynamic trials were individually quality assessed by the researcher with the 3 best trials (which were determined by the placement of the feet in relation to the force plates) using Qualysis Track Manager. For each participant one dynamic trial was conducted, from this file an Automatic Identification File of Markers (AIM) model was generated and used to track two further trials. Marker and ground reaction force (GRF) data were stored within the Qualisys C3D file format with each trial individually processed using visual 3D software in order to generate the .cmo file. The .cmo file consisted of one static trial (used to build the model) and three dynamic trials from each participant (260).

4.11.2. Kinetic data processing

For dynamic data collection the raw GRF signals were filtered using a Butterworth low-pass filter with a cut off frequency of 10 Hz. Data was sampled at 1200 Hz to capture horizontal and vertical ground reaction forces in real-time. Kinetic data was analysed using Visual 3D (C-Motion Inc, USA) software. The vertical GRF was used to determine initial heel contact and terminal stance using rising and falling signals with a threshold of 20 Newtons (N). Horizontal and vertical ground reaction forces were calculated relative to each participant's bodyweight. The GRF data was stored within the C3D file and processed using Visual 3D software. Inverse dynamics were used to derive ankle joint moments and power. Inverse dynamics is the method used to derive joint forces and moments. Inertial properties of segments (mass, centre of mass, moments of inertia) are used in conjunction with the kinematics and external forces (GRF) to derive the joint forces and moments (261). End-points of segments were determined from either skin-marker positions or landmarks. Centre of mass is assumed to be located along the segments' longitudinal axis with a

distance expressed in percentage of the total length of the segment (255, 262). These distances were estimated based on Dempster's data and segments were modelled according to geometric shapes based on the work of Hanavan (255, 262).

4.11.3. EMG data processing

All EMG data reduction procedures were conducted using Visual 3D Professional (Version 5.01.18, C-Motion Inc., Germantown, MD, USA). All EMG raw signals were full-wave rectified and subsequently processed through a linear envelope. The processed EMG data obtained during the walking trials were then normalised to the MVIC.

EMG data were corrected for DC bias and high-pass filtered (4th order zero-phase lag Butterworth) with a cut-off frequency of 50 Hz. This was followed by low pass filtering at a cut-off frequency of 500Hz. A second order Butterworth Bidirectional filter was used (263). Background noise was removed. The purpose was to offset trial data to accommodate for any DC shift. A linear envelope was created. The signal was first high-pass filtered at cut-off frequency of 50Hz, full wave rectified and finally low-pass filtered (cut off frequency 10Hz). Normalised EMG values were expressed as a percentage of the MVIC (%MVIC). To calculate, the linear envelope was normalised to the greatest ½ second of activity of the MVIC trial. A window of twenty five 0.2s intervals of integrated EMG were moved one interval at a time across the MVIC data to find the greatest EMG activity. The average integrated EMG during the ½ second was used to compute the normalization factor (254).

4.12. Gait variables selected for analysis

The gait variables selected for investigation are displayed in Table 4.8.

Table 4.8: Spatiotemporal, kinematic, kinetic and muscle activity parameters selected for analysis

Gait parameter	Gait variable
Spatiotemporal	Walking velocity (m/s)
	Cadence (steps/min)
	Stride length (m)
	Double support time (s)
	Gait cycle time (s)
Kinematic	Ankle range of motion sagittal plane (º)
	Ankle range of motion frontal plane (º)
	Hallux range of motion (º)
Kinetic	Peak ankle joint force (N)
	Peak ankle joint moment (Nm/kg)
	Peak ankle joint power (W/kg)
	Work (Integration under peak power curve) (J/kg)
	Peak angular velocity (º/sec)
	Peak force (percent of gait cycle)
	Peak moment (percent of gait cycle)
	Peak force (percent of gait cycle)
Muscle activity	Muscle activity expressed as %MVIC for the tibialis anterior, medial and lateral gastrocnemius muscles and normalised to stance cycle time

m/s, meters per second; º, degrees; s, seconds; N, Newtons; Nm/Kg, Newton meters per kilogram; W/Kg, Watts per kilogram; J/kg (Joules per kilogram; º/sec, degrees per second; %MVIC, percentage of maximum voluntary isometric contraction

4.12.1. Rationale for selection of spatiotemporal variables

The spatiotemporal parameters of velocity, cadence, stride length, double support time and gait cycle time were selected on the basis for measurement as they have been extensively used to quantify gait strategy in inflammatory arthritis (detailed in Chapter 3).

4.12.2. Rationale for selection of kinematic variables

4.12.2.1. Ankle range of motion (sagittal and frontal plane)

Quantification of ankle ROM was a primary aim of the thesis. The results of Chapter 3 indicated ankle ROM has been described in the sagittal and frontal plane in RA but not in tophaceous gout. On the basis of previous research in RA, ankle ROM was measured in the frontal and sagittal planes (110, 183, 186, 187, 220).

4.12.2.2. Hallux range of motion

Although not extensively investigated previously in any inflammatory arthritic condition, hallux range of motion was selected due to the relevance of the 1MTP joint in gout, with this joint being the most common site of an attack of gout in the foot (77-80). Previous research in tophaceous gout has also postulated that a reduced hallux range of motion may be a significant adaptation to gait strategy (18).

4.12.3. Rationale for selection of kinetic variables

4.12.3.1. Ankle power

Quantification of ankle power was central to investigating hypotheses 3 and 6. Peak ankle power was measured during the stance phase of gait, in line with previous studies in RA as detailed in Chapter 3. Additionally, timing alterations or peak ankle power in relation to the stance phase of gait were investigated. It was postulated that the timing of peak power may be altered in participants with tophaceous gout. Subsequently, the percentage in the stance phase at which peak power generation occurred was calculated. This parameter has not been previously reported in inflammatory arthritic gait research. The amount of positive work (concentric muscle activity) of the ankle plantar flexors that occurred during stance phase of gait was also calculated. It was postulated that the amount of concentric activity may be altered in participants with tophaceous gout. This was represented by the A2 area of ankle power curve as displayed in Figure 4.7 (261). This parameter has been previously reported in a RA study (191).

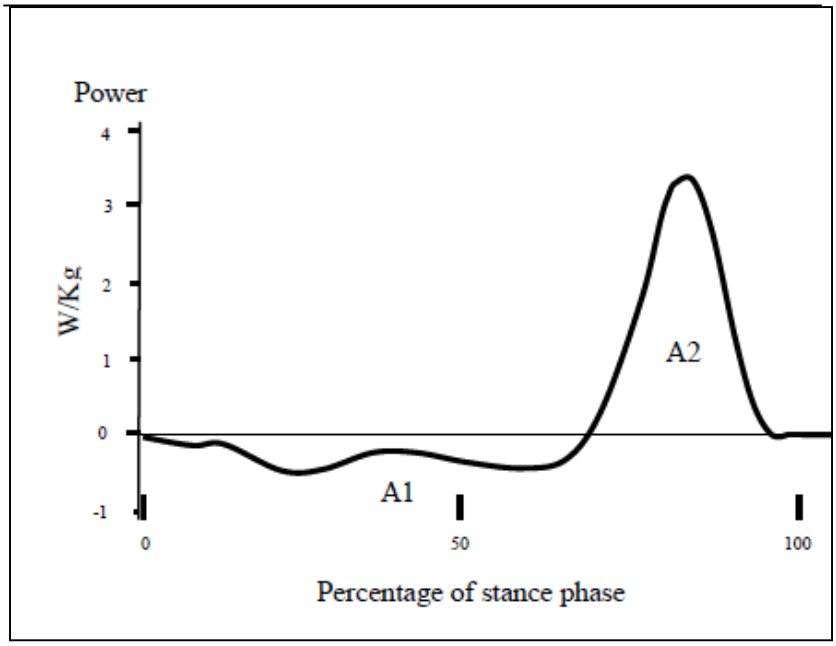


Figure 4.7. Power generation of the ankle during stance phase of gait. A1 represents eccentric muscle activity. A2 represents concentric muscle activity.

4.12.3.2. Peak ankle force and moment

The parameters of peak ankle force and peak ankle moment were also quantified in line with previous research in inflammatory arthritis, as detailed in Chapter 3. Additionally, the timing of the peak values of these parameters during the stance phase was of interest. Subsequently, the percentage of stance phase of gait when peak force and peak moment occurred were calculated.

4.12.3.3. Angular velocity

Reductions in ankle power have been reported in RA and PsA and in RA associated with reductions in angular velocity of the ankle joint (174, 189, 190, 203). Reporting of angular velocity is limited. Subsequently, the magnitude of the angular velocity component at the instant of peak ankle generation power was extracted.

4.13. Statistical analysis

All statistical analyses were performed using SPSS (version 22, SPSS Inc., Chicago, IL).

4.13.1. Assessment of all data for normality

Normality of all data was assessed using a Shapiro-Wilks test and visual inspection of their histograms, normal Q-Q plots and box plots (264, 265). All tests were two-tailed, and p values < 0.05 were considered significant. Data were analysed using SPSS software v20™. Where data was normally distributed it was presented as mean (SD). Where data was not normally distributed, the median (IQR) was reported.

4.13.2. Analysis of patient, clinical characteristics and patient-reported outcome measures

Descriptive statistics, including mean (SD) and percentages, were used to describe the patient and clinical characteristics. Median (IQR) were used to describe PROMs.

4.13.3. Ultrasound imaging

4.13.3.1. Inter-observer agreements

To assess inter-observer agreement, the same 24 participants (12 cases and 12 controls) were scored by a second scorer (an experienced radiologist). Rescoring of images occurred 6 months following the initial scanning session. Inter-observer agreements were estimated using the kappa statistic (ƙ) and 95% confidence intervals (95% CI). Inference of the ƙ-statistic is based upon accepted benchmarks (266). A ƙ-value less than 0.20 was considered poor, between 0.21 and 0.40 fair, between 0.41 and 0.60 moderate, between 0.61 and 0.80 good, and between 0.81 and 1 excellent (266).

4.13.3.2. Analysis of ultrasound lesions

As lesions were nested within participants, a general estimating equation (GEE) approach was used to analyse data (267). This approach accounted for key issues such as sparseness of data, ordinal scales with few observations and allowance for multiple observations on

the same individuals (left and right sides) and 3 zones of measurement in the AT (insertional, preinsertion and proximal).

US lesions were graded 0-2 on a semi-quantitative scoring system (0 = absent, 1 = mild to moderate, 2 = severe). Due to very few lesions being scored '2' the scoring system was restructured into a binary scoring system to enable useful statistical analysis. The grading of 'mild to moderate' was combined with the 'severe' grade to create 2 binary scoring categories (presence/absence). Frequencies of US lesions (absence/presence) were analysed by side (left, right), zone (insertional, mid portion and proximal to mid portion) and group (gout vs control), with a design matrix constructed (2x3x2, x2 for the presence/absence measures). GEE models were used to analyse the binary data, analyses which incorporated the 6 observations per person and compared tophaceous gout and control participants.

In the GEE models, side was set up as a structural variable but was not formally compared. The GEE models also tested the interaction between zone and group (control/gout). This tested for statistically significant differences between zones in the differences between gout vs control. If significant interactions were identified they were further explored by comparing gout vs control for each zone. If there was no significant interaction between AT zone and group then the interaction term was removed from the model. If the zone effect was significant in the model, pairwise comparisons amongst the zones were completed to further explore the zone effect. If there were no significant differences amongst the 3 zone in the AT, pairwise comparisons were not undertaken. A separate model was used to analyse continuous US lesion data.

4.13.4. Analysis of gait parameters

For all variables, data from the 3 dynamic walking trials for each participant were input to Microsoft Excel Version 2010. The ensemble mean (SD) values of the 3 trials were calculated. The predetermined gait variables were then exported into SPSS. Muscle activity in the medial and lateral gastrocnemii and tibialis anterior were expressed as %MVIC and normalised to stance phase duration.

4.13.4.1. Inter-trial reliability of gait parameters

Inter-trial reliability analysis used Intraclass Correlation Coefficients (ICC, 2,1) and 95% confidence intervals (CI) to quantify reproducibility of kinematic and kinetic gait variables and muscular activity. Reliability findings were interpreted by arbitrary benchmarks initially proposed by Fleiss (268). The strength of the agreement was poor if the correlation ranged from 0-0.40; fair to moderate if the correlation ranged from 0.40-0.75 and excellent if the correlation ranged from 0.75-1.00. Standard error of measurement (SEM) calculations assessed differences between the actual measured score across the images and the estimated "true" scores (269).

4.13.4.2. Comparisons of means between tophaceous gout and control participants

To compare means between gait variables, one-way ANOVA was conducted (270). ANOVA is considered robust against violations in normality assumptions (normal distribution, homogeneity of variances) (271). An adjustment to control for type I error such as the Bonferroni was viewed as too conservative and would have yielded very strict thresholds of significance. As this research is novel, the risk of introducing type II error with such an adjustment may have also prevented the discovery of important between-group differences that require further exploration (272, 273).

4.13.5. Bivariate linear associations

To investigate associations between US lesions and gait parameters correlation coefficients were used. The Pearson's product moment correlation coefficient was used for all variables that were normally distributed (274). Where data were not normally distributed the Spearman's rank-order correlation coefficient was calculated (274).

The Pearson's correlation coefficient (ρ) ranges from -1 to +1. A positive association (two variables tend to increase or decrease simultaneously) results in $\rho > 0$, and negative association (one variable tends to increase when the other decreases) results in $\rho < 0$. A ρ value of 0 corresponds to the absence of association. The absolute value of ρ indicates the

strength of the relationship between the two variables, with a ρ of 1 indicating a perfect linear relationship (275). The Spearman's correlation coefficient is a rank-based version of the Pearson's correlation coefficient. As with the Pearson's correlation coefficient, the coefficient varies from -1 to +1 with values to 0 indicative of a weaker relationship between the variables (275). The level of association between variables was quantified using guidelines in Table 4.9.

Table 4.9: Guidelines for interpreting the size of a correlation coefficient **(276)**

Size of correlation	Interpretation
.90 to 1.00 (-.90 to -1.00)	Very high positive (negative) correlation
.70 to .90 (-.70 to -.90)	High positive (negative) correlation
.50 to .70 (-.50 to -.70)	Moderate positive (negative) correlation
.30 to .50 (-.30 to -.50)	Low positive (negative) correlation
.00 to .30 (.00 to -.30)	Negligible correlation

4.13.6. Multiple regression analysis

4.13.6.1. Forward selection stepwise regression

In examining relationships between gait variables and US lesions, data were investigated using forward selection stepwise multiple regression. All model assumptions (normal distribution of errors, linearity and heteroscedasticity) were assessed. The assumption of independence of observations was fulfilled by the study design. Normality or errors was assessed by visual interpretation of the histogram, and distribution of the normal P-P plot, or the residuals. Homoscedasticity was assessed by visual examination of a plot of the standardized residuals (the errors) by the regression standardized predicted value. Homoscedasticity was assumed if the residuals were randomly scattered around the horizontal line of the plot (277). Additionally, collinearity was assessed through assessment of tolerance. Tolerance is a measure of collinearity among independent variables, where possible values range from 0 to 1. A value for tolerance close to zero is an indication of multicollinearity.

4.13.6.2. Model sample size

In recognition of the potential for model over fitting the number of independent variables entered into the model, a general rule of thumb was used based on the recommendations of Hair (278). This general rule of thumb is that the ratio of independent variables should be approximately 5:1. The desired outcome is approximately 15-20 subjects per independent variable (278).

CHAPTER 5

RESULTS

5.1. Introduction

This chapter presents the findings from the US imaging and gait analysis studies. Data from the 48 participants (24 tophaceous gout, 24 controls) were analysed with results presented in 7 subsections to represent the main areas of investigation: (1) population demographics, (2) clinical characteristics, (3) patient-reported outcome measures, (4) US lesion characteristics, (5) gait characteristics, (6) bivariate correlation analysis and (7) multiple regression analysis.

5.2. Population demographics

The demographic characteristics of the cohort are summarised in Table 5.1. The participants with gout and the control participants were age and sex-matched. The majority of the participants were middle aged males (92%) predominately of European ethnicity (77%). The control participants demonstrated a significantly higher number of Europeans ($p \leq 0.01$). Participants with gout had a higher mean BMI compared to controls ($p < 0.01$).

Table 5.1: Demographic characteristics of study population

		Gout participants	**Control participants**	**p-value**
Age, years, mean (SD)		61.88 (12.03)	61.67 (12.29)	0.95
Sex	Male, n (%)	22 (92)	22 (92)	0.70
	Female, n (%)	2 (8)	2 (8)	
Ethnicity	European, n (%)	14 (58)	23 (96)	< 0.01
	Māori, n (%)	1 (4)	1 (4)	
	Pacifica, n (%)	6 (25)	0 (0)	
	Asian, n (%)	3 (13)	0 (0)	
BMI, (kg/m^2), mean (SD)		31.13 (4.05)	26.31 (5.10)	< 0.01

5.3. Clinical characteristics

The clinical characteristics are displayed in Table 5.2. Participants with gout had well-established disease with a mean serum urate level of 0.37 mmol/L. Comorbidities that included hypertension, cardiovascular disease and type 2 diabetes were found in approximately one-third of participants with tophaceous gout. The participants with gout had a higher prevalence of hypertension ($p < 0.01$) and cardiovascular disease ($p = 0.03$) compared to the control participants. The majority of participants with gout were prescribed allopurinol (n = 20, 83%).

