Foot Pain, Impairment and Disability in Patients with Acute Gout; a Prospective Observational Study

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Thesis

Submitted to AUT University in
fulfillment of the requirements for the degree of
Master of Philosophy

2011

School of Podiatry

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Secondary Supervisors: Prof. Peter McNair, Dr Nicola Dalbeth

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Attestation of Authorship

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

Student Name: .....

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Date: .....

Ethics approval

Health and Disability Ethics Committees

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11 March 2010

Professor Keith Rome
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Dear Keith

NTX/10/02/010	**Disability and impairment associated with podiatric problems in patients with acute gout**
Principal Investigator:	Prof Keith Rome
Co-Investigators:	Prof Kathryn McPherson, Dr Nicola Dalbeth, Dr Michael Frecklington
Localities:	Auckland University of Technology, Counties Manukau DHB, Auckland DHB

Thank you for your letter and attachments received 10 March 2010. The above study has been given ethical approval by the Northern X Regional Ethics Committee.

Approved Documents

- Participant Information Sheet/Consent Form V#2 dated March 2010

Certification

The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation

The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports

The study is approved until 11 March 2013. However the Committee will review the approved application in twelve months time and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator's responsibility to forward a progress report covering all sites prior to ethical review of the project by **11 March 2011**. The report form should be forwarded to you prior to this date but if not received, it is available on http://www.ethicscommittees.health.govt.nz (forms – progress reports). Please note that failure to provide a progress report may result in the withdrawal of ethical approval.

Final Report

A final report is required at the end of the study. The report form is available on http://www.ethicscommittees.health.govt.nz (progress reports) and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Requirements for SAE Reporting

The Principal Investigator will inform the Committee as soon as possible of the following:

- Any related study in another country that has stopped due to serious or unexpected adverse events

- all serious adverse events occurring during the study in New Zealand which result in the investigator breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

We wish you well with your study.

Yours sincerely

Pat Chainey
Administrator
Northern X Regional Ethics Committee

Cc: ADHB Research Office A+4641
CMDHB Research Office 854
C. Grinter, AUT Research Office

Acknowledgements

The completion of this thesis would not be made possible without the significant contribution of the following people and organisations:

Firstly I would like to thank Professor Keith Rome for acting as my primary supervisor for this thesis. You have helped me to develop so much as a researcher and without your guidance this thesis would not have been possible.

I would like to thank Professor Peter McNair for acting as my secondary supervisor and providing his insight and constructive criticism throughout the duration of the project.

I would like to thank Dr Nicola Dalbeth for also acting as my secondary supervisor and for offering me advice and guidance throughout the project, particularly during the data collection phase.

To the team at Auckland District Health Board, notably Peter Jones, Yih Jia Poh and all of the rheumatologists, doctors, nurses and reception staff for their assistance during the data collection phase.

To the team at Counties-Manukau District Health Board, notably Peter Gow, Hazra Sahid, Vanessa Thornton and all of the rheumatologists, doctors, nurses and reception staff for their assistance during the data collection phase.

I would also like to thank ASICS, particularly Jason Mansfield and Mike Lilley for supporting my studies once again.

To the podiatry team at Counties-Manukau District Health Board, notably Kathryn Erikson, Anthony Ng and Leonie Newton, for their support and patient referrals during the data collection phase.

To Donna Snell at Mangere Family Doctors for her assistance with patient referrals during data collection phase.

To all of the staff members of the AUT School of Podiatry for their support and encouragement throughout the duration of the study.

I would like to thank my family for their constant support of me and my studies. A special thank you to Kathy Frecklington for proofreading the final manuscript.

Finally, to my partner Jennifer Goodwin, thank you for your constant support, guidance, belief in me and proof-reading of this manuscript.

Abstract

Purpose: Acute gout typically presents as an extremely painful intermittent arthritis affecting the foot. The impact of acute gout flares on musculoskeletal function is not well described. The aim of this study was to evaluate the impact of acute gout on foot pain, impairment and disability.

Design: Prospective observational study.

Methods: A total of 20 patients (17 males, 3 females, mean age of 54.4 years) were recruited from hospital wards and rheumatology outpatient clinics within Auckland and Counties-Manukau District Health Boards. Patients were recruited at the time of an acute flare (baseline visit) and then reassessed at a follow-up visit after the flare had resolved 6-8 weeks later. Clinical characteristics including tender joint count, swollen joint count, patient global assessment, C-reactive protein and serum urate were assessed at both study visits. General and foot-specific outcome measures were used to assess pain, impairment, function and disability. These included the Health Assessment Questionnaire (HAQ-II), Foot Function Index, Lower Limb Tasks Questionnaire and the Leeds Foot Impact Scale. Data was analysed using paired t-tests.

Results: At the baseline assessment, 14 (70%) of patients were suffering from acute flares affecting the foot. Acute flares were associated with high levels of pain, impairment and disability. All measures of pain, impairment, function and disability displayed improvement at the follow-up visit. Pain and disability scores did not return to normal levels after the resolution of the acute flares.

Conclusion: Acute gout is associated with high levels of foot pain, impairment and disability. This suggests the management of gout needs to be improved, particularly foot related health.

Chapter 1: Introduction

1.1 Statement of the problem

This study investigated the impact of acute gout on pain, structure, function, impairment and disability, with respect to the foot.

Historically, gout has been described as the ‘disease of kings’ and conversely ‘the king of diseases’ due to its association with a rich diet, overindulgence and excruciating pain (Garcia, Kutzbach & Espinoza, 1997; Kim, Schumacher, Hunsche, Werheimer & Kong, 2003). Gout is a urate metabolism disorder characterised by the formation of monosodium urate crystals (MSU) deposited in joints and soft tissues (Kim et al., 2003). Gout initially presents as acute attacks, characterised by severe pain, swelling and inflammation of the affected joint(s) (Ho & DeNuccio, 1993). In the presence of prolonged hyperuricaemia and acute flares, crystal deposition into joints can lead to the development of tophaceous disease (Kumar & Gow, 2002; Schumacher et al., 2005). Tophi are collections of MSU crystals encapsulated by chronic inflammatory cells and connective tissue (Schumacher et al., 2005). Tophi typically occur in both joints and subcutaneous tissues, and may result in pain, cosmetic problems, loss of function, and joint destruction (Dalbeth et al., 2007; Kumar & Gow, 2002; Schumacher et al., 2005).

Gout is on the increase worldwide and is the most common form of inflammatory arthritis affecting men (Arromdee, Michet, Crowson, O’Fallon & Gabriel, 2002; Klemp, Stansfield, Castle & Robertson, 1997; Mikuls & Saag, 2006; Wallace, Riedel, Joseph-Ridge & Wortmann, 2004). A number of population based studies have reported the overall prevalence of gout ranging from 0.52% in the United States of America (Wallace et al., 2004), 1.39% in the United Kingdom (Miklus et al., 2005), 1.4% in Germany (Annemans et al., 2008), to 4.71% in Greece (Anagnostopoulous et al., 2010). The prevalence of gout in New Zealand is high, especially Counties-Manukau, South Auckland, which has been dubbed the ‘gout capital of the world’ (Winnard et al., 2008). In New Zealand, the prevalence of gout has been reported as 4.7% (Klemp et al., 1997). The prevalence of gout in European men is 5.8%, Maori men is 13.9% (Klemp et al., 1997) and 14.9% Pacific Island men (Winnard et al., 2008). Maori men are at risk

of early onset, suffering more frequent attacks and progressing on to more severe disease with the subsequent formation of gouty tophi and joint damage (Gibson, Waterworth, Hatfield, Robinson & Bremner, 1984; Klemp et al., 1997; Rose, 1975). Brauer and Prior (1978) reported that 38% of Maori men developed gout between the ages of 15 and 34 years old. The prevalence of gout in Maori females is 1.6-1.8% (Prior, 1981; Rose, 1975). Gout also occurs at a younger age in Maori women with 58% before the age of 45 years old (Brauer & Prior, 1978). A strong genetic element is believed to contribute to the high prevalence rates (Hollis-Moffatt et al., 2009; Merriman & Dalbeth, 2011). Gout typically affects the distal peripheral joints of the body, particularly those within the foot and ankle (Roddy, Zhang & Doherty, 2007a).

Gout most commonly affects the 1st metatarsophalangeal joint (1st MPJ) (Doherty, 2009; Roddy et al., 2007a). Janssens, Janssen, van de Lisdonk, van Riel and van Weel (2008) examined 120 patients with acute gout flares and found that 93% of flares were affecting lower limb joints with 63% of patients experiencing a flare the 1st MPJ. Over 70% of patients with gout will experience at least one episode of acute gout at the 1st MPJ during their lifetime (Garcia et al., 1997; Grahame & Scott, 1970; Puig et al., 1991). McGill (2000) reported that 62% of patients experience a second acute attack within a year and 89% within the following 5 years. Recurrent acute flares can lead to erosive damage and loss of function of the effected joint (Dalbeth et al., 2009).

The foot is the primary organ in the human body for weight-bearing, balance and propulsion (Nielsen et al., 2010). It represents the terminal joint in the lower limb kinetic chain, dissipating the compressive, tensile, shearing and rotational forces associated with everyday activities such as walking and running (Nielsen et al., 2010). The feet are often made to withstand substantial forces, up to five times one's body weight depending on the specific activity (Hills, Hennig, Byrne & Steele, 2002). Function of the 1st MPJ is critical to efficient gait, with restrictions leading to altered walking patterns and pathological changes within the joint (Nawoczenski, Baumhauer & Umberger, 1999). If an individual has difficulty walking, their ability to participate in various activities is drastically reduced, which may lead to impairment and disability (Nystrom, 1972).

Patients with gout have lower quality of life (QOL) compared to aged-matched controls (Lee et al., 2009; Roddy, Zhang & Doherty, 2007b; Singh & Strand, 2008). The poorest QOL is observed in patients who experience recurrent acute attacks (Becker et al., 2009; Lee et al., 2009). Gout also has a negative impact on employment, with gout patients having 4.6 more absences compared to those without gout, per annum (Kleinman et al., 2007). Gout patients also have lower productivity levels within the workplace comparative to others without gout (Kleinman et al., 2007). Becker et al. (2009) observed moderate levels of disability in patients with treatment-failure gout.

The impact of gout on domains such as pain, function, impairment and disability has been investigated; however, the foot has received limited attention. Foot involvement is extremely common in patients with acute gout, irrespective of age, gender or disease duration (Janssens et al., 2008; Park et al., 2000). Despite the prevalence of gout affecting the foot, no studies have examined the impact of acute gout on the foot. Recurrent acute attacks are known to progress to chronic changes, such as erosion and joint destruction in the foot (Dalbeth et al., 2009). Patients with chronic gout have reduced foot function and higher levels of disability than individuals without gout (Rome et al., 2010). A better understanding of the role of acute gout may help to better predict patient outcomes and structural changes within the foot.

1.2 Aim of the study

The aim of the current study was to investigate the impact of acute gout flares on pain, function, impairment and disability, with reference to the foot. Clinical characteristics of acute flares and patient's footwear were also examined. An observational follow-up study design was employed, to examine patients when they were experiencing an acute flare (baseline) and repeated once the flare had subsided (follow-up visit). The objectives of the study included:

1. Prevalence of foot involvement in patients with acute gout;
2. The clinical characteristics of acute flares (tender joints, swollen joints, patient global assessment, C-reactive protein and serum urate);
3. Measures of foot pain, impairment, function and disability.

1.3 Hypotheses

The hypotheses of this thesis were that:

- Prevalence of foot involvement in patients with acute gout will be high.
- Significant differences in the clinical characteristics associated with acute gout between the baseline visit and the follow-up visit.
- Significant differences in foot pain, impairment, function and disability between the baseline visit and follow-up visit in patients with acute gout.

1.4 Significance of the study

Epidemiological and qualitative research suggests that impact of untreated gout is far more significant than many health professionals realise (Harrold, Mazor, Vetlen, Ockene & Yood, 2010; Lindsay, Gow, Vanderpyl, Logo & Dalbeth, 2011; Winnard et al., 2008). The cost to the healthcare system for new cases of acute gout is approximately $27.4 million in the United States of America, although, this is believed to be an underestimation (Kim et al., 2003). Roddy, Mallen, Hider and Jordan (2010) reported 87% of consultations for gout related problems are related to acute flares. Becker et al. (2009) reported that patients with more severe gout had poorer quality of life (QOL) in all areas compared to those with mild/moderate disease. The authors also found that the poorest QOL was observed in with patients who experienced more acute flares with polyarticular involvement. Acute gout flares commonly affect joints within the foot and ankle (Grahame & Scott, 1970). Recurrent acute flares can lead to structural damage and the subsequent formation of tophi (Kumar & Gow, 2002; Schumacher et al., 2005). Previous research has focused on intermittent/chronic gout within the foot (Rome et al., 2010). Therefore there is a need to examine what ‘impact’ of these acute flares has on the foot.

Chapter 2: Literature Review

2.1 Introduction

This chapter will provide a brief overview of the pathogenesis gout. Risk factors in the development of gout and the pathophysiology and clinical characteristics of acute gout will also be discussed.

2.2 Pathogenesis

The course of gout is sequential, progressing through four distinct phases; *asymptomatic hyperuricaemia, acute gout, intermittent gout, and chronic gout* (Mandell, 2008; Schumacher, 2008). There is considerable variation as to the rate at which this progression occurs within an individual and it is largely related to numerous endogenous and exogenous risk factors (Kim et al., 2003; Mandell, 2008).

2.3 Asymptomatic hyperuricaemia

Hyperuricaemia is a common metabolic abnormality characterised by elevated levels of uric acid within the body (Chen & Schumacher, 2008). Uric acid is the by-product of purine metabolism within the body (Doherty, 2009). Through evolution, the ability of humans to produce the uricase enzyme was lost (Doherty, 2009). Uricase is responsible for converting the relatively insoluble uric acid to the highly soluble allantoin (Doherty, 2009). The breakdown of purines within the body accounts for around two-thirds of the total uric acid with the rest coming from dietary sources (Doherty, 2009). Although hyperuricaemia can occur due to overproduction of urate associated with genetic or dietary risk factors, the majority (88%) occurs due to reduced excretion of urate (Chen & Schumacher, 2008). Causes of increased urate production may be a result of dietary, lifestyle, pharmacological or haematological factors (Kim et al., 2003). Factors associated with decreased renal excretion may have renal, metabolic or pharmacological origins (Kim et al., 2003). Approximately 70% of the uric acid the body produces daily is excreted via the kidneys, with the balance eliminated into the biliary tract where it is converted to allantoin (Doherty, 2009).

Hyperuricaemia is not considered a disease rather a predisposing factor in the development of gout (Schumacher, 2008). There is currently no reliable or accurate method for predicting whether an individual with asymptomatic hyperuricaemia will develop gout, thus urate lowering therapy is not recommended in the management of this patient group (Mandell, 2008). Individuals can live with hyperuricaemia for long periods of time and never develop gout (Campion, Glynn & DeLarby, 1987). A large cohort study by Campion et al. (1987) took measurements of serum urate levels of 2,046 'healthy' men over a 15 year period. The five-year cumulative incidence rates of gout were 2.0%, 19.8% and 30% for serum urate levels of <8.0mg/dL, 9.0-10.0mg/dL and >10.0mg/dL, respectively. Although rare, there have been cases reported of individuals developing gout without the presence of hyperuricaemia (Gunawardena, Churn & Blake, 2005; McCarty, 1994).

2.4 Risk factors

Hyperuricaemia is the key risk factor for gout, however, only a small percentage of these patients actually develop gout (Campion et al., 1987; Doherty, 2009). This suggests that there are other associated risk factors in the formation of MSU crystals and subsequently gout (Doherty, 2009). These risk factors include age and gender, family history and co-morbidities.

Traditionally, the onset of gout is reported to occur during the 4th to 6th decades of life (Grahame & Scott, 1970; Puiq et al., 1991). Males outnumber females at all time periods, with the ratio of male to female with gout in individuals under 65 is 4:1, whereas this decreases in those over 65 to a 3:1 ratio (Wallace et al., 2004). Park et al. (2000) reported that the average age of onset was 49.8 years and 54.3 years for Korean males and females, respectively. A large study of a United Kingdom (UK) general practice research database reported the highest incidence of gout in men occurring between the ages of 65 and 84 years old (Mikuls et al., 2005). The incidence of gout in women is much smaller, with gout rarely presenting in those below the age of 45 years old, however, the prevalence rises beyond the age of 85 years old (Mikuls et al., 2005). Increasing age is thought to be a risk factor due to reduced kidney function (increase in serum urate levels) and the use of diuretic drugs (Doherty, 2009). Harrold et al. (2006) found that women with gout were found to be older, had greater reported levels of diabetes, hypertension,

peripheral arterial disease, coronary heart disease, dyslipidaemia, renal insufficiency and failure comparative to their male counterparts. Several studies have also investigated gender differences in gout patients, reporting similar findings in respect to a later age of onset, higher incidence of renal involvement and diuretic use in women (Grahame & Scott, 1970; Park et al., 2000; Puig et al., 1991).

Several reasons for the higher prevalence rates in males comparative to females has been reported in the literature. The low incidence of gout observed in women is associated with the lower serum urate levels comparative to men (Mikkelsen, Dodge & Valkenberg, 1965). The female renal system is more efficient at clearing uric acid prior to the onset of menopause (Mateos, Puig, Ramos, González & Ordás, 1986). Serum urate levels rise after menopause, reducing the difference between males and females (Mikkelsen et al., 1965). Yu (1977) reported that 70% of females with gout experienced their first attack after menopause, whilst Puig et al (1991) reported 86% of women were diagnosed after menopause. Puig et al. (1991) also reported females with gout displayed reduced serum urate clearance compared to males with gout, a finding that was independent of hypertension, renal insufficiency and diuretic use.

A study by Hak and Choi (2008) of 7662 American women reported higher serum uric acid levels were associated with natural and surgical menopause. The use of post-menopausal hormone resulted in lower uric acid levels in postmenopausal women (Hak & Choi, 2008). Both of these findings were independent of several other risk factors including age, BMI, diet, hypertension, diuretic use, renal dysfunction and alcohol use (Hak & Choi, 2008). Nicholls, Snaith and Scott (1973) suggested that oestrogen may enhance the renal clearance of urate, after the administration of oestrogen in males reduced uric acid levels (Nicholls et al., 1973).

Calcium has been implicated in gender differences. Calcium has been found to promote the formation of MSU crystals, due to increased nucleation (new crystal formation) and growth (Wilcox & Khalaf; 1975). A decrease in pH results in a slight increase in the solubility of MSU, however, this appears to be counteracted by the increase in calcium ions (decrease in calcium binding) and therefore nucleation (Wilcox & Khalaf, 1975; Wilcox, Khalaf, Weiberger, Kippen

& Klinenberg, 1972). Wilcox and Khalaf (1975) suggested that any mechanism which decreases pH increases the possibility of MSU crystal formation, both directly (lowered pH leading to nucleation) and indirectly (increase in calcium ion concentration in serum). The ionized concentration of calcium is generally higher in men although this steadily decreases with age. This may explain the incidence and prevalence patterns associated with men and women with gout. This theory must be viewed with caution as it is based on the assumption that these relationships would be observed physiologically. Calcium deficiencies have been reported in females with premenopausal gout (Puig et al., 1991).

The hereditary influence of gout has been explored, but the exact mechanism(s) responsible have not been well defined. Grahame and Scott (1970) reported that 36% of patients with gout had another family member with the disease. A study of Guatemalan gout patients found 28% of the study population had a family history of gout (Garcia et al., 1997). A study of Maori men with gout revealed 50% had a family member with gout, however, the study population was small (Gibson et al., 1984). A retrospective study by Yu (1984) of 2,145 gout patients found that higher incidences of family history were present in those with early onset gout. Those between the ages of 12 and 19 with gout had an 82% incidence for family history compared to only 12% for those with late onset gout (75 to 85 years), with a 30% incidence reported overall. Yu (1984) suggested that poor history taking and a lack of knowledge of family history may in fact mask the true incidence of family history.

It is well documented that there is a correlation between gout and the metabolic syndrome (Colvine et al., 2008; Suppiah, Dissanyake & Dalbeth, 2008). The association with the metabolic syndrome is also more common in gout compared to other forms of arthritis (Mikuls et al., 2005). Milkus et al. (2005) reported that patients with gout had a higher prevalence of diabetes, hypertension, renal impairment and coronary artery disease compared to controls with osteoarthritis (OA) in a study of the United Kingdom General Practice Database between 1990 and 1999. Serum uric acid level is a predictor in the development of Type 2 diabetes, renal failure, hypertension and cardiovascular disease (CVD). A study by Suppiah et al. (2008) of 292 consecutive patients at a New Zealand diabetes clinic reported an overall prevalence of gout in

22% of patients with Type 2 diabetes. Colvine et al. (2008) reported that 87% of gout patients satisfied the NCEP/ATPIII criteria for the metabolic syndrome, with 59% having a high to very high 5 year CVD risk, 60% with hypertension and 33% with diabetes. Becker et al. (2009) reported that 87% of gout patients had other conditions (metabolic or cardiovascular) and 75% had more than one coexisting condition. Patients with gout have also been reported (Wright et al., 2007) to have significantly higher body mass index scores than patients with other forms of arthritis.

The relationship between psoriasis and gout has also been explored. Eisen and Seegmiller (1961) reported that patients with psoriasis display an increased conversion rate of glycine-C14 similar to that of acute primary gout, compared to healthy aged-matched norms. The increased uric acid production and prevalence of hyperuricaemia (50%) in psoriatic patients may act as a risk factor for an acute attack in patients with gout (Eisen & Seegmiller, 1961; Montoya et al., 2008). Contrary to this, Lambert and Wright (1977) reported that hyperuricaemia was not a characteristic of psoriasis or psoriatic arthritis, with elevated cell turnover rates not present in the study population. Similar findings have also been reported in other studies (Bruce, Schentag & Gladman, 2000; Taccari, Gigante, Sorgi & Giacomello, 1985).

2.5 Acute gout

An acute gout attack, also known as a 'flare' is characterised by the rapid onset of inflammatory arthritis, intense pain and reduced range of motion occurring at the affected joint(s) (Grainger et al., 2009; Harris, Siegel & Alloway, 1999). Systemic symptoms associated with acute gout include, fever, chills and malaise, with 30% of patients presenting with temperatures higher than 38^0C during an acute attack (Ho Jr. & DeNuccio, 1993). The majority of attacks are monoarticular, most commonly affecting the 1st MPJ (Grahame & Scott, 1970; Weinfeld & Schon, 1998). Figure 2.1 shows a 'typical' acute flare occurring in the 1st MPJ of the patient's right foot. There may also be involvement in the midfoot, ankle, heel, knee, wrist and fingers (Garcia et al., 1997; Grahame & Scott, 1970). There are several factors which may initiate an acute attack including, trauma (surgery), stress, excessive alcohol consumption, commencement

of uric acid lowering drugs, drugs which raise uric acid levels (diuretics) and non-compliance with pharmacological interventions (Park et al., 2000).