Table 5.2: Clinical characteristics of study cohort

	Gout participants	**Control participants**	**p-value**
Disease duration, years, mean (SD)	17.44 (11.88)	n/a	
Age at first episode, years, mean (SD)	44.29 (18.79)	n/a	
Self-reported flares in preceding 3 months, mean (SD)	1.23 (1.45)	n/a	
Foot tophus count, mean (SD)	2.17 (3.33)	n/a	
Total tophus count, mean (SD)	7.21 (7.35)	n/a	
Serum urate, mmol/L, mean (SD)	0.37 (0.11)	n/a	
Serum creatinine μmol/L, mean (SD)	105.20 (38.90)	n/a	
Hypertension, n (%)	17 (71)	7 (29)	< 0.01
Cardiovascular disease, n (%)	8 (33)	2 (8)	0.03
Type 2 diabetes, n (%)	7 (29)	2 (8)	0.07
Diuretic, n (%)	9 (38)	9 (38)	1.00
Colchicine, n (%)	14 (58)	n/a	
Urate lowering therapy			
Allopurinol, n (%)	20 (83)	n/a	
Probenecid, n (%)	6 (25)	n/a	
Febuxostat, n (%)	2 (8)	n/a	
Benzbromarone, n (%)	1 (4)	n/a	
Other medications			
Prednisone, n (%)	6 (25)	n/a	

5.4. Patient-reported outcome measures

HAQ-II scores indicated participants with gout had significantly greater activity limitation ($p < 0.01$). There were significant differences between participants with gout and control participants for the $LFIS_{IF}$ ($p < 0.01$) and $LFIS_{AP}$ ($p < 0.01$). High levels of impairment (scores ≥ 7 points on the $LFIS_{IF}$) and disability (scores ≥ 10 points on the $LFIS_{AP}$) were found in the participants with gout. The participants with gout had significantly reduced ability in performing activities of daily living ($LLTQ_{ADL}$) and recreational activities ($LLTQ_{AP}$) associated with the lower limb compared to the control participants ($p < 0.01$). Global health, global pain and foot pain were significantly higher in the participants with gout, compared to the control participants (Table 5.3).

Table 5.3: Results from the patient-reported outcome measures

Patient-reported outcome measures	**Gout participant median, (IQR)**	**Control participant median, (IQR)**	**p-value**
HAQ-II	0.50 (0.75)	0.05 (0.20)	< 0.01
$LFIS_{IF}$ (range 0–21)	16.00 (14.00)	1.00 (3.00)	< 0.01
$LFIS_{AP}$ (range 0–30)	9.50 (9.00)	0.50 (1.00)	< 0.01
$LLTQ_{ADL}$ (range 0–40)	32.00 (11.00)	39.00 (2.00)	< 0.01
$LLTQ_{RA}$ (range 0–40)	14.00 (12.00)	37.50 (12.00)	< 0.01
Global pain (per 0–100 mm VAS unit)	27.00 (53.00)	0.00 (15.00)	< 0.01
Foot pain (per 0–100 mm VAS unit)	10.00 (60.00)	0.00 (1.00)	< 0.01
Global health (per 0–100 mm VAS unit)	25.50 (38.00)	2.50 (14.00)	< 0.01

5.5. Ultrasound lesions of the Achilles tendon

5.5.1. Inter-observer reliability of US lesion scoring

The inter-observer agreement analysis of the present study revealed absolute or excellent agreement for all US lesions, with the exception of calcaneal enthesophytes and calcaneal bone cortex irregularities (moderate agreement) (Table 5.4).

Table 5.4: Inter-observer reliability in the assessment of ultrasound lesions

US lesion	κ values (95% CI)
Tophus present	0.91 (0.76, 1.00)
Focal hypoechoic areas with loss of fibrillar echotexture	1.00
Intratendinous hyperechoic spots	0.93 (0.85, 1.00)
Intratendinous power Doppler signal	0.87 (0.82, 1.00)
Tendon tear	1.00
Entheseal echogenicity: focal hypoechoic areas	1.00
Entheseal echogenicity: calcifications	0.92 (0.81, 1.00)
Entheseal vascularity	0.84 (0.55, 1.00)
Bursal snowstorm appearance	1.00
Bursal power Doppler signal	1.00
Calcaneal bone cortex irregularities	0.77 (0.60, 0.94)
Calcaneal enthesophytes	0.68 (0.48, 0.88)
Calcaneal bone erosions	1.00

5.5.2. Frequency of US lesions in the Achilles tendon

5.5.2.1. Tophus burden in AT

Tophi were present through all zones of the AT in the participants with gout, with the frequency similar in zone 1 and 2 of the AT (Figure 5.1). No tophi were present in the AT of the control participants. The frequency of tophus present (combined left and right AT) for the case and control participants are displayed in Table 5.5.

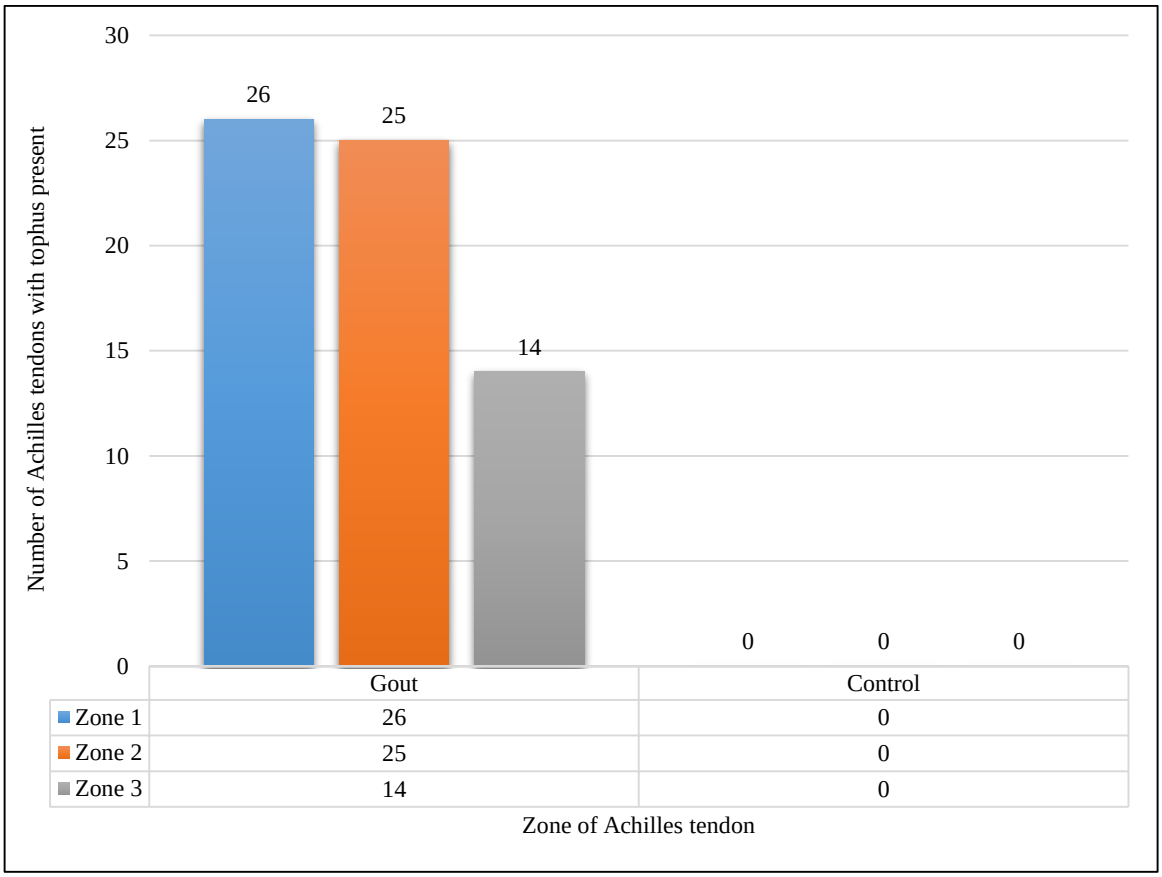


Figure 5.1. Number of tophi present in the Achilles tendon of the gout and control participants in relation to zones of the Achilles tendon.

In the participants with gout, tophi were present in 73% of AT examined. The overall burden of tophus by zone of the AT is displayed in Figure 5.2.

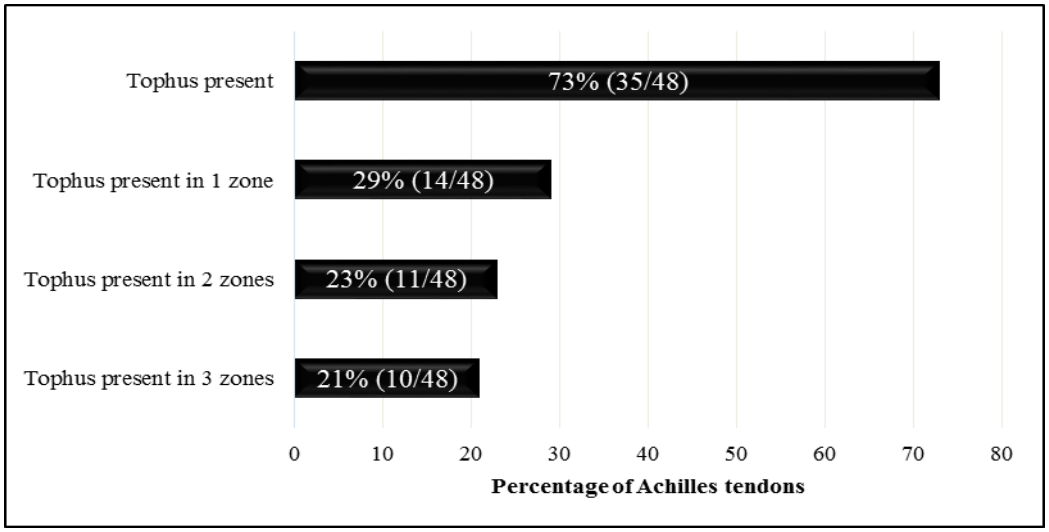


Figure 5.2. Tophus burden in relation to total Achilles tendons examined.

5.5.2.2. Fibrillar echotexture

The frequency of alteration in fibrillar echotexture are displayed in Table 5.5. Ten percent (5/48) of participants with gout and 4% (2/48) of control participants (Table 5.5) demonstrated change in fibrillar echotexture.

5.5.2.3. Intratendinous hyperechoic spots

The frequency of intratendinous hyperechoic spots in the left and right leg are displayed in Table 5.5. Intratendinous hypoechoic spots were most prevalent in participants with gout but also present in control participants ($p < 0.01$). Intratendinous hyperechoic spots were also most prevalent in the insertional zone of the AT both in participants with gout and control participants (Figure 5.3).

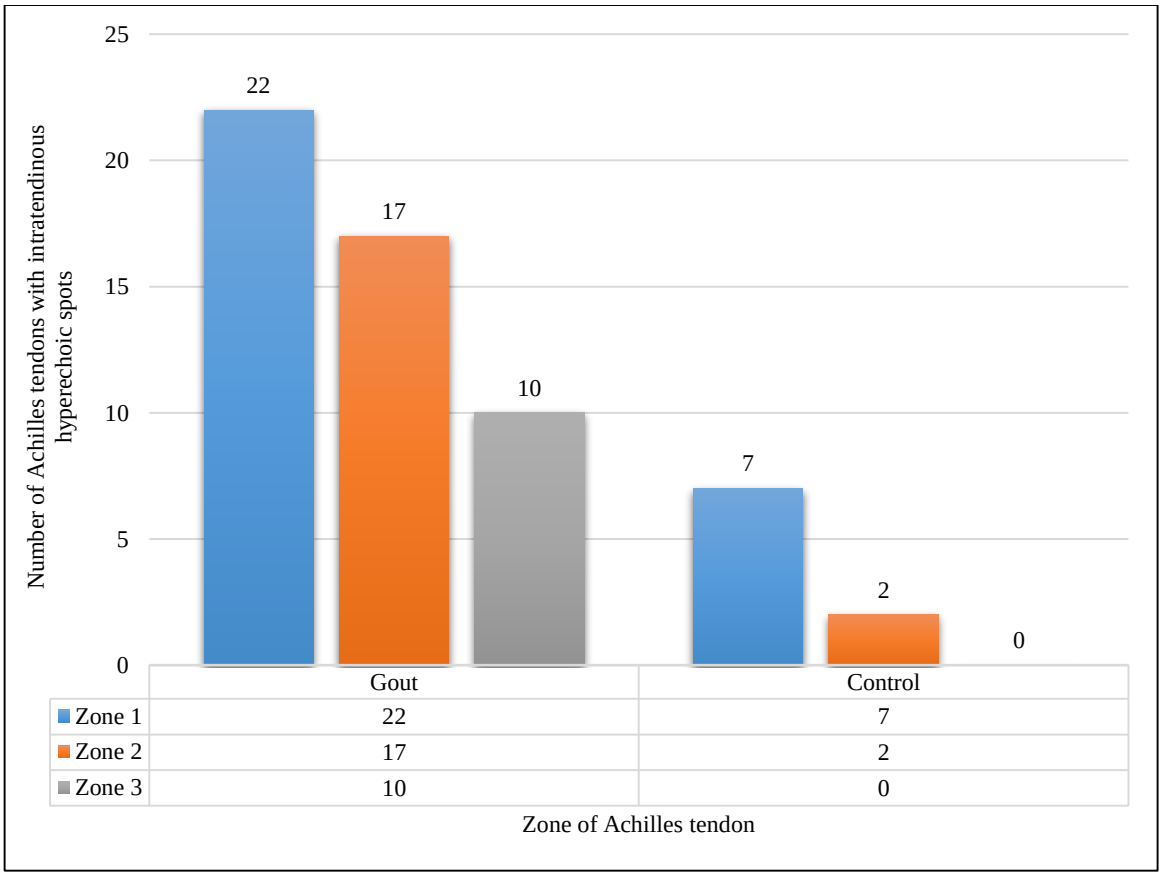


Figure 5.3. Prevalence of intratendinous hyperechoic spots in participants with gout and control participants in relation to zones of the Achilles tendon.

5.5.2.4. Intratendinous Doppler signal

Intratendinous Doppler signal was present in all zones of the AT in participants with gout. Intratendinous Doppler signal was most prevalent in participants with gout but also present in control participants ($p < 0.01$). The frequency of intratendinous Doppler signal in the left and right leg is displayed in Table 5.5. The presence of intratendinous Doppler signal in relation to the zones of the AT is displayed in Figure 5.4.

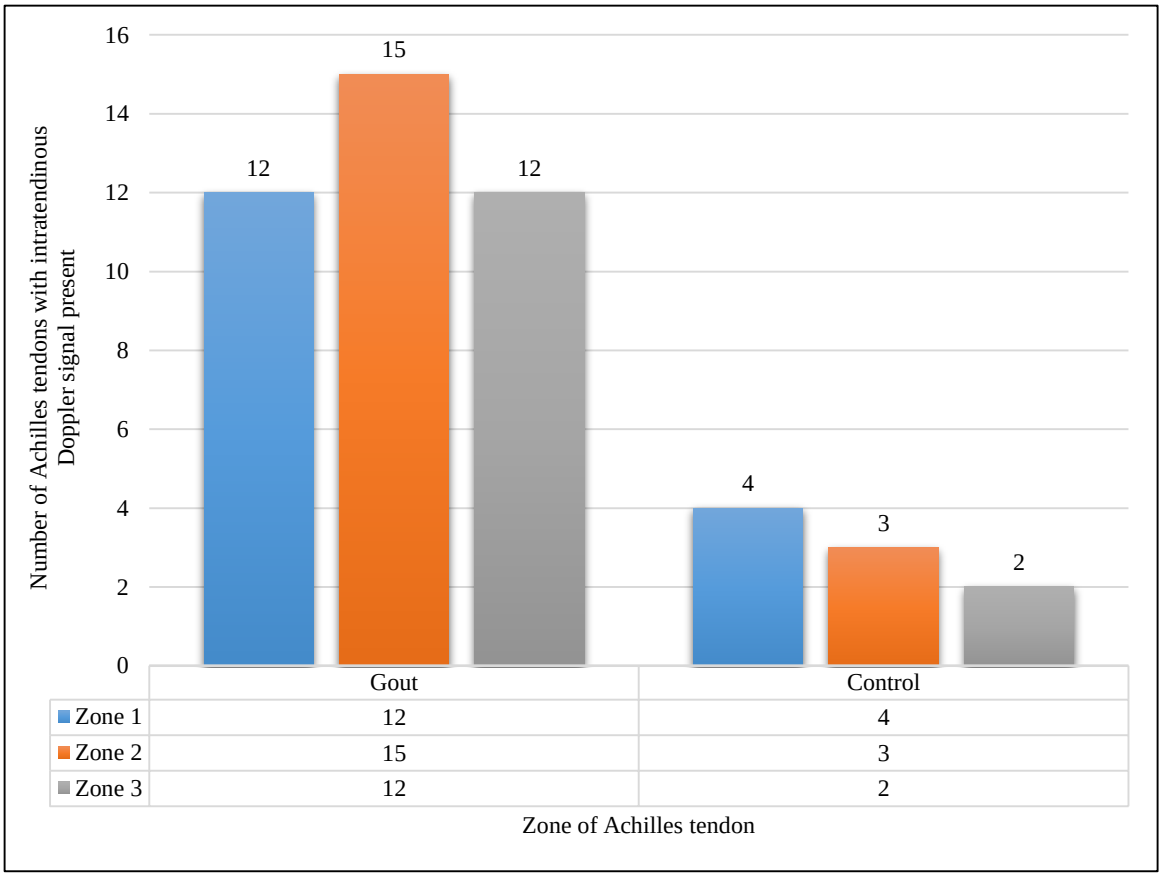


Figure 5.4. Number of Achilles tendons with intratendinous Doppler signal in gout and control participants' relation to zones of the Achilles tendon.