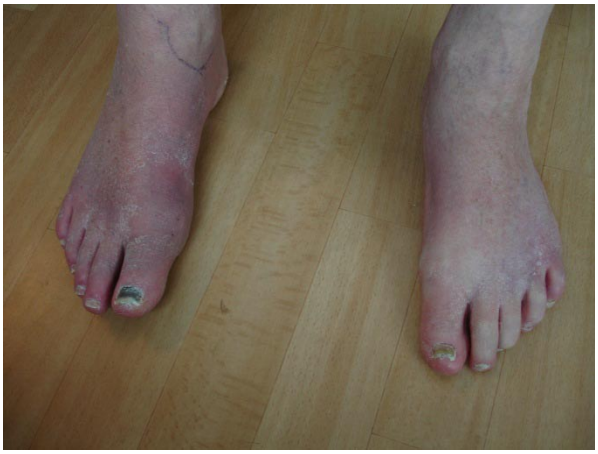

Figure 2.1: Acute flare affecting the 1st MPJ of the right foot.

Several studies have reported the duration of flares (Garcia et al., 1997; Borstad et al, 2004). Garcia et al. (1997) that the clinical course of flare will last less than 9 days in 54% of patients, between 10-14 days in 25% of patients and over 15 days in 21% of patients. Borstad et al. (2004) reported the mean duration of acute flares in groups as 6.0 days and 5.56 days.

The frequency of acute gouty attacks has been discussed in the literature. Yu (1984) investigated the relative frequency of acute attacks prior to the commencement of therapeutic treatment in 1,800 patients. It was reported that 15.1% of patients suffered less than one attack per year, 25.9% having one to two attacks per year, 29.4% having three to four attacks, 14.5% having five to nine attacks and 8.6% having over ten attacks per annum. Irregular and atypical attack frequencies were found in 6.4% of patients. Five or more attacks per annum were reported in 52% of patients with an age of onset between 12 and 24 years, whereas the same rate of attack in patients over the age of 65 was only 6%. The reverse pattern is observed for one or two acute attacks per year, with 1% increasing to 30% in patients with an onset over 65 years. Similar figures over these time periods have been reported in other studies (Khanna et al., 2008).

2.6 Pathophysiology of acute gout

The clinical symptoms of acute gout are a result of the interaction between MSU crystals and neighbouring tissues (Dalbeth & Haskard, 2005). Physiologically, a serum urate level above 6.8mg/dL causes the precipitation of urate as it exceeds the soluble concentration of monosodium urate (MSU) in body fluid, resulting in the formation of MSU crystals (Chen & Schumacher, 2008; Zhang et al., 2006a). The nucleation of MSU crystals is also dependent on several factors including temperature, pH, ionic strength and the binding strength of urate towards plasma macromolecules (Busso & So, 2010). Acute flares can be triggered by events that cause changes in serum urate levels such as trauma, diet (purines) and excessive alcohol consumption (Dalbeth & Haskard, 2005). The early stages of acute inflammation are characterised by the infiltration of leukocytes (neutrophils, monocytes) and the production of interleukin-1ß, interleukin-6, interleukin-8 and tumor necrosis factor α (Martin, Walton & Harper, 2009). The severe pain associated with these acute flares may be a result of the formation of prostaglandins, bradykinin and the sensitisation of nociceptors (Dalbeth & Hazard, 2005).

2.7 Clinical features of acute gout flares

The definition of an acute gout flare has not yet been properly validated (Taylor et al., 2009). Several clinical trials (Rubin et al., 2004; Schumacher et al., 2002; Terkeltaub et al., 2010) have used the American College of Rheumatology (ACR) criteria for the classification of acute arthritis for primary gout to define flares. Taylor et al. (2009) used Delphi methodology and cognitive mapping to devise a shortlist of key features of acute gout flares; swollen joint(s), tender joint(s), warm joint(s), patient self-report of pain, patient self-report global assessment, time to maximum pain level, time to complete resolution of pain, functional status and acute-phase marker (C-reactive protein). The authors stated that these features need further validation against both patient and physician definitions of gout flares. The following features associated with gout flares will be discussed; joint swelling, joint tenderness, patient self-report global assessment, acute-phase marker and serum urate. Taylor et al. (2009) did not outline potential methods to measure time to maximum pain level and time to complete resolution.

2.7.1 Joint tenderness and joint swelling

Inflammation is a striking clinical feature of acute gout flares and subsequently affected joints become tender and swollen (Grainger et al., 2009; Rubin et al., 2004). Joint counts have long been used in rheumatology to examine inflammation, tenderness and swelling (Scott & Houssien, 1996). Tender joints are defined as being painful either at rest, upon palpation or with movement (Scott & Houssein, 1996). Swollen joints are defined as the presence of soft tissue swelling along the margins of the joint (Scott & Houssein, 1996). The most widely used joint counts are the American Rheumatism Association (ARA) 66/68 count (Deandrade & Casagrande, 1965), the 28 count (Fuchs, Brooks, Callahan & Pincus, 1989) and the Ritchie Articular Index (RAI) (Ritchie et al., 1968). A prospective longitudinal study by Prevoo et al. (1993) examined the reliability and validity of several joint indices. The authors found that both the 28 joint count and RAI were reliable and valid. The ARA joint count was not included as the authors did not include the distal interphalangeal joints (IPJs) in their study.

Several studies have examined affected joints when assessing patients with acute gout (Rubin et al., 2004; Schumacher et al., 2002). However, the reliability and validity of these measures has not been reported in this population (Grainger et al., 2009). Rather than adopt a traditional joint count, some clinical trials have typically selected a specific study joint to assess the symptoms of acute gout. Joint tenderness associated with acute gout has been assessed using a 4-point Likert scale (0 = no pain; 3 = patient states there is pain, winces, and then withdraws) with scores of 2.51 and 2.49 (Schumacher et al., 2002) and 2.51 and 2.58 (Rubin et al., 2004) reported. Joint swelling in acute flares has also been assessed using a 4-point Likert scale (0 = none; 3 = bulging beyond margins) with scores of 2.28 and 2.52 (Schumacher et al., 2002) and 2.56 and 2.62 (Rubin et al., 2004) reported. Terkeltaub et al. (2009) reported a joint tenderness, swelling and erythema using a 3-point score (1 = mild, 2 = moderate, 3 = severe) for each symptom. A maximum score of 9 would be achieved if the affected joint was severely tender, swollen and erythematous. During acute flares a median score of 8.0 was reported, indicating moderate/severe joint tenderness, swelling and erythema were present. Terkeltaub et al. (2009) used a 3-point Likert scale to assess erythema in patients with active chronic gout.

One study suggested that either the ARA 66/68 joint count or the Ritchie Articular Index could be used to assess inflammation in chronic gout (Grainger et al., 2009). The Ritchie Index does not include the IPJs of the foot (Ritchie et al., 1968). The ARA 66/68 joint count examines all of the MPJs and IPJs within the foot (Deandrade & Casagrande, 1965). Tophi have been reported in the IPJs of the feet (Bloch, Hermann & Yu, 1980). This would suggest that the ARA 66/68 joint would be more suitable for studies examining the foot, as it captures all of the small joints with the foot. Polyarticular flares are commonly reported in studies examining acute gout (Grahame & Scott, 1970; Rubin et al., 2004), which may suggest that focusing on a specific 'study joint' may lead other areas of involvement being missed.

2.7.2 Patient global assessment

Patient global assessment is used to assess change over time. In the case of a study investigating acute gout, change would be measured from the acute flare to a time once the flare had subsided. The reliability and validity of this measure has not yet been determined in gout (Grainger et al., 2009). Maccargno, Di Giorigio and Romanowicz (1991) used a 5-point Likert scale (1 = very good; 5 = very poor) to measure patient's global assessment of their acute flare, in two groups. Mean baseline scores were 4.3 and 4.0, which over a 7 day period improved to 1.8 and 2.1, respectively. Other studies (Rubin et al., 2004; Schumacher et al., 2002) have reported patient global assessment of treatment during acute flares. This has been measured using a 5-point Likert scale (0 = excellent; 4 = poor). Patient global scores were not reported at baseline, however, following treatment scores were reported as 1.36 and 1.20 (Schumacher et al., 2002) and 1.42 and 1.56 (Rubin et al., 2004). Although the current study is not assessing the effects of treatment on acute flares directly, it is hypothesised there will be a change between the acute and intermittent/chronic phases. Medications will influence this as each patient will have their own management plan which will differ from the next. Several authors (Grainger et al., 2009; Taylor et al., 2009) have suggested that this outcome can also be measured using a 100mm visual analogue scale.

2.7.3 Acute-phase marker

C-reactive protein (CRP) levels obtained from blood samples have been used past studies (Janssens et al., 2008) to measure inflammation in acute gout. Synthesised by the liver, CRP levels remain typically low although stimuli such as trauma and infection cause levels to rapidly increase (Woolf et al., 1985). CRP concentration also influences other processes associated with acute gout flares including the augmentation of phagocytosis (Du Clos, Zlock & Marnell, 1991). Elevated CRP levels (mg/dl) during acute flares have reported as 2.92 (4.43) (Urano et al., 2002) and 31 (38) and 24 (34) (Janssens et al., 2008). Other studies have reported CRP levels ranging from 24.8-542.2 µg/ml (Woolf et al., 1985) and 6-156 µg/ml (Roseff, Wohlgethan, Sipe & Canoso, 1987) in patients with acute gout.

2.7.4 Serum urate

Hyperuricaemia is the dominant factor which predisposes an individual to gout and is measured using serum urate (mmol/L) levels taken from blood samples (Schumacher, 2008; Zhang et al., 2006a). Serum urate is a significant predictor in the development of acute flares (Halpern, Fuldeore, Mody, Patel & Mikuls, 2009a). The incidence of gout has been shown to increase as serum urate levels increase (Brauer & Prior, 1978; Campion et al., 1987). Measuring serum urate is reliable, when appropriate sample handling is employed, with tube additives (heparin) not affecting the results of testing (Grainger et al., 2009). Several studies have reported serum urate levels in patients experiencing acute flares.) Mean (SD) serum urate (mmol/L) has been reported in patients with acute gout as 0.55 (0.11) and 0.55 (0.17) (Ruotsi & Vainio, 1978) and 0.46 (0.10) and 0.48 (0.08) (Janssens et al., 2008). Mean (SD) serum urate (mg/dl) has also been reported during acute flares as 7.5 (1.4) (Urano et al., 2002), 8.49 and 9.15 (Borstad et al., 2004) and 9.66 (1.37) (Wang et al., 2009).

2.8 Intermittent gout

Intermittent gout represents the asymptomatic period after or between acute flares (Harris et al., 1999). Emphasis is placed on a management programme, addressing pharmacological interventions, dietary and lifestyle changes to reduce the risk of recurrent attacks (Hoskison & Wortmann, 2006). Despite such interventions, the likelihood of a patient experiencing a second

attack within a year has been reported as 60% (Gutman, 1973) and 54% (Garcia et al., 1997). Gutman (1973) also reported that only 7% of patients do not experience a recurrence over a 10 year period.

2.9 Chronic gout

Chronic gout, also known as chronic tophaceous gout represents the most advanced stage of the disease. The term itself has several different definitions. Typically it is characterised by the presence of tophi with joints or other soft issue (Kim et al., 2003). One study suggested that the transition from acute/intermittent gout to chronic gout occurs when the intermittent periods are no longer pain-free (Edwards, 2008). Patients with chronic gout can still experience acute flares.

Tophi are a clinical feature of longstanding gout (excess of 10-20 years disease duration) (Wright & Pinto, 2003). Tophi typically present after prolonged, poorly controlled hyperuricaemia and MSU deposition into joint spaces or other subcutaneous tissue (Kumar & Gow, 2002). Tophi can be situated in structures such as joints (synovium and articular cartilage), tendon/tendon sheaths and less commonly in bursae, pinnae and other soft tissue structures, notably those located on the extensor surfaces of the hands and feet (Kerman, Mack & Moshirfar, 1993). The presence of tophi can place excessive pressure on the deeper anatomical structures (Kerman et al., 1993; Kumar & Gow, 2002). Polyarticular involvement of joints may also be present during the chronic stage of gout, affecting the lesser digits of the extremities. Other sites of involvement include the Achilles tendon, olecranon (elbow) bursa, anterior knee (patella) and the helix of the ear (Harris et al., 1999; Reber, Crevoisier & Noseberger, 1996). Tophi can also become inflamed, infected and even ulcerate (Kumar & Gow, 2002).

2.10 Summary

Gout is a disease characterised by MSU crystal formation within joints and soft tissues. The disease typically progresses through a distinct set of phases, however, the exact reasons for the transition from asymptomatic hyperuricaemia to gout is currently unknown. Gout largely affects the peripheral joints of the body, with the foot the most common site of involvement. There is a growing need to explore the role of gout within the foot, particularly the impact of acute flares.

Chapter 3: Literature review of gout within the foot

3.1 Introduction

Gout is a urate metabolism disorder characterised by the formation of monosodium urate crystals (MSU) deposited in joints and soft tissues (Kim et al., 2003). The foot is the most commonly affected site within the body, particularly the 1st MPJ (Janssens et al., 2008; Park et al., 2000). Several studies have identified the negative impact of gout on pain, function (Dalbeth et al., 2007) impairment (Rome et al., 2010) and disability (Survepalli, 2010). Despite these studies, there is limited evidence related to the foot when considering these domains. The aim of this review is to evaluate the literature pertaining to gout affecting the foot. Particular emphasis will be placed on research exploring the domains of foot pain, function/impairment and disability. The areas of epidemiology, diagnosis, assessment and management will also be discussed in relation to the foot.

3.2 Methodology

This literature review is focused on research and review articles published between 1960 and March 2011, concerning gout related to the foot. An initial search was conducted using the Scopus, Pub Med online databases under the following terms; gout, gouty, tophi, tophus, tophaceous, acute, chronic, podagra, foot, feet, pain, impairment, function, disability, footwear, shoes. Citations from the retrieved publications were examined to obtain further references. In addition, hand searches of English full text hard copy journals was also undertaken to retrieve relevant articles. Selected studies had to examine the gout specific to the foot. Those that did not have reference to the foot were excluded. Figure 3.1 outlines the literature search process. Sixty-four articles (n =64) were included in the final review.

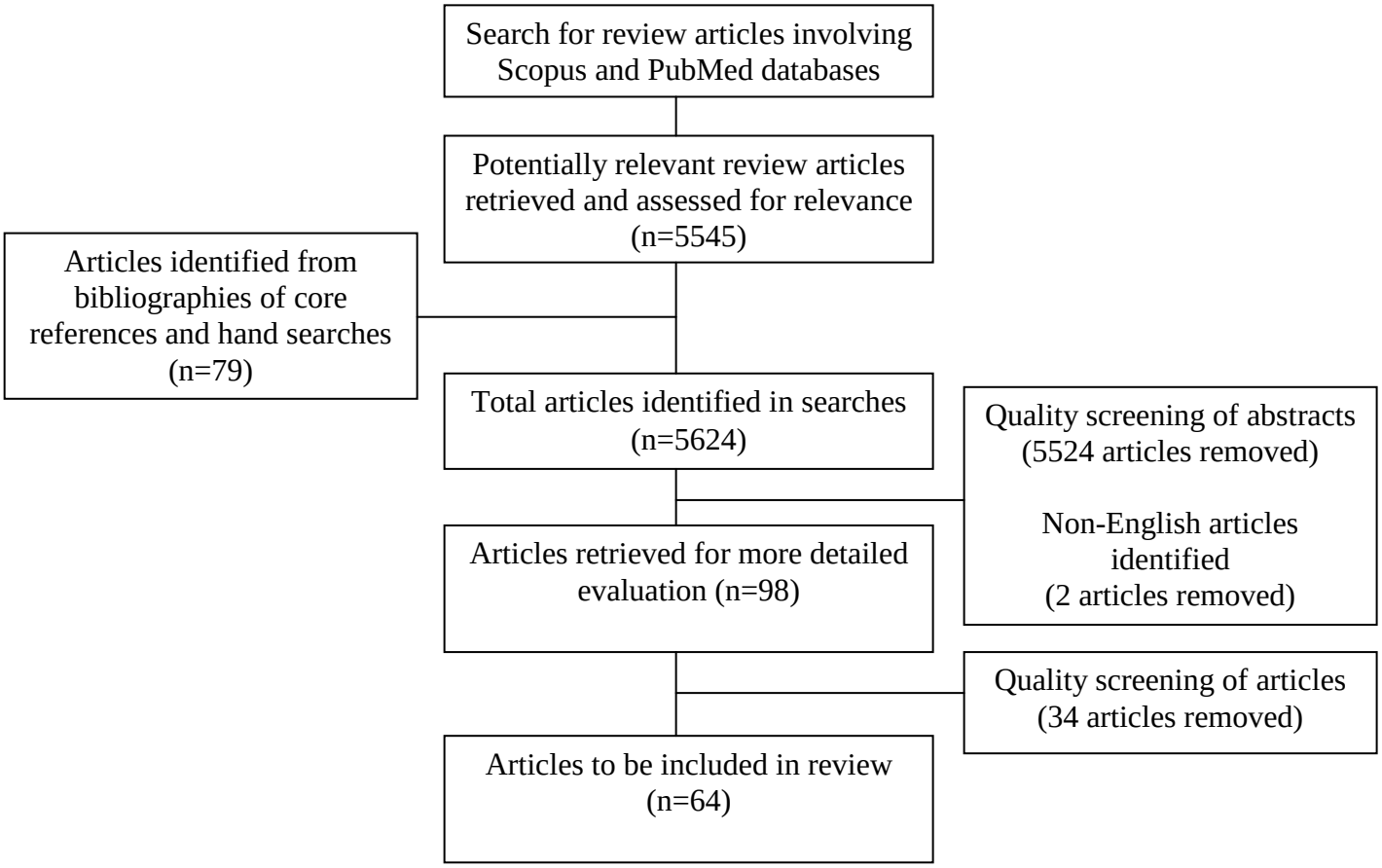

Figure 3.1: Flowchart of the literature search process

3.3 Epidemiology of gout in the foot

Gout localised to the foot, specifically the big toe is also referred to as podagra (Greek for 'foot-trap'). A large prospective study, by Bauer and Prior (1978) of 760 New Zealand Maori between 1962 and 1963 found the prevalence of gout in the foot to be 8.8% in males and 0.8% in females From the original sample, an incidence study of the 531 participants who did not suffer from gout at baseline was reassessed 11 years later (90% response rate). From the revised sample, an incidence of gout affecting the foot was reported to be 10.3% and 4.3% in males and females, respectively. Clinical diagnosis of gout was defined by a history of two or more acute flares affecting the 1st MPJ or foot, thus it can be assumed that the patients in the study all had flares affecting the foot. Puig et al. (1991) reported that men with tophi had 90% located in the foot compared to 40% in females. A retrospective study by Kumar and Gow (2002) of 45 patients who underwent surgery for gouty tophi, reported 18% involvement in the foot. However, the findings of these studies do not provide an indication of the affected site(s) in the foot.

Several studies have reported specific sites in the foot affected by gout. A cross-sectional survey 354 patients with gout, 76% had involvement of the 1st MPJ and 50% had involvement at the foot and ankle (Grahame & Scott, 1970). For this particular survey, gout was defined as having recurrent acute flares and the presence of hyperuricaemia (6 mg/100ml and 5mg/100ml for men and premenopausal women, respectively). It was also observed that involvement in the foot and ankle was irrespective of disease duration. Puig et al. (1991) investigated the clinical characteristics of 257 patients with gout and reported that 70% initially presented with 1st MPJ involvement and 79% had experienced an attack at this site during their lifetime. A retrospective study by Garcia et al. (1997) of 148 patients with acute gout at a Guatemalan rheumatology clinic examined the characteristics of articular involvement in the foot. Diagnosis of gout was established by the presence of MSU crystals or fulfilment of six or more of the ACR criteria for gout. The 1st MPJ was the most common site of involvement seen in 23% of the initial presentations and in 73% of patients at any time. A retrospective study by Park et al. (2000) of 108 patients at a Korean hospital found that 55% of patients initially presented with an acute attack situated at the 1st MPJ, with 62% of those patients experiencing an attack at that site during their lifetime. Roddy et al. (2007a) reported 1st MPJ involvement of acute gout in 164

patients as 61% in their left foot and 66% in their right foot. Midfoot involvement was 13% in the left foot and 20% in the right foot, with ankle involvement 12% and 15% for the left and right foot, respectively. Janssens et al. (2008) examined the effectiveness of prednisolone and naproxen in 120 patients and reported that 63% had 1st MPJ involvement and 29% had involvement in other joints in the foot, ankle and knee. Carter et al. (2009) reported the joints most commonly affected by acute flares in a group of 27 gout patients. The 1st MPJ was the most affected joint as reported by 17 patients, with 5 stating the ankle and 2 the midtarsal joint as the most affected site. Despite numerous studies reporting the epidemiology of gout in the foot, due to the variations in diagnostic criteria, study designs and reported information, comparison of the figures reported in the foot is somewhat restricted.

3.4 Co-morbidities associated with gout in the foot

The correlation between gout and osteoarthritis (OA) has been reported in a number of studies. A hospital-based study by Kawenoki-Minc, Eyman, Leo and Werynska-Przybylska (1974) examined the radiographs of 262 gout patients found degenerative changes indicative of OA at the 1st MPJ (43.5% of patients), 1st interphalangeal joint (IPJ) (28.6% of patients) and tarsal joints (21.4% of patients). Roddy et al. (2007a) used a logistic regression model with the history of an acute gouty attack at a joint input as the dependent variable, with age, gender, body mass index, diuretic use and presence of OA at that joint as independent variables to calculate an adjusted odds ratio (aOR). A significant association between acute attacks and the presence of OA at that same joint was found at the 1st MPJ (aOR 2.06) and the mid-foot (aOR 2.85). Muehleman et al. (2008) reported that the strong relationship between MSU crystal deposition and cartilage degeneration in the talus, with 92.2% of patients with crystal involvement displaying degenerative changes in cartilage. Gout and rheumatoid arthritis (RA) coexisting in the foot is rare and has reported only in case studies (Jessee, Toone, Owen & Irby, 1980). A possible reason was suggested by Wilcox and Khalaf (1975) who reported that the synovial fluid from gout patients increased urate nucleation, whereas, the synovial fluid from RA patients appeared to inhibit urate nucleation. McGill (2000) stated that reported cases of RA and gout coexisting are likely to be a result of one disease getting diagnosed after the first, with the patient

overlooking further investigation as their joint related symptoms had previously been ‘explained’ to them.