5.5.2.5. Entheseal lesions

Only one AT displayed hypoechoic change in the participants with gout. There were no significant differences in entheseal calcifications of the AT between the participants with gout (n = 28, 59%) and control participants (n = 19, 40%) (p = 0.43). There was no significant differences in entheseal vascularity of the AT between the participants with gout (n = 10, 21%) and control participants (n = 7, 15%) (p = 0.65). Frequencies for entheseal hypoechogenicity (focal hypoechoic areas, calcifications and vascularity) in the left and right leg are displayed in Table 5.5.

5.5.2.6. Bursal lesions

A bursal snowstorm appearance was only detected in one AT in a participant with gout. Bursal Doppler signal of the AT was detected in (n = 7, 15%) of participants with tophaceous gout. Bursal snowstorm appearance and bursal Doppler signal was not found in any control participants. Frequencies of bursal snowstorm appearance and bursal Doppler signal in the left and right leg are displayed in Table 5.5.

5.5.2.7. Bone profile

Calcaneal bone cortex of the AT irregularities were detected in both the participants with gout (n = 13, 27%) and control participants (n = 9, 19%), between group differences were not significant (p = 0.43). No significant differences in calcaneal enthesophytes were detected between participants with gout (n = 33, 69%) and control participants (n = 29, 60%), (p = 0.64). Frequencies of calcaneal bone cortex irregularities and calcaneal enthesophyte formation are displayed in Table 5.5.

Table 5.5: Frequency of ultrasound lesions present at the insertion, pre-insertion and proximal zone of the Achilles tendon.

US lesion	Zone of AT	Gout US lesion present n, (%)		Control US lesion present n, (%)	
		Left AT n=24	Right AT n=24	Left AT n=24	Right AT n=24
Tophus present	1	14, (58)	12, (50)	0, (0)	0, (0)
	2	15, (63)	10, (42)	0, (0)	0, (0)
	3	6, (25)	8, (33)	0, (0)	0, (0)
Focal hypoechoic areas with loss of fibrillar echotexture	1	1, (4)	0, (0)	1, (4)	0, (0)
	2	0, (0)	0, (0)	0, (0)	1, (4)
	3	1, (4)	3, (13)	0, (0)	0, (0)
Intratendinous hyperechoic spots	1	12, (50)	10, (42)	3, (13)	4, (17)
	2	9, (38)	8, (33)	2, (8)	0, (0)
	3	4, (17)	6, (25)	0, (0)	0, (0)
Intratendinous power Doppler signal	1	3, (13)	9, (38)	3, (13)	1, (4)
	2	7, (29)	8, (33)	2, (8)	1, (4)
	3	4, (17)	8, (33)	2, (8)	0, (0)
Tendon tear	1	1, (4)	0, (0)	0, (0)	0, (0)
	2	0, (0)	0, (0)	0, (0)	0, (0)
	3	0, (0)	1, (4)	0, (0)	0, (0)
Entheseal echogenicity: focal hypoechoic areas	1	1, (4)	0, (0)	0, (0)	0, (0)
Entheseal echogenicity: calcifications	1	16, (67)	12, (50)	7, (29)	12, (50)
Entheseal vascularity	1	5, (21)	5, (21)	5, (21)	2, (8)
Bursal snowstorm appearance	1	0, (0)	1, (4)	0, (0)	0, (0)
Bursal power Doppler signal	1	3, (13)	4, (17)	0, (0)	0, (0)
Calcaneal bone cortex irregularities	1	7, (29)	6, (25)	4, (17)	5, (21)
Calcaneal enthesophytes	1	15, (63)	18, (75)	13, (54)	16, (70)

Zones; 1, insertion; 2, pre-insertion; 3, proximal to pre-insertion

The majority of AT were less than 5.3mm in thickness, had bursal sizes of less than 2mm and had no bone erosions present at the calcaneus in both participants with gout and control participants. Scoring frequencies for AT thickness, bursal size score and calcaneal erosions are presented in Table 5.6.

Table 5.6: Scoring frequencies for tendon thickness, bursal size and calcaneal bone erosions.

US lesion		**Gout US lesion present n, (%)**		**Control US lesion present n, (%)**	
	Score	Left AT n=24	Right AT n=24	Left AT n=24	Right AT n=24
Tendon thickness score (0: <5.3 mm; 1: between 5.3 and 6.3; 2: > 6.3 mm)	0	20, (83)	19, (79)	23, (96)	24, (100)
	1	4, (17)	4 (17)	1, (4)	0, (0)
	2	0, (0)	1, (4)	0, (0)	0, (0)
Bursal size score (0: <2 mm; 1: between 2–4 mm; 2: > 4 mm)	0	24, (100)	22, (92)	24, (100)	24, (100)
	1	0, (0)	2, (8)	0, (0)	0, (0)
	2	0, (0)	0, (0)	0, (0)	0, (0)
Calcaneal bone erosions (0: no bone erosion; 1: between 0.1 and 2 mm; 2: > 2 mm)	0	0, (0)	1, (4)	0, (0)	1, (4)
	1	0, (0)	0, (0)	0, (0)	0, (0)
	2	0, (0)	0, (0)	0, (0)	0, (0)

5.5.3. Differences between US lesions

The GEE modelling demonstrated significant differences between participants with gout and control participants. The presence of tophi ($p < 0.01$), intratendinous hyperechoic spots ($p < 0.01$) and intratendinous PD signal ($p < 0.01$) were more common in participants with gout compared to control participants (Table 5.7). No significant differences were found for tophus presence ($p = 0.07$) and intratendinous PD signal ($p = 0.60$) between the three zones of the AT.

Significant differences found in intratendinous hyperechoic spots were further analysed using pairwise comparisons (Table 5.8). There were significantly more hyperechoic spots present in zone 3 of the AT compared to zone 1.

The US lesions of focal hypoechoic areas with loss of fibrillar echotexture, tendon tear, tendon thickness score, entheseal echogenicity focal hypoechoic areas, bursal size score, bursal snowstorm appearance, bursal Doppler signal and calcaneal bone erosions were unable to be analysed by the model as insufficient data were available.

Table 5.7: Ultrasound lesion scores between case and control participants and mean ultrasound lesion scores by zone of tendon.

US lesion	Gout participants Mean	Control participants Mean	p-value	Mean of AT zone in gout participants		p-value for between zone difference in gout
Tophus	0.78	0.00	<0.01	Zone 1 Zone 2 Zone 3	0.77 0.72 0.84	0.07
Intratendinous hyperechoic spots	0.95	0.67	<0.01	Zone 1 Zone 2 Zone 3	0.75 0.85 0.93	<0.01
Intratendinous power Doppler signal	0.94	0.73	<0.01	Zone 1 Zone 2 Zone 3	0.87 0.85 0.88	0.60
Entheseal echogenicity: calcifications	0.27	0.19	0.43			
Entheseal vascularity	0.21	0.17	0.65			
Calcaneal bone cortex irregularities	0.27	0.19	0.43			
Calcaneal enthesophytes	0.69	0.60	0.64			

Table 5.8: Pairwise comparisons for intratendinous hyperechoic spots in tophaceous participants with gout.

Zone of AT	Comparison zone of AT	p-value
1	2	0.06
	3	<0.01
2	1	0.06
	3	0.16
3	1	<0.01
	2	0.16

AT length and thickness as assessed by digital measurement did not significantly differ between the participants with gout and control participants (Table 5.9).

Table 5.9: Mean ultrasound lesions measurements for entheseal tendon thickness and tendon length.

US lesion	Gout participants Mean, (SD)	Control participants Mean, (SD)	p-value
Tendon thickness at the insertion of the deeper margin into the calcaneal bone (mm)	4.65 (0.81)	4.32 (0.74)	0.85
Tendon Length (mm)	57.90 (19.83)	57.31 (15.62)	0.90

5.6. Gait analysis

5.6.1. Intra-trial reliability

5.6.1.1. Three-dimensional gait analysis

Reliability between trial 1 and 2 for all gait variables assessed by 3D motion analysis are displayed in Table 5.10.

Table 5.10: Intra-trial reliability indices for gait variables

Gait variable	Gout Trial 1 Mean	Gout Trial 2 Mean	ICC	95% CI	SEM	Control Trial 1 Mean	Control Trial 2 Mean	ICC	95% CI	SEM
Walking velocity (m/s)	1.04	1.02	0.99	0.96, 0.99	0.02	1.23	1.22	0.94	0.86, 0.97	0.03
Cadence (steps/min)	100.50	98.90	0.99	0.97, 0.99	1.43	111.97	115.13	0.77	0.44, 0.90	3.65
Step length (m)	0.61	0.60	0.96	0.92, 0.98	0.02	0.64	0.64	0.94	0.98, 0.97	0.01
Stance cycle time (s)	1.16	1.16	0.98	0.94, 0.99	0.02	1.06	1.07	0.95	0.88, 0.98	0.01
Double support time (s)	0.26	0.27	0.92	0.80, 0.97	0.02	0.22	0.22	0.93	0.82, 0.97	0.01
Sagittal plane ankle ROM (º)	17.83	17.27	0.92	0.86, 0.96	1.13	17.75	17.38	0.94	0.88, 0.96	0.86
Frontal plane ankle ROM (º)	10.85	10.69	0.95	0.92, 0.98	0.86	9.19	8.90	0.97	0.94, 0.98	0.83
Peak eversion (º)	-3.95	-3.97	0.97	0.94, 0.98	0.46	-3.40	-3.67	0.66	0.40, 0.82	1.83
1MTP joint ROM (º)	14.53	13.99	0.83	0.62, 0.93	2.48	21.02	18.48	0.88	0.49, 0.96	2.02
Peak ankle force (N)	281.52	277.29	0.98	0.96, 0.99	10.19	262.56	268.47	0.95	0.92, 0.97	14.09
Peak ankle moment (Nm/kg)	1.20	1.20	0.97	0.94, 0.98	0.04	1.15	1.15	0.97	0.95, 0.99	0.03
Peak ankle power (W/kg)	1.89	1.85	0.96	0.93, 0.98	0.14	2.20	2.15	0.93	0.87, 0.96	0.14
Peak angular velocity (deg/s)	-208.33	-210.52	0.96	0.94, 0.98	-10.47	-252.34	-255.58	0.92	0.87, 0.96	-12.56

5.6.1.2. Muscle activity

Reliability between trial 1 and 2 for muscle activity during the stance phase of gait are presented in Table 5.11.

Table 5.11: Intra-trial reliability indices for muscle activity.

Muscle	Gout Trial 1 Mean	Gout Trial 2 Mean	ICC	SEM	Control Trial 1 Mean	Control Trial 2 Mean	ICC	SEM
Lateral gastrocnemius (%MVIC)	18.49	21.50	0.98	3.96	6.44	6.21	0.97	1.04
Medial gastrocnemius (%MVIC)	20.63	21.71	0.95	2.46	16.73	16.66	0.96	1.60
Tibialis anterior (%MVIC)	9.08	9.13	0.78	2.81	8.68	7.39	0.64	1.80

ICC, intraclass correlation coefficient; SEM, standard error of measurement

5.6.2. Spatiotemporal gait parameters

Differences in spatiotemporal parameters between participants with tophaceous gout and controls are displayed in Table 5.12. Results showed that participant with gout had reduced walking velocity ($F_{1,94} = 36.72$, $p < 0.01$), reduced cadence ($F_{1,88} = 25.16$, $p < 0.01$), reduced step length ($F_{1,85} = 8.04$, $p < 0.01$), increased double support time ($F_{1,88} = 17.99$, $p < 0.01$) and increased stance cycle time ($F_{1,94} = 28.79$, $p < 0.01$) when compared to controls.

Table 5.12: Descriptive statistics for spatiotemporal gait variables

Gait variable	Gout participants Mean, (SD)	Control participants Mean, (SD)	Mean difference (95% CI)	p-value
Walking velocity (m/s)	1.02 (0.19)	1.23 (0.13)	-0.20 (-0.27, -0.14)	< 0.01
Cadence (steps/min)	104.99 (9.07)	113.55 (7.05)	-8.57 (-11.96, -5.17)	< 0.01
Step length (m)	0.61 (0.07)	0.65 (0.16)	-0.04 (-0.06, -0.01)	< 0.01
Double support time (s)	0.27 (0.62)	0.22 (0.38)	0.05 (0.02, 0.07)	< 0.01
Stance cycle time (s)	1.16 (0.10)	1.06 (0.70)	0.09 (0.06, 0.13)	< 0.01

5.6.3. Kinematic gait parameters

Descriptive statistics for between-group kinematic gait analyses are displayed in Table 5.13. Sagittal plane ankle range of motion ($F_{1,94}$ = 0.63, p = 0.43), frontal plane ankle range of motion, ($F_{1,90}$ = 3.24, p = 0.08) and peak eversion ($F_{1,90}$ = 2.51, p = 0.12) were not significantly different between participants with gout and control participants. 1MTP joint ROM ($F_{1,90}$ = 14.98, p < 0.01) and peak angular velocity at the ankle joint ($F_{1,94}$ = 20.55, p < 0.01) were significantly reduced in participants with gout compared to control participants.

Table 5.13: Descriptive statistics for kinematic gait variables.

Gait variable	Gout participants Mean (SD)	Control participants Mean (SD)	Mean difference (95% CI)	p-value
Sagittal plane ankle ROM (º)	18.02 (3.53)	17.48 (3.10)	0.54 (-0.81, 1.88)	0.43
Frontal plane ankle ROM (º)	10.38 (3.18)	9.08 (3.72)	1.30 (-0.13, 2.73)	0.08
Peak eversion (º)	-3.85 (2.60)	-2.99 (2.66)	-0.86 (-1.93, 0.22)	0.12
Sagittal plane 1MTP joint ROM (º)	14.88 (5.26)	19.55 (6.26)	-4.66 (-7.05, -2.26)	< 0.01
Peak angular velocity (º/s)	-210.09 (53.01)	-254.49 (42.37)	44.40 (24.95, 63.85)	< 0.01

By convention eversion and angular velocity are expressed as negative values

5.6.4. Kinetic gait parameters

Descriptive statistics for kinetic gait parameters are displayed in Table 5.14. The analysis revealed participants with gout had reduced ankle power ($F_{1,94}$ = 6.49, p = 0.01) when compared to control participants. There were no significant differences between participants with gout and control participants in peak ankle force ($F_{1,94}$ = 1.37, p = 0.25), peak ankle moment ($F_{1,94}$ = 1.97, p = 0.16), the timing of peak ankle force ($F_{1,91}$ = 0.06, p = 0.81), peak ankle moment ($F_{1,94}$ = 1.97, p = 0.16), the timing of peak power generation in the stance phase ($F_{1,94}$ = 0.55, p = 0.46), or ankle plantarflexor concentric work ($F_{1,94}$ = 2.91, p = 0.09).

Table 5.14: Descriptive statistics for kinetic gait variables

Gait variable	Gout participants Mean, (SD)	Control participants Mean, (SD)	Mean difference (95% CI)	p-value
Peak ankle joint force (N)	279.33 (70.08)	263.74 (59.93)	15.59 (-10.84, 42.01)	0.25
Peak ankle joint force (% of stance phase)	80.00 (5.13)	79.29 (7.12)	0.31 (2.26, 2.88)	0.81
Peak ankle plantarflexor moment (Nm/kg)	1.21 (0.21)	1.15 (0.19)	0.06 (-0.02, 0.14)	0.16
Peak ankle plantarflexor moment (% of stance phase)	78.54 (1.87)	78.04 (1.61)	0.50 (0.21, 1.21)	0.16
Peak ankle joint power (W/kg)	1.86 (0.68)	2.17 (0.49)	-0.31 (-0.55, -0.07)	0.01
Peak ankle joint power (% of stance phase)	88.69 (13.17)	90.10 (1.18)	-1.4 (-5.21, 2.37)	0.46
Ankle plantarflexor concentric work (J/kg)	0.16 (0.06)	0.17 (0.04)	-0.02 (-0.04, 0.00)	0.09

5.6.5. Muscle activity

The results indicated that the cases had significantly more muscle activity in the medial ($F_{1,110} = 5.27$, $p = 0.02$) and lateral ($F_{1,107} = 27.06$, $p < 0.01$) gastrocnemius during the stance phase of gait. No significant difference was found with regard to tibialis anterior muscle activity ($F_{1,104} = 3.51$, $p = 0.06$) (Table 5.15). When normalised to stance phase duration, mean muscle activity was lower in all 3 muscle groups. Cases had significantly increased muscle activity in the medial ($F_{1,110} = 1.14$, $p = 0.04$) and lateral ($F_{1,107} = 7.61$, $p < 0.01$) gastrocnemius. No significant difference was found with regard to tibialis anterior muscle activity ($F_{1,104} = 0.01$, $p = 0.20$) (Table 5.16).

Table 5.15: Descriptive statistics for muscle activity

Muscle	Gout participants Mean, (SD)	Control participants Mean, (SD)	Mean difference (95% CI)	p-value
Lateral gastrocnemius activity (%MVIC)	19.48 (9.44)	11.36 (5.94)	8.01 (5.24, 11.21)	< 0.01
Medial gastrocnemius activity (%MVIC)	20.80 (7.76)	17.48 (7.40)	3.30 (0.45, 6.17)	0.02
Tibialis anterior activity (%MVIC)	9.04 (4.59)	7.44 (4.05)	1.59 (0.08, 3.25)	0.64

Table 5.16: Descriptive statistics for muscle activity normalised to stance phase time

Muscle	Gout participants Mean, (SD)	Control participants Mean, (SD)	Mean difference (95% CI)	p-value
Lateral gastrocnemius activity (%MVIC/s)	16.87 (8.26)	10.71 (5.63)	6.16 (3.39, 8.92)	< 0.01
Medial gastrocnemius activity (%MVIC/s)	18.91 (7.38)	16.20 (6.28)	2.70 (0.01, 5.33)	0.04
Tibialis anterior activity (%MVIC/s)	7.97 (4.30)	6.95 (3.66)	1.02 (0.5, 2.5)	0.19

5.7. Bivariate correlations in participants with tophaceous gout

All significant correlations between gait variables and ultrasound lesions are presented in Tables 5.17, 5.18 and 5.19. All non-significant correlations are presented in Appendix 8.

5.7.1. Walking velocity

All significant bivariate correlations between walking velocity, gait variables and US lesions in people with tophaceous gout are presented in Table 5.17.

Table 5.17: Significant bivariate correlations for walking velocity with gait variables and US lesions.

	r	p-value
Double support time	-0.81	< 0.01
Step length	0.81	< 0.01
Cadence	0.71	< 0.01
Ankle power	0.66	< 0.01
Concentric ankle plantarflexor work	0.61	< 0.01
Stance cycle time	-0.59	< 0.01
Hallux ROM	-0.43	< 0.01
Peak rearfoot eversion	-0.42	< 0.01
Ankle angular velocity	0.40	< 0.01
Tibialis anterior muscle activity	-0.39	< 0.01
Intratendinous Doppler signal (pre-insertion)	0.34	0.02

5.7.2. Ankle power

All significant bivariate correlations between ankle power, gait variables and US lesions are presented in Table 5.18.

Table 5.18: Significant bivariate correlations for ankle power with gait variables and US lesions

	r	p-value
Concentric ankle plantarflexor work	0.83	< 0.01
Walking velocity	0.66	< 0.01
Ankle angular velocity	0.67	< 0.01
Peak ankle moment	0.65	< 0.01
Peak ankle force	0.48	< 0.01
Cadence	0.47	< 0.01
Stance cycle time	-0.47	< 0.01
Double support time	-0.40	< 0.01
Step length	0.38	0.01
Lateral gastrocnemius muscle activity	-0.38	< 0.01
Medial gastrocnemius muscle activity	-0.31	0.03
AT thickness	-0.39	< 0.01

5.7.3. Ankle range of motion (sagittal plane)

All significant bivariate correlations between ankle range of motion in the sagittal and frontal plane, gait variables and US lesions are presented in Table 5.19. No significant correlations were found between ankle range of motion in the sagittal and frontal plane and US lesions.

Table 5.19: Significant bivariate correlations for sagittal plane ankle range of motion and gait variables.

	r	p-value
Peak ankle moment	0.37	0.01
Peak ankle force	0.30	0.01
Peak rearfoot eversion	0.41	0.01
Peak ankle moment	-0.40	0.01

5.8. Multiple linear regressions

5.8.1. Walking velocity in participants with tophaceous gout

Multiple linear regression analysis was used to develop a model for predicting walking velocity from the variables identified above as having a significant univariate association with walking velocity. The variables identified as independently associated with walking velocity from this analysis were entered into a multivariate regression model. These included: step length, cadence, ankle power and double support time ($p < 0.01$). The four predictor model was able to account for 97% of the variance in walking velocity, $R^2 = .97$, $F(4,37) = 265.21$, $p < 0.01$. A summary of the forward selection stepwise regression model is presented in Table 5.20 and the regression coefficients are presented in Table 5.21.

Table 5.20: Walking velocity model summary

Model	R	R^2	R^2_{adj}	ΔR^2	F_{chg}	p-value	df_1	df_2
1. Step length	.81	.65	.64	.65	73.77	< 0.01	1	40
2. Cadence	.98	.95	.95	.30	240.97	< 0.01	1	39
3. Peak ankle power	.98	.96	.96	.01	8.91	< 0.01	1	38
4. Double support time	.98	.97	.96	.01	6.56	< 0.01	1	37

Table 5.21: Coefficients for final walking velocity model

Model	B	β	t
Step length	1.43	.61	15.94*
Cadence	.01	.39	6.60*
Peak ankle power	.03	.13	3.54*
Double support time	-.42	-.16	-2.56**

*$p < 0.01$; **$p < 0.05$

5.8.2. Ankle power in participants with tophaceous gout

Multiple linear regression analysis was used to develop a model for predicting ankle power from the variables identified above as having a significant univariate associations with ankle power. The variables identified as independently associated with ankle power from this analysis were entered into a multivariate regression model. These included: peak angular velocity, peak ankle moment and walking velocity ($p < 0.01$). The three predictor model was able to account for 83% of the variance in ankle power, $R^2 = .83$, $F(3,44) = 69.52$, $p < 0.01$. A summary of the forward selection stepwise regression model is presented in Table 5.22 and the regression coefficients are presented in Table 5.23.

Table 5.22: Ankle power model summary

Model	R	R^2	R^2_{adj}	ΔR^2	F_{chg}	p-value	df_1	df_2
1. Peak angular velocity	.67	.45	.41	.48	37.23	< 0.01	1	46
2. Peak ankle moment	.83	.69	.68	.23	35.39	< 0.01	1	45
3. Walking velocity	.91	.83	.81	.14	34.13	< 0.01	1	44

Table 5.23: Coefficients for final ankle power model

Model	B	β	t
Peak angular velocity	-.01	-.39	-5.49*
Peak ankle moment	1.53	.46	6.99*
Walking velocity	1.42	.41	5.84*

*$p < 0.01$

5.8.3. Ankle range of motion sagittal plane in participants with tophaceous gout

Multiple linear regression analysis was used to develop a model for predicting sagittal plane ankle ROM from the variables identified above as having a significant univariate association with sagittal plane ankle ROM. The variables identified as independently associated with ankle ROM from this analysis were entered into a multivariate regression mode. These included: peak angular velocity, double support time and walking velocity ($p < 0.01$). The three predictor model was able to account for 30% of the variance in ankle ROM, $R^2 = .30$, $F(3,82) = 8.18$, $p < 0.01$. A summary of the forward selection stepwise regression model is presented in Table 5.24 and the regression coefficients are presented in Table 5.25.

Table 5.24: Sagittal plane ankle range of motion model summary

Model	R	R^2	R^2_{adj}	ΔR^2	F_{chg}	p-value	df_1	df_2
1. Peak angular velocity	.40	.16	.15	.16	16.24	< 0.01	1	84
2. Double support time	.50	.25	.23	.08	9.29	< 0.01	1	83
3. Walking velocity	.55	.30	.28	.06	6.74	= 0.01	1	82

Table 5.25: Coefficients for final ankle range of motion model

Model	B	β	t
Peak angular velocity	-.03	-.36	-3.44*
Double support time	34.15	.64	3.94*
Walking velocity	8.21	.45	2.60*

*$p < 0.01$

CHAPTER 6

Discussion

6.1. Introduction

The chapter will commence with a discussion of the demographic and clinical characteristics and the patient-reported outcome measures. The chapter will then explore the structure of the AT through analysis of the US lesions. Gait function will then be discussed with regard to walking velocity, ankle power and ankle range of motion. Finally, strengths and limitations will be addressed.

6.2. Demographics and clinical characteristics

Ninety two percent of participants with tophaceous gout were male (11:1 ratio). This is higher than the reported prevalence rates of (4:1) for males under the age of 65 years old (279). Of the 24 participants with gout 25% were Pasifika and 4% of Māori decent. With regard to the most recent gout prevalence estimates in Pasifika and Māori (Table 1.2) the case population was slightly over-representative of the Pasifika and under-representative of the Māori population (36). However, this is explained by the gout prevalence rates provided by Winnard (36) not being specific to tophaceous gout and representative of gout as a single entity not subdivided by disease stage.

The burden of gout is elevated among overweight and obese adults (280). In the current study participants with gout were considered obese as defined by World Health Organisation (WHO) guidelines (BMI $\geq$ 30 kg/m^2) with a mean (SD) BMI of 31.1 (4.1) kg/m^2 (281). This was significantly higher than the control participants, yet with a mean (SD) BMI of 26.3 (5.1) kg/m^2, the control participants were classified as overweight (BMI $\geq$ 25 kg/m^2) (281). The results are in concordance with Rome (18), where the participants with gout and control participants were also defined as obese with a mean (SD) BMI of 32.1 (5.6) kg/m^2 and 30.3 (6.4) kg/m^2 respectively. The findings of high BMI in the participants with gout is congruent with previous research reporting a dose-response

relationship between BMI and prevalent gout, with prevalence rates of gout twice that of non-obese persons (280, 282).

The prevalence of comorbid obesity related metabolic conditions is high in people with gout (283, 284). Results of the current study showed a significant number (29%) of participants with gout were diagnosed with Type 2 diabetes. This finding is in agreement with previous research indicating the incidence for diabetes mellitus of 25% in those with gout (285). The study findings of cardiovascular disease (8%) and hypertension (71%) are similar to previous studies (283, 286).

Hypertension and diabetes are associated with gout and likely contribute to hyperuricaemia (287). Control of hyperuricaemia is crucial in people with gout as persistently elevated levels lead to the development of long-term disability and reduced health-related quality of life (31, 288). We found in the participants with gout the serum urate levels were well controlled. Serum creatinine levels (marker of renal function) was within normative bands (68). With regard to control of hyperuricaemia, 83% of people were prescribed Allopurinol (xanthine oxidase inhibitor) and 58% prescribed colchicine. Although 38% of people with tophaceous gout were prescribed a diuretic, research has demonstrated an increase of serum urate level due to diuretics, this being most often attributed to thiazide diuretics (44, 289). However, the current study did not capture the class of diuretic the participants with gout were prescribed.

6.3. Patient-reported outcome measures

The burden of illness in gout has a substantial negative health and economic impact (290). Health-related quality of life is greatly reduced in people with gout, due to pain, activity limitation, disability and life quality (2, 291). Participants with gout had reduced overall functional ability and reduced functional ability pertaining to the lower extremity with reference to the performance of activities of daily living and recreational activities. Foot-related impairment and disability were also significantly higher in participants with gout. The degree of foot-related impairment and disability is similar to that observed in previous tophaceous gout research (18, 292). Participants with gout also experienced greater levels of foot pain, greater general pain and perceived their overall level of well-being as poorer when compared to control participants.

In the current study functional ability as assessed by the HAQ-II was significantly reduced in participants with gout compared to the control participants. The results are in agreement with Singh (293), who reported poorer functional ability in people with gout. The findings also parallel those of Rome (18) in a cohort of participants with gout. In addition to the generic measure of functional ability provided by the HAQ-II, the current study used the LLTQ to specifically assess functional ability in the lower extremity. People with tophaceous gout had reduced ability to perform recreational activities related to the lower limb compared to healthy controls. The ability to perform activities of daily living related to the lower limb were also significantly reduced in participants with gout compared to healthy controls. Although ability to perform activities of daily living were significantly reduced, participants with gout were able to perform activities of daily living with less difficulty than their reported ability to perform recreational activities. As shown by the $LFIS_{IF}$ tophaceous gout has an impact on the foot in terms of footwear, impairments and activity limitation/participation. The $LFIS_{IF}$ subscale was significantly higher in participants with gout and indicative high levels of foot pain, impairment and footwear problems.

In agreement with Rome (18), results of the current study showed foot pain and global pain were significantly higher in participants with gout. Although participants with gout had decreased functional ability, decreased function in the lower limb and increased impairment and disability related to the foot in participants with gout, it is unclear how these factors contribute to the process of gait adaptation and, conversely, how adapted gait may influence pain, impairment and disability. Singh (293) demonstrated that a greater proportion of people with gout reported limitations in walking and noted that limitations in activities of daily living were attributable to differences in age, socio-demographics and comorbidities, implying that variables other than gout conferred difficulty in walking.

6.4. Ultrasound lesions of the Achilles tendon

The current study showed that participants with gout had a higher prevalence of US lesions in the AT. Subsequently, hypothesis 1 was accepted that participants with gout have a higher prevalence of US lesions in the AT compared to control participants.

Intratendinous power Doppler signal, and bursal power Doppler signal and intratendinous hyperechoic spots, occurred more frequently in participants with gout.

No previous US imaging research has quantified tophus deposition specific to anatomical zones in the AT. The current study showed that tophi were present in 73% of participants with gout. The prevalence of tophi were higher than reported in previous imaging studies and support previous findings that the AT is a site commonly affected by tophus deposition (17, 244, 294). Using US imaging, Naredo (244) reported 34% of AT examined had tophus deposition. Using DECT imaging Dalbeth (17) reported 39% of participants displayed MSU crystal deposition within the AT. Choi (294) also using DECT reported tophus deposition to the AT, however, the number of tophi in the AT were not described. Despite the results showing tophus prevalence was significantly different between the case and control participants, 27% of AT imaged in the case participants displayed no tophus deposition.

Consistent with previous research, the current results demonstrated the enthesis and body of the AT (zone 1 and zone 2) were prevalent sites of tophus deposition (17). In addition, it was found tophi were present in the proximal section of the AT (zone 3). Previous research has only reported tophus deposition at the insertional zone and areas 5cm proximal to the calcaneal insertion of the AT (17). Dalbeth (17) reported 38% of AT's examined had only non-entheseal involvement, 40% had both entheseal and non-entheseal involvement and 22% had only entheseal involvement. Uri (295) reported in tophaceous gout, a large proportion of the total body MSU crystal burden is found intra-articularly, but tophi can be found in any extra-articular location, preferentially in areas of repetitive mechanical stress or pressure.

Three US lesions were statistically more prevalent in people with tophaceous gout compared to controls; tophus deposition, intratendinous hyperechoic spots and intratendinous power Doppler signal. Whilst the current findings support hypothesis 2, that participants with gout will have a higher prevalence of US lesions in the AT compared to control participants, no other US lesions were significantly different between the case and control participants.

Avascularity of connective tissues has been proposed as a predisposing factor for urate deposition (296). It is established that a zone of avascularity and maximum fibre rotation exists in the AT 2-6 cm proximal to the calcaneal insertion (297, 298). The results of the current study demonstrated that tophus prevalence was similar in Zone 2 (avascular zone) to Zone 1. This suggests that tophus deposition is not preferential to the avascular zone of the AT.

The current study found no significant difference in the presence of focal hypoechoic areas with loss of fibrillar echotexture between case and control participants. Only five hypoechoic lesions recorded in participants with gout and two in control participants. The findings indicate that there was minimal disruption of collagen fibrillar echotexture in the AT, reflective of minimal intratendinous structural damage. The results are in contrast to previous research that has suggested tophus presence in tendons produces focal alteration to fibrillar structure (299). The results also differ from the findings of Grassi (35) who, in 60 participants with crystal related arthropathies using US imaging, reported the normal fibrillar echotexture of tendons can be completely deranged by the presence of intra-tendinous tophus deposits.

Intratendinous hyperechoic spots were present in all zones of the AT in the participants with gout. The hyperechoic spots in the participants with gout may be representative of either intratendinous aggregate formation (83) forming in a linear fashion parallel to the collagen fibril or have represented calcified tophi. de Ávila Fernandes (129) reported calcified tophi in tophaceous gout but found no significant differences between groups of participants in relation to illness duration and the number of calcifications, concluding that calcified tophi were not necessarily older than non-calcified tophi.

With MSU deposition not present in the control participants the intratendinous hyperechoic spots may have reflected a general calcific tendinopathy or may suggest that some of our control participants actually had MSU crystal deposits or asymptomatic gout. In non-rheumatological populations intratendinous calcifications, termed ‘calcific tendinopathy’ by Oliva (300) have been viewed as a sonographic sign of tendinopathy.