Numerous case studies have reported co-morbidities related to gout in the foot, including anorexia nervosa (Nakazawa, Ishihara & Tananka, 2004), sickle cell anaemia (Rothschild, Sienknecht, Kaplan & Spindler, 1980), dactylitis (Andracco, Zampogna, Parodi, Paparo & Cimmino, 2010; Rothschild, Pingitore & Eaton, 1998), reflex sympathetic dystrophy syndrome (Zucchi, Varenna, Binelli & Sinigaglia, 1996), septic arthritis (Coombs, Pinsky & Pandilam, 2001), psoriasis (Cho et al., 2001), hyperparathyroidism (Nirenberg & Carrol, 2007), hypothyroidism (Montoya, Torres, Fraile & Puig, 2008), Hemiparesis (Donegan, Berman & Doherty, 1993), acute glomerulonephritis (Migita et al., 2001), Bartter’s syndrome (Moriwaki, Yamamoto, Takahashi, Tsutsumi & Hada, 2001) and focal segmental glomerulosclerosis (Johnson, Toms & Lee, 2003).

3.5 Pathological changes occurring at the foot in gout

The following section will examine the literature pertaining to reasons for gouty involvement in the foot. The exact reason as to why gout commonly affects the joints within the foot is not well understood, however, it is likely to be multi-factorial (Roddy, 2011). There have been several hypotheses put forward describing factors which may explain the high prevalence of gouty involvement in the foot. These potential risk factors will be described in two sections; the first related to the precipitation of acute flares and the second related to the formation of tophi within the foot. Factors related to acute flares will be discussed in relation to joint structure, temperature and trauma. Factors related to the formation of tophi will be discussed in relation to the structure of the 1st MPJ and other affected sites within the foot.

Katz and Shubert (1970) suggested that a relationship exists between the connective tissue within the joint capsule and deposition of MSU crystal, which subsequently leads to acute flares. Proteoglycans derived from connective tissue can increase the solubility of urate crystals. The authors also found that in vitro, urate solubility increased significantly as cartilage protein polysaccharide concentration increased. Whether or not this finding can be applied in vivo is

unclear. Connective tissue, notably cartilage is avascular, which has been identified as a predisposing factor, however, the synovial membrane of joints is a common site of urate deposition and is reasonably vascular, particularly when inflamed (acute flare) (Katz & Shubert, 1970). Wilcox and Khalaf (1975) found the presence of collagen does not influence nucleation, irrespective of temperature. Both abductor hallucis and flexor hallucis brevis run medial to the 1st MPJ joint capsule (Draves, 1986). Lyburn, Torreggiani, Harris, Zwirewich and Munk (2002) reported lower temperatures in tendons. Temperature has been identified as a risk factor in the development of MSU crystals and subsequently acute gout.

The anatomical position of the extremities relative to the body's core may predispose the foot to acute gouty attacks (Gunawardena et al., 2005; Levy, 1987). Precipitation of MSU crystals can occur with lower concentrations of serum urate at lower temperatures in vitro (Loeb, 1972). Loeb (1972) reported that urate solubility was 6.8mg/100ml at 37^0C, 6.0mg/100ml at 35^0C and 4.5mg/100ml at 30^0C. The more readily MSU crystals form, the likelihood of an acute flare increases (Wilcox & Khalaf, 1975). The relationship between climate change and the precipitation of an acute gout attack have been found to influence acute gout attacks (Arber, Vaturi, Schapiro, Jelin & Weinberger, 1994). However, Arber et al. (1994) observed that colder temperatures and low barometric pressure were not significant predictors in acute gout attacks.

Gout patients have identified trauma as a trigger for acute flares (Lindsay et al., 2011). Thiele and Schlesinger (2007) postulated that the higher levels of free fluid within the 1st MPJ comparative to the other MPJs may be a result of increased mechanical trauma or hydrostatic pressure. Simkin (1977) suggested that fluid accumulation at the 1st MPJ may be a result of humans spending the majority of the day on their feet. Nocturnal re-absorption of fluid may result in greater MSU concentrations within the joint as water clears joints twice as fast as urate (Simkin, 1977; Thiele & Schlesinger, 2007). Gouty attacks have been reported to occur during the night (Alexander, 1986). Arthrocentesis (fluid aspiration) is known to reduce the pain associated with acute flares at the 1st MPJ (Scott, 2000). Increased free fluid levels within the 1st MPJ were also observed in the control group of the study, suggesting that other risk factors and processes occur within the 1st MPJ.

The 1st MPJ is subject to more load than any other joint, per square inch (Levy, 1987). Pathological changes such as bone erosion, joint space widening and the double contour sign are common features of gout affecting the 1st MPJ (Pineda et al., 2011). Roddy et al. (2007a) reported that osteoarthritis (OA) and gout commonly coexist within the 1st MPJ. Whether or not the reported association between gout and OA (Foldes, Petersilge & Resnick, 1996; Roddy et al., 2007a) is a result of articular damage caused by repeated acute flares or that MSU deposition favours previously damaged joints, is currently unknown (Muehleman et al., 2008). However, Muehleman et al. (2008) did suggest that the pattern of MSU deposition within the foot has a strong biomechanical underpinning.

Roth (1993) postulated that abnormal structure and biomechanical function of the foot and ankle may increase the likelihood of a gout attack of the 1st MPJ. Anatomical deviations and the associated compensatory mechanisms of the foot which increase the load of the medial column of the foot, which result in trauma to the internal structures of the 1st MPJ and big toe (Gunawardena et al., 2005; Roth, 1993). Wilcox and Khalaf (1975) reported that mechanical shock can act as a catalyst for urate nucleation and therefore the formation of MSU crystals. Phagocytosis of MSU crystals lowers pH, creating an environment which enhances nucleation (Wilcox & Khalaf, 1975). It has also been suggested that there is a high correlation between the occurrence of tophi and anatomical sites subjected to repeated micro-trauma and/or acute injury (Kerman et al., 1993).

Imaging modalities such as X-ray (Bloch et al., 1980; Steinbach & Jensen, 1976), ultrasound (Thiele & Schlesinger) have reported that tophi are commonly located on the medial aspect of the 1st MPJ. The exact reason for this occurrence is currently unknown; however, some authors have postulated ideas as to why this may be occurring. Thiele and Schlesinger (2007) reported that smaller, unformed tophaceous material (micro-tophi) exist within the 1st MPJ joint capsule. The authors suggested the relationship between the location of established tophi and that of unformed micro-tophi in the 1st MPJ. Unlike established tophi, micro-tophi are not in a fixated position and can move within the joint capsule as the joint acts through its range of motion. The distal aspect of the joint capsule is occupied by the extensor tendon which inserts into the base of

the proximal phalanx, so dorsiflexion of the 1st MPJ forces micro-tophi against the proximal dorsal margin of the proximal phalanx. Tophi located medial to the 1st MPJ may be a result of micro-tophi being forced in to the medial aspect of the 1st metatarsal head and proximal phalanx, as dorsiflexion of the 1st MPJ causes expansion of the joint capsule medially. German and Holmes (1986) stated that tophi commonly form over sites of high pressure, which supports this idea of micro-tophi being forced into these specific regions leading to the formation of tophi.

Periosteal proliferation can lead to the formation of osteophytes which over-hang the 'punched-out' tophus deposit (Bloch et al., 1980; Egan, Sartoris & Resnick, 1987; Steinbach & Jensen, 1976). Thiele and Schlesinger (2007) reported that this results in the characteristic C-shaped appearance of the adjacent bone, is present in 65% of 1st MPJs affected by gout (Thiele & Schelsinger, 2007). The authors suggested this may be due to the inflammatory cells which surround tophi will often attach to bone upon contact. Under ultrasound, tophi are encapsulated by an anechoic rim which may be representative of the outer border macrophages, lymphocytes and large body giant cells which surround tophi in vitro (Thiele & Schlesinger, 2007). This may explain the ability of tophi to erode into adjacent bone. Although the 1st MPJ is the most commonly reported site in the foot, there have been other reported cases of gout in close proximity to this joint.

Several authors have described gouty involvement in the tibial sesamoid bones (Lemont & Sabo, 2001; Liu, Yeh, Chou Chen & Pan, 2003). It has been suggested that because the sesamoids share the same joint capsule as the 1st MPJ that disease affecting the sesamoids would be a reflection of the pathology of the adjacent articular structures (Resnick, Niwayama & Feingold, 1977). Despite this, the reported cases of gouty presentation in both non-partite and tri-partite sesamoids have been accompanied by a 'normal' 1st MPJ (Lemont & Sabo, 2001; Reber, Crevoisier & Noseberger, 1996; Reber, Patel & Noseberger, 1997). Other reported sites in the foot include the navicular (Thomas et al., 1998), talus (Raikin & Cohn, 1997) and ankle (Lacey & Harrison, 1981). There have also been reported cases of tendon rupture, secondary to gout in the peroneal (Lagoutaris, Adams, DiDomenico & Rothenberg, 2005) and tibialis anterior tendons (Jerome, Varghese, Sankaran, Thomas Thirumagal, 2008).

3.6 Foot pain, impairment, function and disability

The following section will investigate the following outcomes of pain, impairment, function and disability in patients with gout. These outcomes will be explored in relation to the foot and the tools that have been used previously to assess them in the gout population. More severe foot problems are associated with greater impairment and disability in terms of pain and foot function (Bennett, Patterson, Wearing & Baglioni, 1998; Bal, Aydog, Aydog & Cakci, 2006).

3.6.1 Foot pain

Intense pain is characteristic with acute flares, thus pain is used as a primary outcome measure in all clinical trials relating to gout (Grainger et al., 2009). Both VAS and Likert pain scales have been used in studies relating to acute gout, however, they have not been compared in terms of performance in research concerning gout (Grainger et al., 2009). It has been suggested that both measures perform similarly when investigating pain in osteoarthritis (Bolognese, Schnitzer & Ehrich, 2003). Reported outcome measures used to assess the pain associated with acute gout include; 5-point Likert scale (0 = none, 1 = mild, 2= moderate, 3 = severe, 4 = extreme) (Rubin et al., 2004; Schumacher et al., 2002) and a 100mm VAS scale (Borstad et al., 2004; Janssens et al., 2008; Schlesinger et al., 2002). Typical values for the pain during acute flares can be found in Table 3.1.

Table 3.1: Typical values for pain during acute gout flares

Author(s):	Scale	Intervention	Mean Baseline Pain
Schumacher et al., 2002	5-point Likert	Etoricoxib Indomethacin	2.9 3.0
Rubin et al., 2004	5-point Likert	Etoricoxib Indomethacin	2.9 3.0
Schlesinger et al., 2002	10cm VAS	Ice Control	8.6 9.6
Borstad et al., 2004	10cm VAS	Colchicine Placebo	3.6 5.1
Janssens et al., 2008	100mm VAS	Prednisolone Naproxen	61.5 58.9

Previous studies have also described the sites at which the acute flares were occurring. Rubin et al. (2004) reported baseline figures of pain in acute gout including the number of patients in their sample (n = 189) with foot involvement. Metatarsophalangeal involvement was reported in 56/189 patients (30%), proximal interphalangeal involvement of the 1st toe was reported in 20/189 patients (11%) and 48/189 patients (25%) had an acute gout flare affecting the ankle. Janssens et al. (2008) reported 76/120 patients (63%) with 1st MPJ involvement and 35/120 (29%) with other foot, ankle and knee joint involvement. Although these studies have reported the specific joints involved, including those within the foot and ankle, we can only gain an appreciation of pain during acute flares and not during intermittent/chronic periods.