Consideration must also be given that the hyperechoic spots observed in the participants with gout may be representative of a general calcific tendinopathy. With the single

mineral component of calcific deposits identified as calcium carbonate and the structural and cellular components of tophi identified, histological analysis of intratendinous calcification would be required to clarify the specific components of intratendinous calcifications and allow differentiation between calcified tophi and calcific tendinopathy in people with tophaceous gout (301). Previous research has postulated calcifications may be increased in tophaceous gout due to increased aberrations in calcium metabolism, related in part to chronic renal disease (129). However, Fernandes (129) found no statistical relationship between the presence of calcification in tophi and chronic renal failure in people with chronic tophaceous gout.

Vascularisation of the fibrovascular matrix surrounding tophi as evidenced by positive Doppler signal is a common finding in tophaceous gout and is regarded as an indicator of inflammatory activity (130, 302). Previous research has shown that persistent low-level inflammation is present in asymptomatic chronic tophaceous gout, with Doppler signal present in and around tophaceous deposits in more than half of participants with asymptomatic chronic gouty arthritis (303). In support of these findings the results of the current study showed that participants with gout displayed significantly increased levels of power Doppler signal in the AT compared to controls (Figure 5.5).

Although the prevalence of tophus and vascularisation were similar in all zones of the AT, due to limitations of the scoring system used vascularisation cannot be solely attributed to the presence of tophus. Particularly as data indicated 52% of AT imaged had no evidence of intratendinous vascularisation by zone of AT. This may reflect that not all AT in those with tophaceous gout demonstrate inflammatory activity. Previous research based on analysis of synovial fluid has also reported that participants with chronic gout are frequently found without any signs of inflammation (304). This finding also supports the notion proposed by Chhana (305) that tendon involvement in gout may be an indolent process, suggesting that a containment of inflammation may occur. Recent research has reported that neutrophils recruited to sites of inflammation undergo oxidative burst and form neutrophil extracellular traps (NETs) (306). This finding indicates a possible shutdown mechanism of aggregated NET-mediated inflammation in gout. NET formation itself can also trigger a process of regulated cell death referred to as NETosis (307). NETosis provides another mechanism of efficient shutdown and removal of neutrophils thereby supporting inflammatory resolution. Tophi share characteristics with aggregated

NETs, and MSU crystals can induce NETosis and aggregation of NETs (308). The research also identified that, in people with impaired NETosis, MSU crystals induce uncontrolled production of inflammatory mediators from neutrophils and persistent inflammation (306).

No previous studies have measured entheseal AT thickness in people with gout. The results indicate that entheseal thickening was not a significant US lesion, with no significant differences being found in AT entheseal thickness in participants with gout compared to control participants. The mean values of AT thickness in both the case and control participants were also not considered indicative of pathological thickening when referenced to the cut-off values proposed by Balint stemming from a study in SpA (150). The thesis is the first to quantify AT entheseal thickness in tophaceous gout, however AT thickness was not measured proximally to the enthesis. As discussed in Chapter 2 quantifying thickness proximal to the enthesis is now considered an important comparator as the recent OMERACT definition of entheseal tendon thickness references the body of the tendon as a point of comparison (153). There are currently no defined normative bands to enable categorisation of tendon thickness in gout, both at the enthesis or in the mid-portion of the AT.

In the current study, evidence of tendon tear was only seen in 2 of the 48 ATs imaged in participants with gout. This result coupled with the finding of no significant alteration to fibrillar echotexture provides further evidence that the AT was not structurally altered in participants with gout. Previous single case reports have proposed a link between tophus deposition and AT rupture (85, 86). Whilst our results may be seen to contrast this link, based on minimal structural derangement, the results of the current study only demonstrated minimal structural alteration to the AT. The results provide no evidence or insight surrounding the mechanical properties (elasticity, stretch and strain) of the AT.

Results showed no significant differences in entheseal vascularity or entheseal calcifications between the case and control participants. The results are suggestive that the enthesis is not preferentially targeted by the disease process in tophaceous gout as opposed to SpA (179). Doppler signal was observed in the enthesis and may be associated with MSU crystal deposition. Histological samples from participants with chronic gout have shown MSU crystals to be present in the enthesis (305). Entheseal inflammation has

also been linked to obesity and associated with systemic inflammation and high levels of proinflammatory cytokines (309). Research has also postulated that inflammation is a mediator mechanism for the increased entheseal abnormalities in obese individuals (310). However, research specific to gout has demonstrated that, whilst obesity elevates the inflammatory background in naive, non-adipose macrophages, obesity does not exacerbate inflammatory responses to MSU crystals (311). Entheseal vascularisation was also reported in the control participants. Although the healthy enthesis is generally considered an avascular point of attachment the results of the current study are consistent with previous research that has reported evidence of vascularisation through power Doppler assessment in healthy elderly populations (312-314).

Data indicated that bursal morphology was not significantly affected by the tophus deposition. Bursal Doppler signal was positive in only 7 AT of the participants with gout. Although this is suggestive of a degree of inflammation the lesion is frequently found in other types of inflammatory arthritis (126, 141). Previous research has described floating hyperechoic foci, likely to be representative of micro-tophi, resulting in "snow storm appearance" (35, 141). The snow storm appearance was only observed in the retrocalcaneal bursae of one AT participant with gout. Delle Sedie (315) has suggested this lesion is not specific to gout.

Only one AT in both the case and control participants displayed erosive change to the calcaneal enthesis. The finding of minimal erosive damage is suggestive that the calcaneal enthesis is not a common site of bone erosion in tophaceous gout. This finding is supported further by research that has demonstrated that bone erosions in tophaceous gout are predominately an intrarticular lesion (316). Tophus location in relation to bone also appears to be an important factor in formation of bone erosions, with tophi adjacent to bone likely to be in direct contact with bone cells (317). While tophus burden was recorded the in the distal 2 cm of the AT (calcaneal enthesis), the location and number of tophi that were in close vicinity to, or direct contact with the enthesis, were not recorded.

As highlighted in Chapter 2 there was variation in the definitions associated with US lesions. It is possible that the presence of erosions at the calcaneal enthesis may have also been under-reported. The current definition applied to define erosion was based on the OMERACT recommendation stemming from work in RA (152). The definition of RA

erosions is less applicable to gout, because in RA it is specified that an erosion is an intra-articular lesion, whereas gouty erosions may occur in extra-articular sites (318).

The study found no difference between the cases and controls for calcaneal enthesophyte formation. The presence of calcaneal enthesophytes in control populations has also been demonstrated by previous research in inflammatory arthritis (166, 168). Enthesophytes are commonly found in healthy individuals and are, therefore, not necessarily an indication of disease. Previous studies have been attributed to secondary degenerative/mechanical factors rather than inflammatory mediated factors (319, 320).

Formation of enthesophytes has been attributed to either a mechanical, degenerative, traumatic or metabolic origin (321). Benjamin (321) postulated that enthesophytes form resultant from an adaptive mechanism to ensure the integrity of the interface between the AT and calcaneus in response to increased mechanical loads. The results of similar prevalence rates compared to healthy controls, combined with the current findings indicating tendon degeneration, was not prevalent at the enthesis (no alteration to echogenicity, no entheseal tendon thickening) are suggestive that calcaneal enthesophyte formation in people with tophaceous gout may also be an adaptive response to increased mechanical load.

6.5. Gait analysis

6.5.1. Spatiotemporal parameters

The current study showed that walking velocity was significantly reduced in people with tophaceous gout compared with healthy controls. The results agree with hypothesis 3 that walking velocity is significantly reduced in participants with tophaceous gout compared to control participants. Based on evidence that decreased walking velocity is reflective of reduced functional ability (322), and as evidenced by Chapter 3 which noted walking velocity to be decreased across various forms of inflammatory arthritis, and the most frequently assessed gait parameter, the current thesis considers walking velocity to be the most significant gait parameter to quantify in the description of altered gait strategy.

The results of decreased walking velocity and significant differences in the velocity-dependent parameters of cadence, step length and double limb support time compared to the control participants are in agreement with the previous research of Rome (18) in tophaceous gout. Table 6.1 shows the walking velocity values from the current study, compared to previous research into tophaceous gout. Interestingly, the mean walking velocity values in people with tophaceous gout in the current study were higher than both the studies by Rome (18) and Stewart (292). Across the three studies the age, sex, BMI, ethnicity, disease duration, comorbidities and patient-reported outcome measures were comparable.

Table 6.1: Comparative baseline walking velocity values between the current study and previous studies in tophaceous gout.

Study	Case walking velocity (m/s) Mean (SD)	Control walking velocity (m/s) Mean (SD)
Current study*	1.02 (0.19)	1.23 (0.13)
Rome (18)*	0.90 (0.30)	1.10 (0.30)
Stewart (292)**	0.85 (NR)	N/A

*, walking velocity acquired barefooted; **, walking velocity acquired shod; NR, not reported; N/A, not applicable

The walking velocity of the control participants in the current study is closely aligned to the ranges reported for the control populations by previous research and also within proposed normative ranges of 1.2-1.4 m/s^{-1} (323). Variation in walking velocity between the current study and other forms of inflammatory arthritis may be attributable to the population characteristics. These include disease type, disease status (early vs established), population size, age and sex. The differing methods of acquiring walking velocity must also be considered. As demonstrated in Chapter 3, there is no one universally agreed method of quantifying walking velocity. In participants with tophaceous gout, both Rome (18) and Stewart (292) acquired gait velocity using an instrumented walkway as opposed to 3D gait analysis used in the current study. Acquisition of walking velocity also varied across differing forms of inflammatory arthritis. However, no previous research has accessed how comparable or reliable spatiotemporal gait parameters are that are collected by instrumented walkways compared to 3D gait analysis. Other acquisition factors including the distance walked and instructions surrounding walking pace must also be considered for their impact upon variation of walking velocity.

Foot pain is considered the most influential factor leading to a reduced walking velocity in inflammatory arthritis (182, 186). In tophaceous gout a pain-avoidance strategy has been attributed as the driver of gait adaptation (18). Pain is driven by articular and periarticular effects of tophus deposition creating structural and functional alterations in the foot, necessitating the development of a pain avoidance strategy. This strategy ultimately has been demonstrated to culminate in a decreased walking velocity, and subsequent alterations to associated velocity-related spatiotemporal parameters, i.e. reduced cadence, increased double limb support time and decreased step length (18).

The understanding of foot pain in relation to gait adaptation is not as advanced in tophaceous gout when compared other inflammatory arthritic conditions, particularly RA. This is attributable to the minimal study of gait analysis and foot and ankle function in tophaceous gout. There is also less understanding of the role foot deformity plays in the process of gait adaptation. No previous research has explicitly defined the characteristics of the foot in people with tophaceous gout. In the current study measures of self-reported pain were not specific to anatomical regions of the foot. Therefore, the thesis cannot

equivocally state whether pain in the foot is derived from the 1MTP joint, the forefoot as a whole, the rearfoot, or a combination of all regions.

Although gait adaptation in RA is well described and related to alterations in foot function and pain avoidance, it is arguable that, in inflammatory arthritic conditions, particularly RA, the explanations to describe gait adaptation have been very focused on associations to foot function. Numerous foot models have been used to quantify kinematic and kinetic function inflammatory arthritis (as described in Chapter 3). Subsequent to this, the understanding of the role foot function plays in gait adaptation has increased. However, these explanations for adaptive change have become very narrow and solely focused on the foot, with little consideration for the role of the upper limbs, pelvis and trunk.

The pain-avoidance strategy proposed by Rome (18) in gout provides no consideration for how the upper limb and trunk may contribute to an adaptive gait strategy. The pain avoidance strategy fails to take account of comorbidities (obesity, diabetes and cardiovascular disease) associated with tophaceous gout, and how these comorbidities may interplay to contribute to gait adaptation. However, the current thesis acknowledges that a pain avoidance strategy may partially explain gait adaptations.

The results of the current study indicate that, although foot pain was present in people with tophaceous gout, there were also significant alterations to muscle activity. The alteration in gastrocnemius muscle activity provides a novel insight into alternative strategies that must be considered for their role in gait adaptation. Consequently, foot pain should not be considered the only significant driver of gait adaptation in tophaceous gout.

6.5.2. Muscle activity

Medial and lateral gastrocnemius muscle activity in the participants with tophaceous gout were significantly higher compared with healthy controls. This indicates that greater levels of muscular effort are being invested by the gastrocnemii to maintain progression during the stance phase of gait. In the only previous case/control gait study in tophaceous gout, Rome (18) postulated that reduced walking velocity due to a pain avoidance strategy would lead to reduced ankle plantar flexor muscle activity and subsequent disuse and weakness of the ankle plantarflexor muscles. The current findings contradict the

conclusions of Rome (18), with ankle plantarflexor muscle activity being increased in people with tophaceous gout.

Whilst our findings have demonstrated differences exist in muscle activity, there have been no studies undertaken in gout to enable comparison. Studies have been undertaken in RA by Keenan (324) and Barn (203), indicating no significant alterations to gastrocnemius, soleus or tibialis anterior activity (intensity or timing) during gait when compared to control subjects (203), or between RA participants with valgus rearfoot deformity (324). The conclusions of both studies are interesting, in that the only consideration for increased muscle activity was related to foot function. No consideration was presented for other factors above the foot that may influence muscle activity, such as knee, hip or pelvic function.

Despite the differences in muscle activity, no significant correlational relationships were observed between muscle activity and gait parameters examined in people with gout. Muscle activity was also not a significant explanatory predictor in the regression models constructed to explain walking velocity, ankle power or ankle joint range of motion. Numerous compensatory factors adjunct to foot function may explain the increased gastrocnemius muscle activation reported in the current study. These include: (1) increased neural drive to the muscle, (2) a reduction in muscular strength, (3) structural characteristics of the muscle fibres, (4) AT compliance and (5) muscle fatigue.

Firstly, increased muscle activity is indicative of increased motor unit recruitment and may reflect the increased central drive to the gastrocnemius muscle to maintain torque output, which is the major contributory factor for the increased force per unit area (325). The kinetic results of the current study showed that while peak power was decreased in people with tophaceous gout, the total amount of concentric work and total joint force generated did not significantly differ. This suggests people with tophaceous gout require more muscular output to maintain a similar degree of mechanical work. Even though similar degrees of concentric work were maintained, walking velocity was still reduced. Conversely, walking at a slower velocity may be mechanically less efficient (e.g. deviating more from natural frequency of the pendular movement). This would necessitate additional muscular effort as indicated by the increase in muscle activity. The significant differences seen medial and lateral gastrocnemius activity when normalised to

stance phase duration also indicate that the higher degree of muscle activity observed in the participants with gout was not simply a function of increased muscle activation time, stemming from increased stance phase duration.

Secondly, the increased muscular activity may be reflective of reduced muscle strength and the increased need to generate muscle force. However, it must be noted that, although SEMG is widely used to quantify muscle activity, the relationship between force and surface EMG during voluntary contractions is not fully understood (326). Factors that prevent the direct quantification of muscle force from EMG signal include cross-talk, variations in the location of the recording electrodes and the involvement of synergistic muscles in force generation (326). Although concentric or eccentric muscular strength were not measured in the current study, strength reductions may be present in people with tophaceous gout. Previous research has demonstrated that muscular mass and strength decline from the sixth decade of life in both men and women (327). Age-associated loss of muscle mass is postulated as a major factor in strength decline, with aging associated with functional impairments and a decline in the quantity and intensity of daily physical activities (328-331). There are additional interpretations of the association between age-related loss of muscle mass and strength. Muscle weakness leads to decreased function, diminished physical activity, leading to secondary muscular disuse atrophy. The weak positive correlation observed in the current study between the foot impairment and muscle activity in the medial gastrocnemius and tibialis anterior support the notion that alterations to muscle function in tophaceous gout are in part related to alterations in activity participation.

Two important factors seen in the people with tophaceous gout that may relate to a decline in muscle strength are inflammation and obesity. In chapter 5 demonstrated inflammation was a feature in the AT and indicative of a persistent state of low grade inflammation. Inflammation must be considered for its potential associations with strength reductions and increased physical decline in people with tophaceous gout. Recent studies implicate proinflammatory cytokines in the development of age-related decline in muscle mass, strength, power and physical performance (332, 333). TNF-α has been associated with muscle wasting and lower quadriceps strength reported in older men and women with high IL-6 and TNF-α levels (334, 335).

The level of obesity seen in the participants with tophaceous gout may also be associated to alterations in muscle strength. With weight gain there is a trend to replace muscle mass with fat (336). Individuals with high levels of body fat and low lean muscle mass are at risk of functional declines in the lower extremity (330, 336, 337). Excess body weight in older adults is also associated with a decline in physical function (338-340). Obesity itself is associated with an elevation of inflammatory markers (341, 342), and adipose tissue is a source of both IL-6 and TNF-a, and is increasingly viewed as a critical tissue in the inflammatory process (343). Elevated cytokine levels have been associated with both increased fat mass and reductions in muscle mass in older men and women (342).

The third explanation for a difference in muscle activity may be related to architecture of the gastrocnemius muscle. The force-velocity relationship in a muscle states that the maximum force generated by a muscle is a function of its velocity (344). This relationship can also be stated in the reverse; that is, muscle contraction velocity is dependent on the force resisting the muscle (344). Altered force velocity characteristics may influence neural activation patterns because of altered proprioceptive feedback and coordination (345, 346). The alteration to the force-velocity relationship may also be attributable to the reductions in walking velocity demonstrated in the current study. Walking velocity influences each muscle's contractile state (i.e. fibre length and velocity), which may alter the muscle's ability to generate force and power. A previous study using simulated walking modelling demonstrated the ability of the ankle plantar flexors to produce force as walking velocity increased was greatly impaired, despite an increase in muscle excitation, due to sub-optimal contractile conditions i.e. increased muscle fibre lengths (347).

Fourthly, the increased level of muscle activation may be an indicator of suboptimal AT compliance (reduced elasticity or increased AT stiffness). Tendon compliance can influence the length and the shortening velocity of the contractile elements and so affect the muscles force generating potential due to alteration of the force–length–velocity relationship (348). Subsequently the timing and duration of muscle stimulation and the amplitude of the change in length of the muscle–tendon unit are also likely to affect the capacity of a tendon to increase the power output and efficiency (349).

Finally, muscular fatigue is reflected by an increase in EMG activity (350). Muscle fatigue can be defined as an exercise-induced reduction in the ability of muscle to produce force or power, whether or not the task can be sustained (351). A critical feature of this definition is the distinction between muscle fatigue and the ability to continue the task. Accordingly, muscle fatigue is not the point of task failure or the moment when the muscles become exhausted. Rather, muscle fatigue is a decrease in the maximal force or power that the involved muscles can produce, and it develops gradually soon after the onset of the sustained physical activity (352). The results of the current study regarding significantly decreased peak ankle joint power production is supportive of the concept of fatigue.

6.5.3. Ankle power and ankle range of motion

The current study showed that peak ankle joint power during the stance phase of gait in participants with gout was significantly reduced compared to the controls. The results confirm hypothesis 4, that ankle power is different in participants with gout compared to control participants.

The result of increased peak ankle power compared to the control participants is in agreement with the previous research in RA (174, 189, 190, 203). Table 6.2 indicates that case participants in the current study demonstrated similar magnitudes in peak ankle joint power to one study, Barn (203). Data indicated that the mean peak ankle joint power magnitudes of the case and control participants in the current study were lower in comparison to previous research in inflammatory arthritis. The control participant's ankle joint power magnitudes were also lower than the majority of the case participants in previous research. However, there were a number of dissimilarities in the methodology between these studies, including the condition type, disease status (early vs established), the age and sex of study participants and the biomechanical model used to estimate kinematic and kinetic data.

Table 6.2: Comparative baseline ankle joint power between the current study and previous studies

Study	Condition	Case ankle joint power (W/kg) Mean (SD)	Control ankle joint power (W/kg) Mean (SD)
Current study	Tophaceous gout	1.86 (0.68)	2.17 (0.49)†
Turner (190)	RA	3.40 (1.00)	4.60 (1.60)†
Turner (189)	RA	2.42 (1.22)	4.23 (1.30)†
Barn (203)	RA	1.70 (0.80)	3.10 (0.60)†
Woodburn (174)	PsA	2.93 (0.98)*	3.68 (0.75)†*
		2.40 (0.83)**	3.63 (0.69)†**

†, ($p < 0.01$); *, enthesitis absent; **, enthesitis present

With regard to the biomechanical model, both studies by Turner (189, 190) used the same foot model as the current study (Oxford Foot Model) but it was not clear by which method the studies estimated kinetic parameters. The studies by Barn (203) in RA and Woodburn (174) in PsA used a seven-segment foot model to derive kinetic parameter estimations, a model originally developed in people with PsA (109). The variation in the magnitude of peak ankle joint power may be attributable to overestimation of power derived from a single segment model as used in the current study, versus kinetic data estimated from a 3D multi-segment foot models (353). Dixon (353) demonstrated in an adolescent population through comparison of a one-segment foot model to a multi-segment foot model that a one-segment foot model overestimates ankle joint power magnitudes, and may also overestimate the contribution of the triceps surae in ankle joint power.

Joint power (Pj) is the scalar product of the joint moment (Mj) and the joint angular velocity (ωj):$Pj = Mj \times \omega j$ (354). Alteration in one or both of these parameters may explain variation in ankle joint power mean magnitudes. The current study showed that peak ankle joint plantarflexion moments during the stance phase of gait in participants with gout were not significantly different compared the control group. The peak ankle joint plantarflexor moments in the current study are similar in magnitude to previous research in inflammatory arthritis (Table 6.3). In contrast to previous research, in the current study the mean peak plantarflexor moment in the participants with gout were higher than the control participants, however not statistically significant. The increased magnitude in peak plantarflexor moment may be explained by the increased level of ankle plantarflexor muscular activity.

Table 6.3: Comparative baseline ankle joint plantarflexion moments between the current study and previous studies

Study	Condition	Case ankle joint power (W/kg) Mean (SD)	Control ankle joint power (W/kg) Mean (SD)
Current study	Tophaceous gout	1.21 (0.21)	1.15 (0.19)
O'Connell (186)	RA	1.13 (0.29)	1.43 (0.19)†
Turner (190)	RA	1.5 (0.1)	1.6 (0.1)
Weiss (191)	RA	1.05 (0.37)	1.49 (0.15)†
Turner (189)	RA	1.39 (0.28)	1.63 (0.15)†
Barn (203)	RA	1.2 (0.3)	1.4 (0.1)
Woodburn (174)	PsA	1.54 (0.16)*	1.67 (0.19)†*
		1.55 (0.23)**	1.63 (0.17)†**

†, ($p < 0.01$); *, enthesitis -; **, enthesitis +

The current study showed that peak ankle joint angular velocities during the stance phase of gait in participants with tophaceous gout were significantly reduced compared with the control participants. Previous research has established that ankle joint power increases with walking speed because of increased ankle rotational velocity (355). Although no angular velocity magnitudes were reported, Turner (190) attributed reduced ankle joint power to reductions in angular velocity on the basis that no significant difference in ankle joint plantarflexion moment were demonstrated in people with RA.

Previous research in RA indicates numerous gait parameters including peak ankle joint moment, peak ankle joint angular velocity, ankle joint ROM, muscular activity and walking velocity interplay to affect peak ankle joint power magnitudes. Turner (189) and Barn (203) linked reductions in ankle joint power to walking velocity, postulating that with increases in walking velocity there will be accompanied increase in joint angles, ankle joint moments and subsequently increased ankle joint power. Turner (190) stated that factors contributing to reduced ankle joint angular velocity included reduced walking velocity and reduced ankle joint range of motion. The results of the current study parallel the findings in RA research relating ankle joint power with ankle joint moment, ankle joint angular velocity and walking velocity (190). Regression analysis showed 83% of variation in ankle joint power being accounted for by peak angular velocity, peak ankle joint moment and walking velocity. There was also moderate correlations between peak ankle joint angular velocity, peak ankle joint moment and walking velocity.

The results showed no significant differences in the amount of ankle joint plantarflexor concentric work produced between the participants with tophaceous gout and control participants. No previous research has quantified concentric muscular work in the ankle plantarflexors in gout. Only one previous study in a population with RA has calculated concentric muscular work of the ankle plantarflexors (191). Weiss (191) reported reduced concentric muscular work of the ankle joint plantarflexors, postulating this to be a consequence of the reduced internal plantarflexor moments during the pre-swing phase of gait. Weiss (191) further stated that reduced plantarflexor moments could be attributed to reduced walking velocity, pain and muscular weakness in the plantarflexor muscle group.

The results of the current study contrast with the findings of Weiss (191). There were no significant differences in concentric ankle joint plantarflexor work or peak ankle joint plantarflexor moments between the case and control participants. The results relating to concentric plantarflexor work may be explained by the increase in gastrocnemius muscle activity. Due to the reductions in walking velocity, ankle joint angular velocity and peak ankle joint power production the body may increase muscular activity. This may be a central mechanism by which the body maintains muscular work output to maintain forward progression.

The current study showed that ankle joint range of motion both in the sagittal plane (plantarflexion/dorsiflexion) and frontal plane (inversion/eversion) during the stance phase of gait in participants with gout were not significantly different compared with the control participants. The results of the current study refute hypothesis 5 that there is a significant difference in ankle range of motion in participants with gout compared to control participants.

Few studies have reported the frequency of ankle involvement in tophaceous gout. Choi (294) with the use of Dual Energy Computed Tomography in 20 participants found tophus deposition in 70% of ankles. General mid-foot and ankle involvement has been reported to occur in 18-60% of participants (10, 81, 356).

The results provide an insight into the effect tophaceous gout has on the rearfoot and provides a tentative explanation as to why people with tophaceous gout may be less impaired by their foot function. The results also support the notion that pain avoidance resulting from foot deformity should not be considered the only significant driver of gait adaptation in tophaceous gout. The results indicate a lesser degree of rearfoot deformity than that observed in RA (357).

Inflammatory synovitis and dysfunction of the peritalar joints and the tibialis posterior muscle-tendon unit are postulated mechanisms leading to instability of the rearfoot and midfoot in RA (357). As a consequence, people with RA may progressively develop a pes planovalgus foot type, as evidenced by a reduced longitudinal arch height and an increase in the maximum rearfoot eversion reached during the stance phase of gait (110, 183, 187). Pes planovalgus foot deformity has a reported prevalence of between 46–64% in RA (183, 187, 358, 359). In contrast, the results of the current study showed no significant differences in rearfoot eversion or total range of motion in the sagittal plane when compared to the control participants. In the current study a peak eversion value of 3.85º was observed in people with tophaceous gout. In RA, peak eversion values have been reported at 8.2 º (110), 5.5º (190) and 9.0º (189). The results of similar ankle ranges of motions in the sagittal plane with lower ranges of peak eversion are suggestive of less alteration to rearfoot and ankle joint function in people with tophaceous gout compared to RA.

The results of the current study show that 1MTP joint range of motion is reduced during dynamic movement in people with tophaceous gout. This result is reflective of the functional consequences of the gout disease process. Previous studies have indicated a tendency for gout to affect the 1MTP joint with the initial attack of gout reported to affect the 1MTP joint in 56-78% of participants (77-80). The 1MTP joint is also reported to be involved at some point in the course of disease in 59-89% (10, 77, 79, 81).

Osteoarthritis has been associated with the 1MTP joint with significant associations observed between the 1MTP joint and osteoarthritis (81). The presence of osteoarthritis also predisposes the 1MTP joint to formation of urate crystals (81). With this in mind, the reduced range of motion may be explained by two factors. Firstly, the 1MTP joint of the case participants may have been affected by osteoarthritis. Secondly, the reduced range

of motion may have occurred as a result of joint damage secondary to tophaceous gout. As the current study did not clinically assess the 1MTP joint prior to testing or use radiography to assess and grade 1MTP joint structure, the current thesis is unable to discriminate whether one or both of these factors were predominant in the participants with tophaceous gout. Coupled with the findings of Rome (18), who demonstrated reduced peak plantar pressures under the 1MTP joint, current evidence indicates joint function at propulsion is adapted through alterations to plantar pressure and restriction of joint ROM. Functionally, this may manifest as a disruption of the sagittal rocker function (22).

6.6. Relationships between gait variables and US lesions

The results of the current study reject hypothesis 6 that there is a relationship between ankle power, ankle range of motion, walking velocity and US lesions in the AT in participants with tophaceous gout.

The lack of statistical relationships between US lesions and gait function also support the US imaging findings that MSU crystal deposition does not cause significant structural alteration to the AT and adversely affect gait function. Furthermore, research by Chhana (305) has postulated that tendon involvement in gout may be an indolent process. While the current study investigated AT structure, consideration must also be given that the mechanical tendon properties such as tendon compliance and the response to stress and strain may be altered. AT compliance, tendon force transmission, energy storage and release during locomotion may be affected by intratendinous MSU crystal deposition. This may limit the effective use of strain energy (elastic recoil) by the AT during walking. This mechanism is thought to provide a significant proportion of propulsive energy for walking (360, 361).

Factors associated with changes in the elastic properties of tendons include alteration to collagen deposition, histological changes affecting tendon architecture such as disruption of collagen fibres, increased ground substance and vascularisation, and an increase in fibroblast activity leading to an increase in tenocytes within the tendon tissue (27). Channa (305) demonstrated there was a down regulation of catabolic tendon enzymes in tenocytes following culture with MSU crystals. The author suggested this may be part of a protective mechanism to limit MSU crystal-induced degradation of tendon matrix (305).

Drawing from the results of both US imaging and gait analysis studies the current thesis proposes two theoretical strategies that may coexist to explain gait adaptation or indeed drive gait adaptation in people with tophaceous gout. The strategies outlined in Figure 6.2 are not definitive models of gait adaptation but should be used as the basis to guide future research. The strategies are not an alternative to the proposed pain avoidance strategy of gait adaptation however, as acknowledged in the thesis, the pain avoidance strategy is narrow, in that it is focused on the foot as the driver of gait adaptation.

Strategy 1 (in blue boxes): Chapter 3 reported that walking velocity is the most measured gait parameter in the explanation of gait adaptation. Strategy 1 raises the possibility that walking velocity should not simply be viewed as a gait adaptation. Regulation of walking velocity may well be the central strategy by which the body modulates joint forces and moments and subsequently joint kinematics and kinetics during locomotion. A reduction in walking velocity may lead to alterations in spatiotemporal and kinematic and kinetic parameters of the ankle joint. The novel findings with regard to muscular activity also raise the critical question as to whether the changes in motor unit activation plays a causal role in the functional changes in muscle activity in participants with gout or represent mechanism of compensation and adaptation aimed at conserving musculoskeletal performance. Conversely, they may be as a compensation and adaptation resultant from the deposition of MSU crystals in muscle or tendon fibres altering the internal tendon mechanical properties.

Strategy 2 (in red boxes): This strategy considers an opposite approach to strategy 1 whereby intratendinous changes may be associated with gait adaptation. Intratendinous and intramuscular MSU deposition may alter the mechanical properties of the tendon and muscle fibres. Changes to tensile force transmission, storage and release of energy during locomotion may drive changes in spatiotemporal, kinematic and kinetic gait parameters.

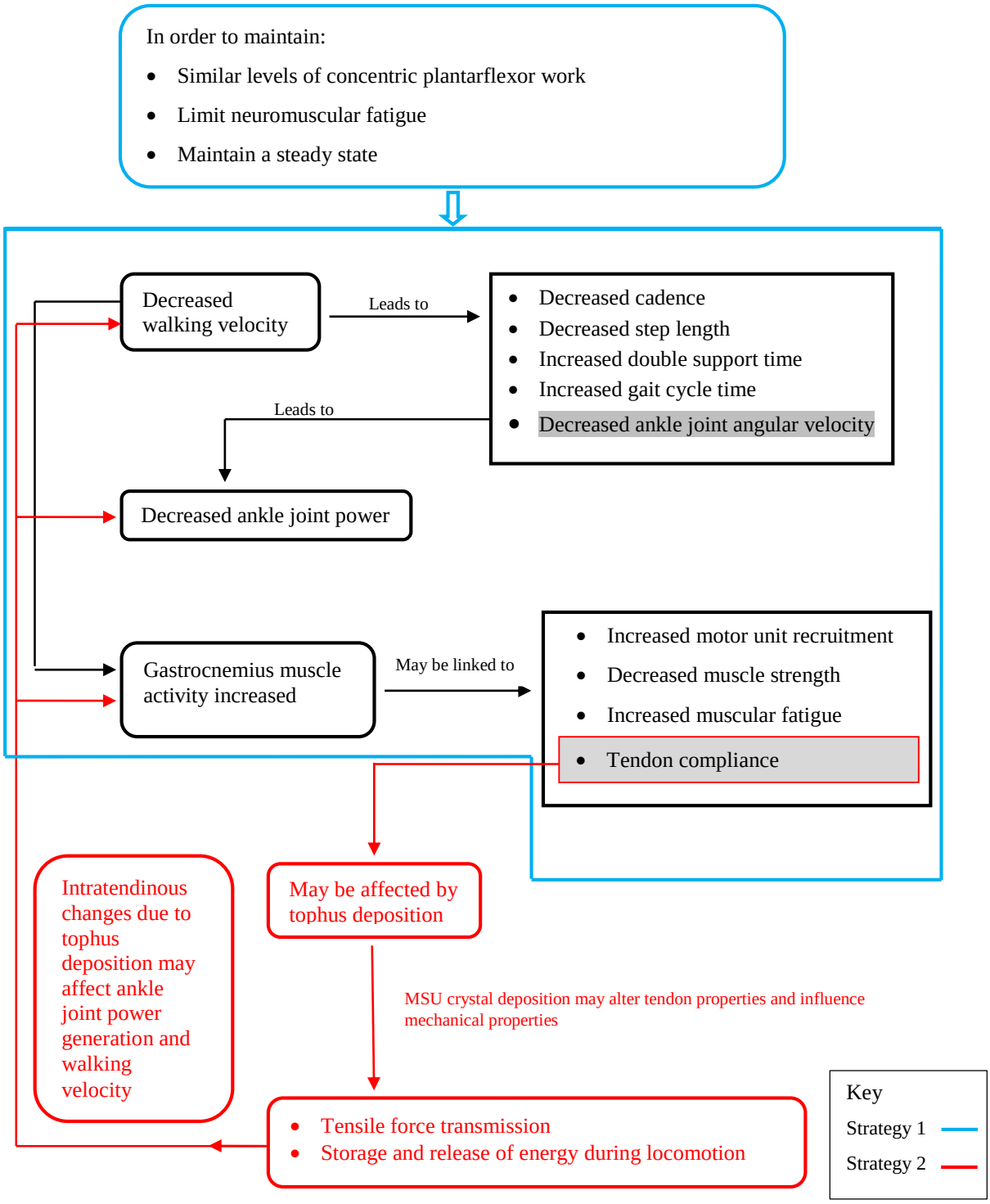


Figure 6.2. Proposed theoretical strategies of gait adaptation

6.7. Methodological strengths and limitations

The thesis has numerous strengths. A case-control research design was an efficient way to contrast both the characteristics US imaging and gait analysis in two areas where no such evidence exists. The sample size of n = 48 (24 case and 24 control) participants was similar to previous case control imaging studies in tophaceous gout and larger than many previous study populations using 3D gait analysis in inflammatory arthritic conditions. The current work assessed participants with long disease duration and compared to a gender and age matched-control participants. The age-matching was a particular strength as previous studies have described numerous musculoskeletal changes to occur in the sixth decade of life (327). The scoring system used to grade lesion presence in the AT was also a strength with excellent inter-observer reliability observed. The gait study used a biomechanical foot model that has previously been used in RA, paediatric and various adult populations. The model was chosen as inter-trial reliability was high for all kinematic and kinetic parameters assessed in previous research. The intra-rater reliability results also support the use of the biomechanical model, with excellent reliability of the gait parameters obtained from the model demonstrated.