A previous study (Rome et al., 2010) investigated foot pain in chronic gout using the Foot Function Index (FFI) pain subscale. The pain sub-scale displays moderate reliability (ICC = 0.695) (Budiman-Mak, Conrad & Roach, 1991). The FFI displays good construct and criterion validity (Budiman-Mak et al., 1991). MID value for the pain subscale is -12 (Landorf & Radford, 2008). Although the FFI was originally designed for the RA population, Budiman-Mak et al. (1991) suggested that the FFI could be applied to other forms of degenerative joint diseases and is suitable for use in the clinical and research setting. Rome et al. (2010) reported mean (SD) foot

pain using the FFI pain subscale as 28.2 (25.2) in a case-control study of chronic gout. This value was significantly higher comparative to a control group. These findings indicate that patients with chronic gout will often be experiencing foot pain, even if they are not suffering from an acute attack. Other studies have reported FFI pain scores of 4.51 and 4.57 in RA (Saag, Saltzman, Brown & Budiman-Mak, 1996) and 42.70 in a range of patients attending a foot and ankle clinic (SooHoo, Samimi, Vyas & Botzler, 2006). No data relating to acute gout and the FFI has been reported.

3.6.2 Foot impairment

The term ‘impairment’ can be defined as the presence of abnormal structure (tophus) and/or function (reduced range of motion) (Cieza & Stucki, 2004). Structural abnormalities such as tophi (Migita et al., 2001; Nakazawa et al., 2004), metatarsophalangeal subluxation (Bloch et al., 1980) and reduced range of motion (Survepalli, 2010) have been reported in the feet of patients with gout (Bloch et al., 1980). Despite these reports of specific pathological changes, there is little evidence relating to the foot as a whole in patients with gout.

Platto, O’Connell, Hicks and Gerber (1991) first described The Structural Indices for Fore and Hindfeet Deformity (SI) to record the presence of clinical deformity in the feet of patients with RA. The reliability and validity of the SI has not been discussed in the literature. Each deformity is weighted equally to give an overall score, with higher scores representing greater deformity. The authors assessed 31 patients with RA and reported forefoot and rearfoot mean scores of 66.8 and 47.0, respectively. Turner, Helliwell, Emery and Woodburn (2006) reported median (range) scores of 2 (0-10) for the forefoot SI and 0 (0-2) for the rearfoot SI in a cohort of patients with established RA. The SI captures the presence of various structural and functional impairments throughout the foot; however, it does not provide an ‘overall’ picture of the foot.

The Foot Posture Index (FPI) was developed after previous studies (Cowan, Robinson, Jones, Polly & Berrey, 1994; Dahle, Mueller, Delitto & Diamond, 1991; Sell, Verity, Worrell, Pease & Wigglesworth, 1994; Weiner-Ogilvie & Rome, 1998) had identified the need for a

universal, validated method for quantifying foot posture (Redmond, Crosbie & Ouvrier, 2006). Originally unpublished, the FPI consisted of eight specific criteria, however, after validation, two constructs were omitted from the FPI due to poor construct, concurrent and content validity (Keenan, Redmond, Horton, Conaghan & Tennant, 2007; Redmond et al., 2006). This lead to a six item modified FPI also known as the FPI-6 and the discontinuation of the eight item FPI (Redmond et al., 2006).

The FPI-6 displays excellent intra-rater reliability and moderate inter-rater reliability, with mildly improved scores from the original FPI (Cornwall, McPoil, Lebec, Vicenzino & Wilson, 2008; Scharfbillig et al., 2004). Validation of the FPI-6 using Rasch analysis concluded that the tool displayed good metric properties, individual item fit and overall fit (Keenan et al., 2007). Nielsen et al. (2010) found that FPI-6 scores were significantly linked to midfoot position at the midstance stage of the gait cycle. The FPI-6 has been used to assess foot type in numerous populations including the elderly (Aurichio, Rebelatto & de Castro, 2011), osteoarthritis (Reilly et al., 2009) and paediatric populations (Morrison & Ferrari, 2009).

The Leeds Foot Impact Scale (LFIS) was developed to evaluate foot health status in patients with RA (Helliwell et al., 2005). The LFIS is comprised of two separate components; impairment/footwear ($LFIS_{IF}$) and activity limitation/participation restriction ($LFIS_{AP}$). These two components relate closely to the domains outlined by the ICF (World Health Organisation, 2001). The LFIS also measures the psychological effect(s) of the disease on the individual. The $LFIS_{IF}$ subscale has been used in to measure foot related impairment in patients with chronic gout. Rome et al. (2010) reported a mean (SD) score 10 (6.1) which was significantly higher than a control group 0.9 (1.7), indicating that gout patients suffer from greater levels of impairment. The LFIS has also been used in studies investigating RA (Rome, Gow, Dalbeth & Chapman, 2009; Silvester, Williams, Dalbeth & Rome, 2010). No studies have examined the relationship between impairment and acute gout.

3.6.3 Foot function

Function relates to the physiological function of body systems (Cieza & Stucki, 2004). Function can be measured using self-administered questionnaires asking patients to provide an estimate of their functional status and by observing a patient's ability to perform specific tasks (McNair et al., 2007). The Health Assessment Questionnaire (HAQ) (Fries, Spitz, Kraines & Holman, 1980) is considered the most influential and commonly used measure of function in rheumatology (Wolfe, Michaud & Pincus, 2004). The HAQ also covers a wide range of areas including pain, disability, effects of medication, costs of care and mortality (Bruce & Fries, 2005). The HAQ is not without its criticisms, often considered too long and difficult to score (Bruce & Fries, 2005; Wolfe et al., 2004). The HAQ-II was developed using Rasch analysis, and is a reliable (Cronbach's alpha: 0.88) and valid, 10 item questionnaire (Wolfe et al., 2004). The HAQ-II has been used to assess function in patients with chronic gout.

Mean HAQ-II scores in gout patients have been reported as 0.54 (0.5) (Rome et al., 2010) and 0.73 (0.74) (ten Klooster, Oude Voshaar, Taal & van der Laar, 2011). Wolfe, Michaud and Pincus (2005) reported mean HAQ-II scores as 0.9 (0.6) patients with RA. Several studies have used the Health Assessment Questionnaire Disability Index (HAQ-DI) to assess function in gout. Mean HAQ-DI scores in patients with gout have been reported as 0.61 (ten Klooster et al., 2011), 0.54 (Van Groen, Ten Klooster, Tall, Van De Laas & Glas 2010) and 0.59 (Álvarez-Hernádez et al., 2008). The HAQ-II provides a broad perspective of function status, however, measures more specific to the lower limb and foot have also been discussed in relation to gout.

The Lower Limb Tasks Questionnaire (LLTQ) focuses solely on physical tasks associated with lower-limb function, more specifically the difficulty in completing such tasks and the importance of each task (McNair et al., 2007). The LLTQ is divided into two sections; activities of daily living (ADL) and recreational activities, both of which are key features of the International Classification of Functioning, Disability and Health (ICF) (World Health Organisation, 2001). McNair et al. (2007) reported that the LLTQ displays high levels of reliability for both sections, with ICC scores of 0.96 for the ADL domain and 0.98 for the recreational activities domain. MID values were calculated as 2.6 for the ADL questionnaire and

2.2 for the recreational activities questionnaire. The use of the LLTQ in both a research and clinical setting is also supported by the authors. In measuring function across both the ADL and recreational activities domains, the LLTQ may offer a more broad perspective of function. Gout typically affects joints within the foot and ankle, however, gouty involvement is regularly reported in the knee and less commonly the hip. This further suggests that the LLTQ is a suitable tool to assess lower limb function in patients with gout.

McNair et al. (2007) states that the LLTQ should reflect the difficulty to perform an activity within the past 24 hours, to ensure that the information recalled by the patient is accurate, whilst also appreciating the resulting musculoskeletal changes over short time periods. The current study design aims to capture the participants within 48 hours of experiencing an acute gout attack and hence the LLTQ appears a suitable measure. Survepalli (2010) used the Lower Limb Tasks Questionnaire (LLTQ) when assessing function in 25 patients with chronic gout. Mean scores for the ADL domain was 28 and 19 for the recreational domain were reported.

Wang et al. (2009) reported foot function in 28 male patients who experienced recurrent attacks at the 1st MPJ. The sample was divided into two groups, one whom underwent arthroscopy (n=15) and another group who were managed medically (n=13). Foot function was measured using the American Orthopaedic Foot and Ankle Society (AOFAS) ankle hindfoot scale. The AOFAS is a reliable and valid measure used to assess function post-surgery (Ibrahim et al., 2007). The authors reported AOFAS mean scores of 68.8 and 89.7, at baseline and after intervention, respectively. The group who underwent surgery had improved foot and ankle function compared to the non-surgical group, however, both groups displayed an improvement in foot and ankle function (Wang et al., 2009). A limitation of this study was that the treatment offered to the non-surgical group was not well described, nor was the use of gout specific medications in both groups.

Rome et al. (2010) investigated the impact of gout on foot function and foot biomechanics. Function was assessed using self-administered questionnaires (HAQ-II) and through functional tasks (gait analysis). Temporal-spatial parameters of gait were measured

using the GAITMAT II ™ in patients with chronic gout. Significant differences were noted in walking velocity, cadence, step and stride length. Gout patients were found to walk slower, with altered stride and toe off mechanisms compared to control patients.

3.6.4 Foot disability

The definition of the term disability is still widely debated, largely due to the lack of a universal definition which is applicable to all people, captures the varying types of disability and does not indicate the causes of disability (Leonardi, Bickenbach, Ustun, Kostanjsek & Chatterji, 2006). The International Classification of Function, Disability and Health (ICF) defined disability as "the negative aspects of the interaction between an individual (with a health condition) and that individual's contextual factors (personal and environmental factors)" (Leonardi et al., 2006, page 1220).

Activity refers not only the execution of a task, but the individual's perception of function (Cieza & Stucki, 2004). Any problems encountered when undertaking a particular activity are denoted as 'activity limitation' (Cieza & Stucki, 2004). Participation relates to one's involvement in a life situation, representing society's perception of functioning (Cieza & Stucki, 2004). 'Participation restriction' refers to any difficulty that a person may experience when involved in life situations (Cieza & Stucki, 2004). Activity and participation do provide a slight indication of one's life, but only after investigating the contextual factors do you gain a complete background of one's life and living situation (Cieza & Stucki, 2004). The $LFIS_{AP}$ subscale assesses both activity limitation and participation restriction. $LFIS_{AP}$ scores have been reported in patients with chronic gout. Rome et al. (2010) reported mean scores of 14.7 for the $LFIS_{AP}$ subsection and an overall LFIS mean score of 24.0.

The Foot Function Index (FFI) is a questionnaire designed to measure the impact of foot pathology on function, originally designed for the RA population (Budiman-Mak et al., 1991). The FFI is comprised of 17 questions, divided into three different subscales; pain, disability and activity restriction. The FFI displays high test-retest reliability for the disability (ICC = 0.84) and activity restriction (ICC= 0.81) sub-scales as well as the total score (ICC = 0.87). The FFI also

displays good construct and criterion validity. Budiman-Mak et al. (1991) suggested that the FFI could be applied to other forms of degenerative joint diseases and is suitable for use in the clinical and research setting.

Janssens et al. (2008) measured ‘general disability’ and ‘walking disability’ using 100mm VAS in patients suffering from acute flares, with higher scores representing greater disability. General disability means score was reported as 59.2 and 55.1 during the acute flares and 17.2 and 12.7 ninety hours later. Walking disability was reported as 70.9 and 67.4 during the acute flare and 17.4 and 13.0 ninety hours later. The authors did state that both measures were not validated.

3.7 Summary

Gout is a monosodium urate disorder which is extremely prevalent within the foot. Despite the high levels of foot involvement, there is very limited evidence related to both acute and chronic gout affecting the foot. Case studies formulate the majority knowledge base, with the only clinical trials related to imaging and pharmacological interventions, acknowledging the foot to a limited degree. Although it is recognised that chronic gout affects foot function, no studies have investigated the impact of acute flares on foot function. Functional scores have been reported in patients with chronic gout and those with a history of recurrent acute flares, however, these measures were not undertaken when patients were experiencing flares. It is widely recognised that recurrent acute gout flares and poor management can lead to chronic problems. The negative impact of chronic gout on foot pain, function and disability has been reported, however, there is little evidence related to acute gout.

Chapter 4: Methodology

4.1 Study design

This observational follow-up study assessed the impact of acute gout on the foot.

4.2 Participants

Patients with acute gout flares were recruited from emergency departments, hospital wards and rheumatology outpatient clinics at Auckland and Counties-Manukau DHB. Patients were reassessed six weeks after their baseline assessment (once the acute gout attack had settled). Northern X Regional Ethics Committee approved the current study and all procedures involved prior to the commencement of data collection (page 8).

Inclusion criteria: An acute gout attack within the previous 48 hours, ability to provide informed consent and clinical diagnosis of acute gout determined if any of the following three criteria are fulfilled: (a) the presence of characteristic urate crystals in 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 from the American College of Rheumatology (ACR) criteria for the classification of acute arthritis for primary gout (Wallace et al., 1977) (Appendix 1).

Exclusion criteria: Patients were excluded from the study if they did not display clinical characteristics of acute flares or were unable to provide informed consent.

4.3 Procedure

Patients were assessed on two separate occasions by an independent examiner (MF). Prior to the commencement of the study a diagnosis of gout was confirmed, based on the criteria outlined under 4.2. Patients had the opportunity to read and/or have explained the patient information sheet, detailing the study and what it involved (Appendix 2). Patients who provided informed consent were recruited into the study (Appendix 3).

Both at baseline and follow-up visit, clinical information of each patient was recorded from the patient's medical notes. This included the patient's age, gender, height, weight, body mass index (BMI), ethnicity and current occupation. General medical history was also recorded, including the presence of hypertension, cardiovascular disease and diabetes mellitus. The patient's current medications and dosages were recorded as well as their weekly alcohol consumption (units/week).

Clinical information specific to the patient's gout and their current flare was also taken. This included the age of the patient's first episode, the site of the first episode, site of the current flare, disease duration, flare frequency (past three months) and the number of days the patient has taken off work in the past three months. Photographs of the patient's feet and the site(s) of their flares were also taken. The following assessments and questionnaires were used to assess acute flare characteristics at baseline: tender joint count, swollen joint count, patient global assessment visual analogue scale (VAS), acute-phase marker (C-reactive protein) and serum urate.

The following assessments and questionnaires were also undertaken at baseline to measure foot pain, function, impairment and disability: Pain VAS, Structural Indices of the Forefoot and Hindfoot, Foot Posture Index (FPI), Health Assessment Questionnaire II (HAQ-II), Lower Limb Tasks Questionnaire (LLTQ), Foot Function Index (FFI), Leeds Foot Impact Scale (LFIS) and Footwear Assessment Form. Chapter 3 describes a review of each of the outcomes used in the current study.

4.4 Primary outcome measures

The primary outcome measures assessed in the current study were flare characteristics (tender joints, swollen joints, patient global assessment, acute-phase marker (C-reactive protein) and serum urate, foot pain, impairment, function and disability.

4.5 Flare characteristics

The assessment of flare characteristics comprised of tender joint count, swollen joint count, patient global assessment, acute-phase marker and serum urate.

4.5.1 Joint tenderness and joint swelling

The American Rheumatology Association (ACA) 66/68 joint count for swollen and tender joints was used (Appendix 4). Joint tenderness was defined as pain within a joint at rest or elicited with pressure or movement (Scott & Houssien, 1996). Pressure was applied using the thumb and index finger, adequate force is determined by 'whitening' of the nail bed (Scott & Houssien, 1996). Tender joints were graded from 0-1, where 0 represents not tender and 1 represents tender. There are 68 joints assessed in total for tenderness. Joint swelling refers to soft tissue swelling and is present along the joint margins, in the case of synovial effusion (Scott & Houssien, 1996). Joint swelling is not to be confused with bony swelling or joint deformities, such as subcutaneous tophi. Swollen joints were graded from 0-1, where 0 represents not swollen and 1 represents swollen. There are 66 joints assessed in total for swelling (hip is not assessed).

4.5.2 Patient global assessment

Patient global VAS was used to determine the patient's overall wellbeing. Overall wellbeing is scored along a 100mm horizontal line with the left-most boundary representing 'completely well' and the right-most boundary representing 'completely unwell'. Patients mark along the line with a cross which they fell best represents their current status. This is then measured in mm from the left-most border to the marked cross to give an overall score out of 100, expressed as a percentage.

4.5.3 Acute-phase marker

C-reactive protein (CRP) was collected via a blood sample using a 4ml heparin tube by the investigator (MF). Samples were transferred to a single laboratory (LabPlus, Auckland Hospital) within two hours of collection. CRP levels were obtained from a blood sample taken from the patient at the baseline and follow-up visit.

4.5.4 Serum urate

Serum urate levels were collected via a blood sample using a 4ml heparin tube by the investigator (MF). Samples were transferred to a single laboratory (LabPlus, Auckland Hospital) within two hours of collection. Serum urate levels were obtained from a blood sample taken from the patient at the baseline and follow-up visit.

4.6 Foot pain

A pain visual analogue scale (VAS) was used to examine pain (Appendix 5). Pain intensity is scored along a 100mm horizontal line with the left-most boundary representing ‘no pain’ and the right-most boundary representing ‘extreme pain’. The patient marks a point along the line which they feel best describes their current pain levels, which is then measured in mm to give an overall score out of 100, expressed as a percentage.

The modified Foot Function Index (FFI) contains a total of 17 questions which are divided into three different subscales (Appendix 6). The self-administered questionnaire asks the user to answer each question as how they have been feeling the previous week (Budiman-Mak et al., 1991). The FFI pain subscale contains five questions related to foot pain. Questions are scored against a scale ranging from 0-10, where a score of 0 represents ‘no pain’ and a score of 10 represents ‘worst pain imaginable’. If a patient cannot answer a question it is recorded as not ‘applicable’ and that question score is removed from total possible score. For example, if a patient could not answer one of the questions in the pain subscale, the patient’s total score would be divided by 40 opposed to 50.

4.7 Foot impairment

Impairment was assessed using the Structural Indices for Forefoot and Hindfoot (rearfoot) Deformities (SI) (Appendix 7), the Foot Posture Index (FPI-6) (Appendix 8) and the Leeds Foot Impact Scale Impairment/Footwear subsection ($LFIS_{IF}$) (Appendix 9).

The SI (Platto et al., 1991) is broken down into two categories, forefoot and hindfoot (rearfoot). The forefoot deformities investigated are hallux valgus, 5^{th} MPJ exostosis (Taylor's bunion), claw toes (digits 1-5) and subluxation of MPJs (joints 1-5). If a deformity is present it is scored as 1, with a total of 12 forefoot deformities measures in each foot. The sum of the scores from the left and right foot gives the overall SI forefoot score. Rearfoot deformities investigated are calcaneal valgus/varus, total ankle joint range of motion (ROM) and pes planus foot type. Calcaneal valgus/varus was measured using a hand-held goniometer, with $0\text{-}5^0$ deviation scored as 0, $6\text{-}10^0$ as 1, $11\text{-}15^0$ as 2 and $\geq 15^0$ as 3. Total ankle joint ROM (maximum plantarflexion to maximum dorsiflexion) was measured using a hand-held goniometer, with $46\text{-}60^0$ ROM scored as 0, $31\text{-}45^0$ ROM scored as 1, $15\text{-}30^0$ ROM scored as 2 and $\geq 15^0$ ROM scored as 3. The presence of pes planus foot type is scored as 1. The scores of both feet are then added to give an overall SI for the rearfoot.

The Foot Posture Index (FPI-6) contains six different items (three specific to both the forefoot and rearfoot) each scored using a 5-point Likert scale ranging from -2 (more supinated) to +2 (more pronated). Each foot is assessed with the six components added together to give a FPI-6 score for each foot, which can range from -12 (highly supinated) to +12 (highly pronated) (Redmond et al., 2006). During the assessment, patients stood in double limb support in their normal base of support. This position is adopted as it accommodates for individuals with impaired balance and postural control (McClay, 2001; Redmond et al., 2006).

The LFIS comprises of 51 questions, divided into two sub-categories; impairment/footwear ($LFIS_{IF}$) and activity limitation/participation restriction ($LFIS_{AP}$) (Helliwell et al., 2005). Questions 1-21 make up the $LFIS_{IF}$ section (Helliwell et al., 2005). Each question is

answered as being ‘true’ or ‘false’, with a true response scored as one point and a false response as zero. Scores are then totalled to provide an overall score for each subsection, with a maximum overall score of 51. Higher scores are indicative of greater levels of impairment. Turner et al (2006) reported that a $LFIS_{IF}$ score of >7 points is indicative of moderate-to-high levels of foot impairment.

4.8 Foot function

The Health Assessment Questionnaire II (HAQ-II) was used to measure functional status (Appendix 10). The HAQ-II contains 10 questions, 9 of which measure function and 1 disability (Wolfe et al., 2004). Each question can be answered as either ‘without any difficulty’, with some difficulty’, ‘with much difficulty’ or ‘unable’. Each of these answers is then scored; without any difficulty as 0, with some difficulty as 1, with much difficulty as 2 and unable as 3. To gain the overall HAQ-II score the sum of the item scores is divided by the total number of items answered (if all 10 items are answered the sum of their scores is divided by 10) (Wolfe et al., 2004). If less than 8 items are completed the HAQ-II is not scored (Wolfe et al., 2004). Lower scores are indicative of better functional status (Wolfe et al., 2004).

The Lower Limb Tasks Questionnaire (LLTQ) was used to measure function in the lower extremity (McNair et al., 2007). The LLTQ captures the patient’s account of their functional status within the previous 48 hours and is divided into two domains; activities of daily living (Appendix 11) and recreational activities (Appendix 12), each containing ten questions. Each section contains 10 questions which are scored using a 5-point Likert scale (0 = unable, 1 = severe difficulty, 2 = moderate difficulty, 3 = mild difficulty, 4 = no difficulty). The scores from each of the four questions are then totalled to give an overall score out of forty. Higher overall scores represent greater levels of function. Each question/task is also graded in terms of its importance to the patient using a 4-point Likert scale (1 = not important, 2 = mildly important, 3 = moderately important, 4 = very important).

4.9 Foot disability

Disability was measured using the FFI (disability) subscale, FFI (activity limitation) subscale and $LFIS_{AP}$ subsection. The FFI disability and activity limitation subscales contain nine and three questions, respectively (Budiman-Mak et al., 1991). For the disability domain, a score of 0 represents “none of the time” with 10 representing “all of the time”. For the activity restriction domain, 0 represents “no difficulty” and 10 representing “so difficult unable to do”. If a patient cannot answer a question it is scored as not applicable and that question score is subtracted from total possible score. For example, if a patient could not answer one of the questions in the disability domain, the subscale score would be obtained by dividing the patient’s score by 80 opposed to 90. A total foot function score is calculated by dividing the patient’s total score from the 17 questions by 170 and multiplying that figure by 100 to give an overall percentage. Higher scores represent greater levels of pain, disability and activity limitation.

The $LFIS_{AP}$ subsection (Helliwell et al., 2005) comprises of questions 22-51 of the overall questionnaire (Appendix 9). Each question is answered as being ‘true’ or ‘false’, with a true response scored as one point and a false response as zero. Scores are then totalled to provide an overall score for each subsection, with a maximum overall score of 51. Higher scores are indicative of greater levels of disability. Turner et al (2006) reported that a $LFIS_{AP}$ score of >10 points is indicative of moderate-to-high levels of foot disability.