The study was limited by the lack of generalisability of the participants. The study was undertaken in New Zealand and may not represent findings in other countries around the world. The US study did not use a gold standard method for comparison of ultrasound findings. The lack of a gold standard is justified by the inclusion criteria relating to diagnosis of tophaceous gout and because the definitive proof of tophi would be through the surgical extraction or needle biopsy of the tophi; however these invasive methods are not justified as routine nor are they ethically appropriate for research. Differences in BMI in the participants with gout and control participants may have led to differences in AT structure and function and gait parameters.

In the gait study the knee and hip were not included in the biomechanical model. Subsequently, the study was unable to assess the relationship and contributions to gait strategy between ankle, knee and hip joint moments and powers. Specifically, kinetic data from the hip would have enabled the contribution that the ankle plantarflexion moment adds to knee and hip energy during gait to be examined (362).

Several factors must be taken into account when comparing current gait analysis results with previous research. These include differences in sampling rate, filtering techniques, data analysis, biomechanical models and walking velocity tested. As demonstrated, there was variation in reported walking velocities, ankle power and ankle moments when compared to previous research in gout and to research in other forms of inflammatory arthritis. An inverse dynamics approach, which is widely accepted for biomechanical analyses, was used to estimate foot and ankle joint moments through creation of a single-segment foot model. Subsequently, it was not possible to distribute the contribution of net joint moments onto individual anatomical structures. The use of skin markers for measuring lower limb kinematics implies the risk of errors due to inaccurate placement and soft tissue artefacts. To limit errors due to inaccurate marker placement, the same researcher was responsible for placing all markers during testing.

The multiple regression analysis was exploratory and needs to be interpreted with caution. Finally, the EMG normalization technique used in the gait study may not have produced true MVICs in participants with tophaceous gout. It is possible that relative muscle activity may have been the same in both the cases and controls. In participants with gout the ability to produce maximum contractions may have been limited by the presence of joint, tendon or muscular pain. While the results are encouraging in terms of detecting a difference between the participants with tophaceous gout and control participants, it was not possible to separate the contribution of the normalization method to the differences recorded.

CHAPTER 7

Conclusions, implications for practice and future research

7.1. Introduction

The chapter will present the main conclusions of the thesis, followed by the implications for practice, implications for future research and an overall conclusion of the work.

7.2. Ultrasound

The systematic review identified that the majority of studies reports US lesions in SpA, but limited evidence relating to tophaceous gout. US lesions were not consistently defined with regard to OMERACT definitions (153) and numerous scoring systems were used across the majority of studies. Consistent application of the OMERACT US definitions and the scoring of US lesions is required in future studies of AT disease in inflammatory arthritis.

Although tophus deposition was common throughout the entire AT there was minimal disruption to fibrillar echotexture in all zones of the AT. This suggests there is minimal intratendinous structural derangement in the AT. There was also no increase in deposition in the reported avascular zone of the AT, indicating no link between tophus deposition and avascularity in the AT. Inflammation was present throughout all zones of the AT as evidenced by Doppler signal and indicative of low grade persistent inflammation. The AT did not display entheseal thickening, significant erosive or cortical irregularities. This suggests that there was minimal entheseal pathology in the AT in participants with tophaceous gout. The high frequency of calcaneal enthesophytes in both the case and control participants may be suggestive of mechanical strain to the insertion of the AT rather than an inflammatory-driven enthesophyte formation.

7.3. Gait analysis

The understanding of foot and ankle function and the progression of gait adaptation in tophaceous gout is limited. There is currently no one universal method of capturing

spatiotemporal, kinematic and kinetic gait parameters. 3D gait analysis is evolving rapidly with the complexity of foot models increasing in order to explain the multi-segment behaviour of foot function. With the development of foot models the understanding of the functional relationships within the foot and ankle has increased. However, knee and hip function are rarely reported in inflammatory arthritic conditions. Subsequently, the current explanations for gait strategy are considered narrow in focus.

Explanations of gait adaptations in various types of inflammatory arthritis, particularly RA, are heavily focused on foot pain and pain avoidance. There is minimal research investigating alternative factors that may explain gait adaptation in inflammatory arthritis. Currently a pain avoidance strategy due to increased foot pain is postulated to initiate gait adaptation in tophaceous gout. However, the results of the current work indicate alternative pathways of gait adaptation should be considered by future research.

Participants with tophaceous gout walked with a slower velocity and a reduction in peak ankle joint plantarflexor power. Despite the reduction in ankle joint power and walking velocity, the total concentric work produced by the ankle plantarflexors and the ankle joint, force and moments did not differ when compared to controls. In light of this evidence the current thesis found that gastrocnemius muscle activity is increased. Although speculative, the thesis proposes that the increased muscle activity maybe be reflective of many processes related to both the presence of tophus, the presence of comorbidities associated with tophaceous gout, or reflective of adaptations aimed at conserving musculoskeletal performance.

7.4. Implications for practice

Imaging modalities should be carefully considered when managing musculoskeletal complaints and assessing pathological change in people with gout. Imaging allows the clinician to assess current pathological status and can also benchmark the success of intervention. Grey-scale and power Doppler US imaging are non-invasive and relatively low cost. US imaging can provide insight into inflammatory activity and structural damage of the entire AT and assess the characteristics of intratendinous tophus, but is limited in its ability to examine the intra-articular effects of tophus deposition.

Walking velocity should be viewed as a key outcome measure when assessing and managing musculoskeletal pathologies in the foot and ankle in people with tophaceous gout. Walking velocity should be measured at baseline and assessed following the implementation of treatment, specifically if the goal of the treatment is aimed at increasing walking mobility. As highlighted in the thesis there are numerous methods to quantify walking velocity. Expensive systems are not required. Walking velocity can be measured by simple, cost-effective techniques such as stopwatch timing while walking over a short distance.

When assessing musculoskeletal function assessment should include: determination of ankle ROM and lower leg muscle strength (particularly ankle plantar flexor strength). Due to the potential compensatory effects of restricted joint ROM, the ankle joint should be quantified. If joint motion is limited, discrimination should be made if the joint restriction is functional (soft tissue restriction), structural (restricted due to bony limitation) or related to pain shielding. Muscle strength is also important to determine as identified. As highlighted by the thesis weakness and associated fatigue may be present and able to be improved with an appropriate rehabilitation programme.

7.5. Implications for future research

The current findings have produced various important findings that require additional investigation. Highlighted below are the areas of necessary research that will help develop greater understanding of musculoskeletal structure and function in tophaceous gout.

Through imaging of AT lesions at differing stages of gout a sequence or severity of alterations to development of US lesions may be discovered. This may enable the categorisation of US lesions into those reflective of active (inflammatory) and chronic (structural) damage. This would involve imaging of AT lesions in populations with varying stages of gout (acute, intercritical and tophaceous gout).

As the current thesis only considered the structural characteristic of the AT and the effects of MSU, deposition on the mechanical properties of the AT are unknown further investigation is warranted. This would include determination of AT elasticity, energy storage, stiffness and the stress strain relationship.

The results indicated there were a percentage of participants with tophaceous gout where there was little evidence of MSU deposition. There may be numerous clinical and biomechanical features associated with this subgroup, therefore further investigation is warranted to determine if such a subgroup exists and if there are clinical and biomechanical features unique to this group.

As postulated by the thesis, walking velocity may be the central mechanism by which the body modulates kinematic and kinetic parameters. Subsequently, determining mechanisms of how walking velocity acts as a modulator of other gait parameters is required. This would involve quantification of kinematic, kinetic, plantar pressure and muscle activity parameters in relation to variations in walking velocity.

As the current thesis only quantify joint moments, force and torque at the ankle, future research should detail kinematic and kinetic data relating to the hip and the knee as well as the ankle. This would begin to build the picture as to distribution of joint moments, torque and power patterns in the lower limb. Quantification of knee and hip function would also provide information surrounding the weight acceptance component of stance phase (braking phase) not just the propulsive phase as presented in the thesis. Future

research should also quantify the contact and midstance period of stance phase. Although the current thesis examined terminal stance phase, the flow-on effects of poor propulsion may lead to alterations in the acceptance of bodyweight distinguishable by alterations to ground reaction forces and delayed progression of bodyweight.

Further exploration of muscle structure and function in gout is required. From a structural perspective, it would be pertinent to determine the burden and presentation of MSU deposition in muscle fibres, as the current thesis only investigated tophus burden in the AT. From a functional perspective quantification of flexor and extensor muscular strength in the ankle and knee is required to determine if strength is reduced in people with tophaceous gout. It would also be useful to determine if a strengthening targeting the lower limb muscles can alter gait parameters, for example, increase walking velocity. As the thesis identified increased muscle activity in the gastrocnemius muscle group, a finding that may precede muscular fatigue, further study surrounding the concept of muscular fatigue is warranted. Further progression of quantification of muscle activity is also required specifically to determine the levels of muscle activity in the upper limb during walking.

Further investigation into muscle activity in participants with gout is required. Specifically, investigation of co-contraction of lower limb muscles and the phasing and time duration of muscle activity. As pain may have limited the ability to produce true MVICs, further investigation is warranted surrounding EMG normalisation techniques in those with tophaceous gout. This may involve normalisation of muscle activity to peak or mean muscle activation levels obtained during the gait cycle.

With evidence that numerous gait parameters are altered in people with tophaceous gout it would be of benefit to explore if interventions such as footwear, foot orthoses and strengthening exercises can modify gait parameters.

7.6. Thesis summary

The aim of the thesis was to characterise the structure of the AT and gait adaptations in people with tophaceous gout. Two systematic literature reviews with meta-analysis and two experimental studies were conducted: the data describing US lesions of the AT in different forms of inflammatory arthritis, gait adaptation across different forms of inflammatory arthritis, the prevalence of US lesions of the AT and gait adaptations occurring at the foot and ankle in people with tophaceous gout.

The systematic review presented in Chapter 2 was the first to pool data of US lesions in the AT. The review demonstrated poor data describing US lesions of the AT in gout. Additionally, the review demonstrated that no universally agreed and accepted definitions have been devised that can characterise between US lesions reflective of inflammatory and structural change in differing forms of inflammatory arthritis.

The systematic review with meta-analysis detailed in Chapter 3 was the first review to pool gait data and demonstrate differences in key gait parameters compared to healthy controls across inflammatory arthritic conditions that included other forms of inflammatory arthritis with previous reviews only considering RA. The pooled results showed that gait pattern in RA was characterised by decreased walking speed, decreased cadence, decreased stride length, decreased ankle power, increased double limb support time and peak plantar pressures at the forefoot. Walking velocity was reduced in psoriatic arthritis and gout with no differences in ankylosing spondylitis. The review demonstrated the differences that exist in the instrumentation and acquisition methodologies used to assess spatiotemporal, kinematic and kinetic gait parameters. This finding highlights a significant issue in gait analysis: that there is no universal agreement or standardisation surrounding the capture and processing of data used to describe gait analysis. The review also highlighted that, while the understanding of foot and ankle function has increased with the rapid development of multi-segmented foot models, there has been less description of the relationships between foot, knee and hip. Subsequently, explanations of why and how gait adaptations occur in people with inflammatory arthritis are explained by alterations in foot function with minimal consideration for compensations that occur at the knee and hip. The review also showed that poor data exists describing gait adaptation in gout and how muscle activity is affected by gait adaptations across all forms of inflammatory arthritis.

The first study examined the prevalence of US lesions in three zones of the AT. This was the first study to examine US lesions of the AT in the insertional, pre-insertional and proximal zones of the AT. Results showed participants with tophaceous gout had significantly more intratendinous tophi, intratendinous hyperechoic spots and intratendinous inflammation throughout all zones of the AT compared to control participants. Despite this, there was no significant data indicating internal fibrillar derangement. These results raise two possibilities, firstly the presence of tophus deposition and associated inflammation in the AT may be a clinically silent process, with containment of inflammation. Secondly, whilst the current thesis examined the structure of the AT alterations to the mechanical properties in the AT due to MSU deposition and inflammation are unknown and may be significant in the development of pathology.

The second study investigated key spatiotemporal, kinematic and kinetic gait parameters during walking. Significantly walking velocity and ankle power were reduced in people with tophaceous gout. The reduction in walking velocity could be viewed as the most significant gait adaptation due to the relationship between reduced walking velocity and reductions in other gait parameters reported. Reductions in walking velocity were associated with alterations in cadence, step length, double support time and gait cycle time. Reductions in walking velocity were also associated with decreased ankle joint angular velocity. With the ankle joint moments preserved and not significantly different, the reductions in ankle joint angular velocity explain the reduced ankle joint power output. These finding highlight the importance of walking velocity and imply that walking velocity may be the central mechanism by which the body modulates gait adaptation.

The thesis challenges the presumption that avoidance of foot pain is the sole driver of gait adaptation in people with tophaceous gout. Based on the significance of MSU deposition in the AT, the unknown effect of deposition on the mechanical properties of the AT, the decrease in walking velocity and the potential reasons explaining alterations in muscle activity, the thesis proposes that future explanations of gait strategy in gout must not only consider foot and ankle function in isolation. Knee and hip function must be considered. Further consideration must also be given to the role deposition of MSU crystals in both tendon and muscle, comorbidities such as obesity, diabetes and cardiovascular disease

and poor physical conditioning contribute to the process of gait adaptation in tophaceous gout.

The current work is clinically important, suggesting that when managing AT pathologies in people with tophaceous gout both structure and function must be considered. Firstly, the structural integrity of the AT must be determined. Secondly, the degree of gait adaptation must also be quantified. Quantifying walking velocity provides the clinician with a good overall perspective of functional ability. Other markers of function that should be considered in the assessment of foot and ankle function include ankle plantarflexor muscle strength, and ankle joint and 1MTP joint motion.

The thesis has also identified important areas for the focus of future research. Gait compensations at the knee and hip must be quantified. The relationship between MSU deposition and mechanical properties of the AT must be investigated to further the understanding of tendon integrity. The interplay between adaptive mechanisms and the order at which gait adaptations occur also requires further research to establish if gait adaptation occurs in a sequential fashion and is related to increasing chronicity of gout. The impact of non-surgical interventions such as footwear, foot orthoses and strength training must also be considered for their ability to alter the process of gait adaptation. The impact of urate-lowering pharmacological intervention on lower limb function and soft tissue characteristics is warranted.

CHAPTER 8

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APPENDIX 1

Patient information sheet

The effect of tophaceous gout on structure and function of the Achilles tendon.

An Invitation

We would like to invite you to take part in a research study. Information from this research will be published as a PhD thesis and will also be presented within academic publications and verbal presentations. This research project is a related to my PhD studies, and I will be conducting the research with Professor Keith Rome, Associate Professor Nicola Dalbeth and Associate Professor Mark Boocock from AUT University and Auckland University. My name is Matthew Carroll and I am a PhD student. Participation is completely voluntary, and you may withdraw from the study at any time without giving a reason or being disadvantaged.

What is the purpose of this research?

The objective of the research is to investigate how changes of the Achilles tendon (muscle at the back of the heel) affects walking in people with tophaceous gout. We believe that leg and foot joint movement, the walking velocity and the strength of the calf muscle will be less in people with tophaceous gout. We are looking to invite 25 patients with tophaceous gout and 25 people without gout. We will be using ultrasound to image the muscle and equipment to measure your leg and foot motion whilst you are walking.

How was I chosen for this invitation?

Consent was provided by the Auckland District Health Board that we were able to contact you and your details were available through the Auckland District Health Board patient database.

<u>Subjects with chronic gout</u>

If you are over 18 years old and have been diagnosed with chronic gout, have at least one tophus and can walk 10m without the need of crutches or a walking stick you may want to take part in the study. We are unable to have you involved if you are under 18 years old, have previously ruptured your Achilles tendon, have a current injury to the foot or leg or have any loss of sensation in your feet.

<u>Subjects without chronic gout</u>

If you are over 18 years old and do not have gout or any other form of inflammatory arthritis, and can walk 10m without crutches or a walking stick you may wish to take part in the study. We are unable to have you involved if you have had a previous rupture of the Achilles tendon, a current injury to the leg or are experiencing a current gout flare.

Where will the research take place?

Data collection will take place in the Horizon Radiology and the Gait Analysis room located in AA Building, AUT University, Akoranga Campus, Northcote, Auckland.

When will the research take place?

Data collection is planned from July 1st to October 30th 2013. You will be contacted 2 weeks prior to confirm the date and time. Data collection will take approximately 2 hours 30 minutes.

What will happen in this research?

When you first arrive you will have your height and weight measured, you will then be asked to fill out 3 forms that measure how you are affected by your gout. You will then have two tests on your legs. First you will have an ultrasound test on your calf muscle and tendon; second you will have your walking measured. For the ultrasound test you will be asked to lie on your stomach on an examination table. You will then have gel put on your calf muscle and the person taking the ultrasound will then put the ultrasound tool on your leg and record pictures which will take about 30 minutes.

To see how well you walk small marker balls will be stuck onto both of your legs with tape. To measure how much your muscle works during the walking we will also apply another set of markers to each leg, before we can attach the markers we will need to remove any hairs with a disposable razor. You will then be asked to walk along a flat walkway ten times. Before you walk on the walkway we will show you where to walk. This will take about 1 hour and 30 minutes.

Support during the research

You are more than welcome to bring a family member or friend along if you agree to participate in the study.

What to wear for the research appointment?

During the research you will need to wear either shorts or pants that are able to be rolled up to just over the knee.

What are the discomforts and risks?

If this discomfort becomes too uncomfortable we will stop the procedure. You may want to leave the study and if you wish to leave the study, we will respect your decision.

What are the benefits?

The findings of this study will allow us to look at rehabilitation programmes that may benefit people with walking difficulties related to chronic gout.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of you being 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 privacy will be protected by your identification being a number, and access to the data is restricted only to the researchers.

We would like permission for your rheumatologist to access hospital records to obtain and release information about your current blood tests and any X-rays undertaken in the foot. The reasons we ask this information is that it allows us to understand more about the impact chronic gout has on the foot.

What are the costs of participating in this research?

The cost of your travel will be reimbursed through taxi or fuel vouchers. To collect all of the information it will take approximately 2 hours 30 minutes of your time. Because of the long time we would like to offer you a fuel voucher. We would also like to offer you a pair of walking socks.

What opportunity do I have to consider this invitation?

Before volunteering, please consider carefully whether you are prepared to be part of the study. We have a number of bookings available throughout July to October and we will organise a convenient time for you to come.

How do I agree to participate in this research?

If you wish to participate in the study please contact the Researcher Matthew Carroll (see contact details below). You will need to read and sign the Consent Form dated 19th March 2013 to participate in this study. A consent form can be obtained from the Researcher.

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. 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 Principal Investigator, Professor Keith Rome, krome@aut.ac.nz, 921-9999 ext 7688.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Madeline Banda, *mbanda@aut.ac.nz*, 921 9999 x8044

Whom do I contact for further information about this research?

Please contact the research assistant Matthew Carroll

Research assistant details:

Matthew Carroll (Research student responsible for administration and data collection)

Phone: 021 245 8796

email: matthew.carroll@aut.ac.nz

Project Supervisor contact details:

Professor Keith Rome

phone: 921-9999 ext 7688; email: krome@aut.ac.nz

APPENDIX 2

Consent form

Consent Form

AUT UNIVERSITY
TE WĀNANGA A RONGO O TAMAKI MAKAU RAU

The effect of chronic gouty arthritis on structure and function of the Achilles tendon.

Project Supervisors: ***Professor Keith Rome, A/Prof Mark Boocock, A/Prof Nicola Dalbeth***

Research Assistant: ***Matthew Carroll***

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 19th March 2013.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ 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 have not: any current injury to either leg or foot, a current history of peripheral neuropathy, or have had a previous rupture to the Achilles tendon.
- ○ All information will remain confidential, anonymous and kept in a locked cabinet. The information will then be destroyed after 10 years.
- ○ I give permission for my rheumatologist to access my medical records to obtain and release information relating to current blood tests and recent X-rays.
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes ☐ No ☐

Participant's signature: .....

Participant's name: .....

Participant's Contact Details (if appropriate):

.....

.....

Date:

Approved by the Auckland University of Technology Ethics Committee on .....

AUTEC Reference number: .....

Note: The Participant should retain a copy of this form

APPENDIX 3

A) Pain visual analogue scale

Patient Pain VAS (100mm):

How much pain have you had because of your gout in the past week:

No Pain _____ Extreme Pain

B) Foot pain visual analogue scale

Patient Foot Pain VAS (100mm):

How much foot pain have you had because of your gout in the past week:

No Pain _____ Extreme Pain

C) Patient global health visual analogue scale

Patient wellbeing (global) VAS (100mm):

Considering all the ways that your gout affects you, please indicate your overall level of wellbeing in the past week by marking an (X) through the line:

Very well _____ Very poor

APPENDIX 4

Health Assessment Questionnaire II (HAQ II)

We are interested in learning how your illness affects your ability to function in daily life.

Place an x in the box which best describes your usual abilities over the past week.

Are you able to:	**Without any difficulty [0]**	**With some difficulty [1]**	**With much difficulty [2]**	**Unable to [3]**
Get on and off the toilet?				
Open car doors?				
Stand up from a straight chair?				
Walk outdoors on flat ground?				
Wait in a line for 15 minutes?				
Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?				
Go up 2 or more flights of stairs?				
Do outside work (such as yard work)?				
Lift heavy objects?				
Move heavy objects?				
Subtotal				
Total				

APPENDIX 5

Lower Limb Tasks Questionnaire - Recreational Activities section

Patient: _____ **Date:**_____

INSTRUCTIONS

Please rate your ability to do the following activities in the **past 24 hours** by circling the number below the appropriate response.

If you did not have the opportunity to perform an activity in the **past 24 hours**, please make your *best estimate* on which response would be the most accurate.

Please also rate how important each task is to you in your daily life according to the following scale:

1. = Not important
2. = Mildly important
3. = Moderately important
4. = Very important

Please answer all questions.

		UNABLE	SEVERE DIFFICULT	MODERATE DIFFICULTY	MILD DIFFICULTY	NO DIFFICULTY	IMPORTANCE OF TASK
1.	Jog of 10 minutes	0	1	2	3	4	1 2 3 4
2.	Pivot or twist quickly while walking	0	1	2	3	4	1 2 3 4
3.	Jump for distance	0	1	2	3	4	1 2 3 4
4.	Run fast/sprint	0	1	2	3	4	1 2 3 4
5.	Stop and start moving quickly	0	1	2	3	4	1 2 3 4
6.	Jump upwards and land	0	1	2	3	4	1 2 3 4
7.	Kick a ball hard	0	1	2	3	4	1 2 3 4
8.	Pivot or twist quickly while running	0	1	2	3	4	1 2 3 4
9.	Kneel on both knees for 5 minutes	0	1	2	3	4	1 2 3 4
10.	Squat to the ground/floor	0	1	2	3	4	1 2 3 4

Lower Limb Tasks Questionnaire - Activities of daily living section

Patient: _____ **Date:**_____

INSTRUCTIONS
Please rate your ability to do the following activities in the **past 24 hours** by circling the number below the appropriate response.

If you did not have the opportunity to perform an activity in the **past 24 hours**, please make your *best estimate* on which response would be the most accurate.

Please also rate how important each task is to you in your daily life according to the following scale:

1 = Not important
2 = Mildly important
3 = Moderately important
4 = Very important

Please answer all questions.

		UNABLE	SEVERE DIFFICULTY	MODERATE DIFFICULTY	MILD DIFFICULTY	NO DIFFICULTY	IMPORTANCE OF TASK
1.	Walk for 10 minutes	0	1	2	3	4	1 2 3 4
2.	Walk up or down 10 steps (1 flight)	0	1	2	3	4	1 2 3 4
3.	Stand for 10 minutes	0	1	2	3	4	1 2 3 4
4.	Stand for a typical work day	0	1	2	3	4	1 2 3 4
5.	Get on and off a bus	0	1	2	3	4	1 2 3 4
6.	Get up from a lounge chair	0	1	2	3	4	1 2 3 4
7.	Push or pull a heavy shopping trolley	0	1	2	3	4	1 2 3 4
8.	Get in and out of a car	0	1	2	3	4	1 2 3 4
9.	Get out of bed in the morning	0	1	2	3	4	1 2 3 4
10.	Walk across a slope/uneven ground	0	1	2	3	4	1 2 3 4

TOTAL (/40):_____

APPENDIX 6

Leeds Foot Impact Scale

LFIS-RA

Date:

Name:_____ Age:_____ Sex:

On the following pages you will find some statements which have been made by people who have Arthritis in their feet

Instructions: This questionnaire consists of 51 statements. Please read each statement carefully, and then pick out the **one statement** that best describes the way you have been feeling. Choose **True** if the statement applies to you and choose **Not True** if it does not apply to you **at the moment**. Circle the number beside the statement you have picked.

1. **My feet get painful when I'm standing**
   1 True
   0 Not True

2. **My feet hurt me**
   1 True
   0 Not True

3. **I find the pain in my feet frustrating**
   1 True
   0 Not True

4. **The pain is worse when I've been on my feet all day**
   1 True
   0 Not True

5. **At the end of the day there is pain and tension in my feet**
   1 True
   0 Not True

6. **I never get rid of the stiffness in the background**
   1 True
   0 Not True

7. **My feet throb at night**
   1 True
   0 Not True

8. **My feet wake me up at night**
   1 True
   0 Not True

9. **I feel as though I've got pebbles in my shoes**
   1 True
   0 Not True

10. **I get pain every time I put my foot down**
    1 True
    0 Not True

11. **I get a burning sensation all the time**
    1 True
    0 Not True

Subtotal Page 1

Continue on Back

12. **I cry with pain**
    1 True
    0 Not True

13. **I can only walk in certain shoes**
    1 True
    0 Not True

14. **I need shoes with plenty of room in them**
    1 True
    0 Not True

15. **I am limited in my choice of shoes**
    1 True
    0 Not True

16. **I need a wider fit of shoes**
    1 True
    0 Not True

17. **I feel I need a lot of padding under my feet**
    1 True
    0 Not True

18. **My footwear always feels heavy**
    1 True
    0 Not True

19. **I have to keep swapping and changing my shoes**
    1 True
    0 Not True

20. **I can't get any shoes on**
    1 True
    0 Not True

21. **I walk barefoot all the time**
    1 True
    0 Not True

22. **I feel unsafe on my feet**
    1. True
    2. Not True

23. **I have to walk for a bit and sit for a bit**
    1 True
    0 Not True

24. **I can't run**
    1 True
    0 Not True

25. **I find I shuffle around**
    1 True
    0 Not True

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26. **I am limping about all the time**
    1 True
    0 Not True

27. **I have to use a walking stick or walking frame**
    1 True
    0 Not True

28. **It takes me all my time to climb the stairs**
    1 True
    0 Not True

29. **I need help to climb stairs**
    1 True
    0 Not True

30. **I can't walk on cobbles**
    1 True
    0 Not True

31. **I am unsteady on uneven surfaces**
    1. True
    2. Not True

32. **I can't walk as far as I would like to**
    1 True
    0 Not True

33. **It takes me longer to do things**
    1 True
    0 Not True

34. **My whole life has been adapted**
    1 True
    0 Not True

35. **My feet restrict my movement**
    1 True
    0 Not True

36. **I get annoyed because I'm slower**
    1 True
    0 Not True

37. **I get frustrated because I can't do things So quickly**
    1 True
    0 Not True

38. **My whole life has slowed down**
    1 True
    0 Not True

39. **It's reduced the range of things I can do**
    1 True
    0 Not True

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40. **I have to plan everything out**
    1. True
    2. Not True

41. **I can't keep up like I used to**
    1 True
    0 Not True

42. **Socially it's affected my a lot**
    1 True
    0 Not True

43. **I am ashamed of how I walk**
    1 True
    0 Not True

44. **I'm nervous of missing a curb edge**
    1 True
    0 Not True

45. **I feel isolated because I can't go very far**
    1 True
    0 Not True

46. **I feel I slow other people down**
    1 True
    0 Not True

47. **I can't do some of the things I take for granted**
    1 True
    0 Not True

48. **I can't go for walks with the people close to me**
    1 True
    0 Not True

49. **I'm finding it difficult to be independent**
    1 True
    0 Not True

50. **I dread finishing up in a wheelchair**
    1 True
    0 Not True

51. **I get frustrated because I can't do things for myself**
    1 True
    0 Not True

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APPENDIX 7

Ultrasound scoring system

		Insertion		Pre-insertion to midsection (2cm from insertion)		Proximal to midsection	
		Left	Right	Left	Right	Left	Right
Tophus Characteristics	Tophus present	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
	If tophus present, longest diameter	mm	mm	mm	mm	mm	mm
Tendon echogenicity	Focal hypoechoic areas with loss of fibrillar echotexture	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2
	Intratendinous hyperechoic spots	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2
Tendon vascularity	Intratendinous power Doppler signal	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2
Tendon morphology	Tendon tear: 0: absent, 1: partial tear, 2: complete rupture	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2	0 1 2
	Tendon thickness at the insertion of the deeper margin into the calcaneal bone	mm	mm				
	Tendon thickness score (0: <5.3 mm; 1: between 5.3 and 6.3; 2: > 6.3 mm)	0 1 2	0 1 2				
	Tendon Length	mm	mm				
Enthesis	Entheseal echogenicity: focal hypoechoic areas	0 1 2	0 1 2				
	Entheseal echogenicity: calcifications	0 1 2	0 1 2				
	Entheseal vascularity	0 1 2	0 1 2				
Bursal morphology	Bursal size	mm	mm				
	Bursal size score (0: <2 mm; 1: between 2–4 mm; 2: > 4 mm)	0 1 2	0 1 2				
	Bursal snowstorm appearance	0 1 2	0 1 2				
	Bursal power Doppler signal	0 1 2	0 1 2				
Bone profile	Calcaneal bone cortex irregularities	0 1 2	0 1 2				
	Calcaneal Enthesophytes (new bone formation at enthesis-bone junction)	0 1 2	0 1 2				
	Calcaneal bone erosions (0: no bone erosion; 1: between 0.1 and 2 mm; 2: > 2 mm)	0 1 2	0 1 2				

Scoring unless specified
0 = None / absent
1 = mild to moderate
2 = Severe

APPENDIX 8

Non-significant correlations between gait parameters and US lesions in participants with gout

Table 8.1: Non-significant bivariate correlations for walking velocity US lesions

	r	p-value
Intratendinous power Doppler signal (zone 1)	-0.13	0.38
Intratendinous power Doppler signal (zone 2)	0.25	0.82
Intratendinous power Doppler signal (zone 3)	0.06	0.67
AT thickness	-0.24	0.10
Calcaneal enthesophyte formation (zone 1)	-0.20	0.18
Tophus present (zone 1)	0.12	0.14
Tophus present (zone 2)	0.35	0.82
Tophus present (zone 3)	0.02	0.88
Intratendinous hyperechoic spots (zone 1)	-0.31	0.83
Intratendinous hyperechoic spots (zone 2)	-0.17	0.29
Intratendinous hyperechoic spots (zone 3)	-0.09	0.56
Entheseal echogenicity (zone 1)	-0.78	0.59

Table 8.2: Non-significant bivariate correlations for ankle power with and US lesions

	r	p-value
Intratendinous power Doppler signal (zone 1)	-0.15	0.31
Intratendinous power Doppler signal (zone 2)	0.04	0.80
Intratendinous power Doppler signal (zone 3)	-0.30	0.87
Calcaneal enthesophyte formation (zone 1)	-0.12	0.41
Tophus present (zone 1)	0.16	0.27
Tophus present (zone 2)	0.17	0.25
Tophus present (zone 3)	0.22	0.13
Intratendinous hyperechoic spots (zone 1)	-0.005	0.97
Intratendinous hyperechoic spots (zone 2)	-0.11	0.49
Intratendinous hyperechoic spots (zone 3)	-0.17	0.24
Entheseal echogenicity (zone 1)	-0.14	0.32

Table 8.3: Non-significant bivariate correlations for ankle range of motion with and US lesions

	r	p-value
Intratendinous power Doppler signal (zone 1)	-0.13	0.38
Intratendinous power Doppler signal (zone 2)	-0.10	0.50
Intratendinous power Doppler signal (zone 3)	-0.18	0.90
Calcaneal enthesophyte formation (zone 1)	0.17	0.26
Tophus present (zone 1)	-0.02	0.86
Tophus present (zone 2)	0.002	0.99
Tophus present (zone 3)	0.05	0.74
Intratendinous hyperechoic spots (zone 1)	-0.05	0.75
Intratendinous hyperechoic spots (zone 2)	-0.04	0.77
Intratendinous hyperechoic spots (zone 3)	-0.05	0.75
Entheseal echogenicity (zone 1)	-0.23	0.12