4.10 Data analysis

Data analysis was undertaken to compare significant differences between the baseline and follow-up visits. Dependent t-tests with 95% CI were used to analyse all demographic characteristics, clinical flare characteristics (tender joint count, swollen joint count, patient global assessment, C-reactive protein and serum urate), pain visual analogue scale, Health Assessment Questionnaire II, Foot Function Index, Lower Limb Tasks Questionnaire, Leeds Foot Impact Scale, Foot Posture Index and the Structural Indices of the Forefoot and Hindfoot Deformities. Non-parametric Sign-tests were used to evaluate significant differences between baseline and follow-up with current pharmacological management.

Pharmacological management, gender, occupation, ethnicity and structural index scores were described as n (percentages). All other demographic characteristics were described as the mean (SD). All data was analysed using SPSS V18.0 for Windows.

The Bonferroni correction is a method used in research to control Type I error (Ottenbacher, 1991). The Bonferroni correction is calculated by dividing the α level (0.05) by the number of statistical comparisons. For example if there were 10 dependent t-tests performed the Bonferroni correction would be calculated as:

$$0.05/10=0.005$$

This suggests that each statistical test is evaluated against a 0.005 level of significance opposed to 0.05. Ottenbacher (1991) stated that one of the limitations of the Bonferroni method is that a result of decreasing the risk of Type I error, the risk of committing Type II error increases. An adjusted Bonferroni method can be used to reduce Type I error whilst also having lower Type II error rates. Holm (1979) described the first 'adjustment' to the original Bonferroni method. The obtained P values are placed into sequential order from smallest to largest. The following formula is then used to reject the null hypothesis:

$$P_j = \alpha/(m-j+1)$$

P_j: represents the probability of the jth contrast
α: represents overall α level (0.05)
m: represents the total number of P values (contrasts)
j: the specific contrast from the series

Hochberg (1988) has described a variation on the Holm's method, whereby P values are arranged from largest to smallest. If the largest P value is rejected at α then all other hypothesis are rejected. Hochberg's adjustment places obtained P values in descending order, making it

more sensitive with a lower Type II error rate than Holm's adjustment (Hochberg, 1988; Ottenbacher, 1991).

Chapter 5: Results

5.1 Introduction

This chapter is divided into nine subsections; clinical characteristics of the patients, gout history, flare characteristics, pain, function, impairment, disability. Based on the 16 outcomes measured a Bonferroni correction was calculated as p = 0.003 (Appendix 13). Figure 5.1 below provides an overview of the recruitment over a six month period of the study.

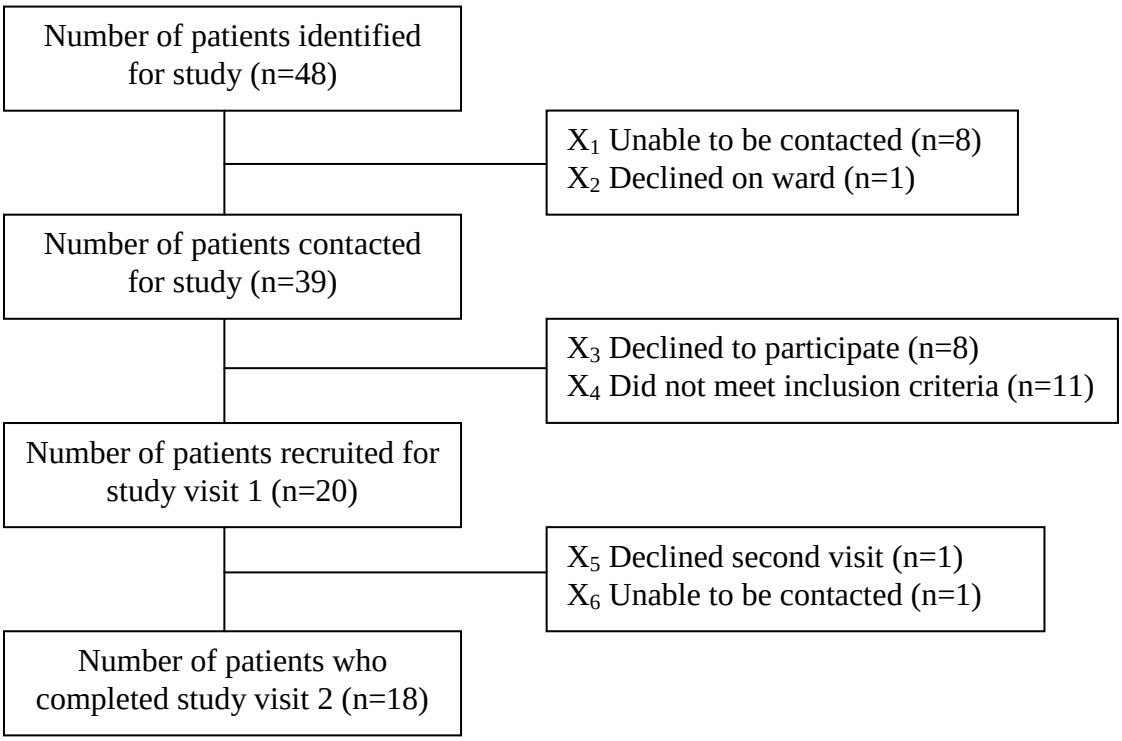

Figure 5.1: Disposition of study patients

5.2 Clinical characteristics

A total of 20 patients were included at baseline (17 males and 3 females). Of those 20 patients, 18 were followed up for the follow-up visit. The mean time between visits was 74 days. Data from one patient was not obtained for the follow-up visit due to chemotherapy for a malignant basal cell carcinoma. Data from another patient was unable to be obtained as they could not be contacted. Descriptive information including age (years), gender, body mass index (kg/m^2), ethnicity and co-morbidities is presented in Table 5.1.

Table 5.1 Descriptive information for study sample at baseline

Variable	Mean (SD)
Age (years), mean (SD)	54.4 (16)
Body mass index (kg/m^2), mean (SD)	34.7 (11)
Ethnicity:	
NZ European, n (%)	7 (35)
NZ Maori, n (%)	6 (30)
Pacific Island, n (%)	7 (35)
Co-morbidities:	
Hypertension, n (%)	13 (65)
Cardiovascular disease, n (%)	10 (50)
Diabetes mellitus, n (%)	2 (10)
Patients with at least one comorbidity, n (%)	14 (70)
Patients with two or more comorbidities, n (%)	10 (50)

5.3 Gout history

Table 5.2 displays information about patient history in relation to their gout. General information related to gout was measured only at the baseline visit and included disease duration, diagnostic criteria, site of the first gout flare, sites of acute gouty involvement, family history and number of tophi. Gout specific medications were recorded at both the baseline and follow-up visits. No significant differences were found between baseline and follow-up allupurinol, ($p = 0.06$), colchicine ($p = 0.375$), prednisone ($p = 0.219$) and diuretics use ($p = 1.000$). A significant difference was found in NSAID use between the two study visits ($p= 0.004$).

Table 5.2 Gout history

Variable	**Baseline visit (n=20)**	**Follow-up visit (n=18)**	**P-value**
Disease duration (years), mean (SD)	13.2 (11.4)	NA	
Aspirate proven disease, n (%)	12 (60)	NA	
Site of first flare: 1st MPJ, n (%) Midfoot, n (%) Ankle, n (%) Knee, n (%) Elbow, n (%) Hands, n (%)	 12 (60) 1 (5) 6 (30) 0 (0) 0 (0) 1 (5)	NA	
Other sites of involvement: 1st MPJ, n (%) Midfoot, n (%) Ankle, n (%) Knee, n (%) Elbow, n (%) Hands, n (%)	 15 (75) 2 (10) 15 (75) 12 (60) 5 (25) 9 (45)	NA	
Family history of gout, mean (%)	13 (65)	NA	
Total number of subcutaneous tophi, mean (SD)	1.90 (3)	NA	
Total number of subcutaneous tophi affecting feet, mean (SD)	0.30 (1)	NA	
Number of flares in past 3 months, mean (SD)	3.4 (3)	NA	
Allopurinol use, n (%)	8 (40)	11 (61.1)	0.06
Colchicine use, n (%)	13 (65)	9 (50)	0.375
Prednisone use, n (%)	10 (50)	5 (28)	0.219
NSAID use, n (%)	16 (80)	5 (28)	0.004
Diuretic use, n (%)	5 (25)	4 (22)	1.00

5.4 Clinical features of acute flares

The clinical features of acute flares are described in two sections. The first is related to descriptive information taken at the baseline visit, including the site(s) of the acute flare, the duration of the current flare, the presence of polyarticular involvement and the number of flares in the past three months (Table 5.3). The second section describes the clinical features of acute flares. These included: joint tenderness, joint swelling, patient global assessment and acute phase-marker/C-reactive protein (CRP). These measures along with serum urate were recorded at both the baseline and follow-up visit. Figure 5.2 shows changes in tender joint count scores during and after an acute flare, while Figure 5.3 indicates changes in swollen joint count scores during and after an acute flare. Figure 5.4 provides changes in patient global scores during and after an acute flare**.** Figure 5.5 indicates changes in C-reactive protein levels during and after an acute flare. Finally, Figure 5.6 shows changes in serum urate levels during and after an acute flare.

Table 5.3: Clinical features of gout flares

	Baseline visit (n=20)	Follow-up visit (n=18)	P-value
Site of current flare*:		NA	NA
1st MPJ, n (%)	6 (30)		
Midfoot, n (%)	1 (5)		
Ankle, n (%)	10 (50)		
Knee, n (%)	3 (15)		
Elbow, n (%)	2 (10)		
Hands, n (%)	3 (15)		
Polyarticular flare, n (%)	9 (45)	NA	NA
Duration of flare (days), mean (SD)	13 (15)	NA	NA
Tender joint count, mean (SD)	8 (9)	1 (1)	0.006
Swollen joint count, mean (SD)	3 (3)	0 (1)	<0.0001
Patient global assessment score, mean (SD)	65 (23)	32 (23)	<0.0001
C-reactive protein (mg/L), mean (SD)	54.8 (61.6)	3.2 (1.4)	0.025
Serum urate (mmol/L), mean (SD)	0.50 (0.15)	0.42 (0.12)	0.646

*These figures represent the number of patients experiencing a flare at a particular joint at baseline. Patients with polyarticular flares may have been experiencing flares at multiple joint sites.

Table 5.4: Descriptive information of measures of pain, impairment, function and disability

Variable	**Baseline Mean (SD)**	**Follow-up Mean (SD)**	**P-value**
Pain VAS	60 (28)	16 (16)	<0.001
Foot Function Index (pain)	75 (19)	34 (25)	<0.001
Structural Index (forefoot)	5 (5)	5 (5)	1.000*
Structural Index (rearfoot)	6 (3)	5 (3)	0.245
Foot Posture Index	5 (3)	6 (3)	0.132
Leeds Foot Impact Scale $_{IF}$	16 (4)	9 (5)	<0.001
Health Assessment Questionnaire-II	1.9 (0.6)	0.9 (0.6)	<0.001
Lower Limb Task Questionnaire (activity)	16 (7)	28 (7)	<0.001
Lower Limb Task Questionnaire (recreational)	4 (3)	12 (8)	<0.001
Leeds Foot Impact Scale $_{AP}$	25 (5)	18 (8)	0.002
Foot Function Index (disability)	81 (11)	41 (24)	<0.001
Foot Function Index (activity limitation)	62 (33)	25 (30)	<0.001
Total Leeds Foot Impact Scale Score	41 (7)	28 (13)	<0.001
Total Foot Function Index Score	76 (13)	36 (22)	<0.001

*All values computed over two visits were identical

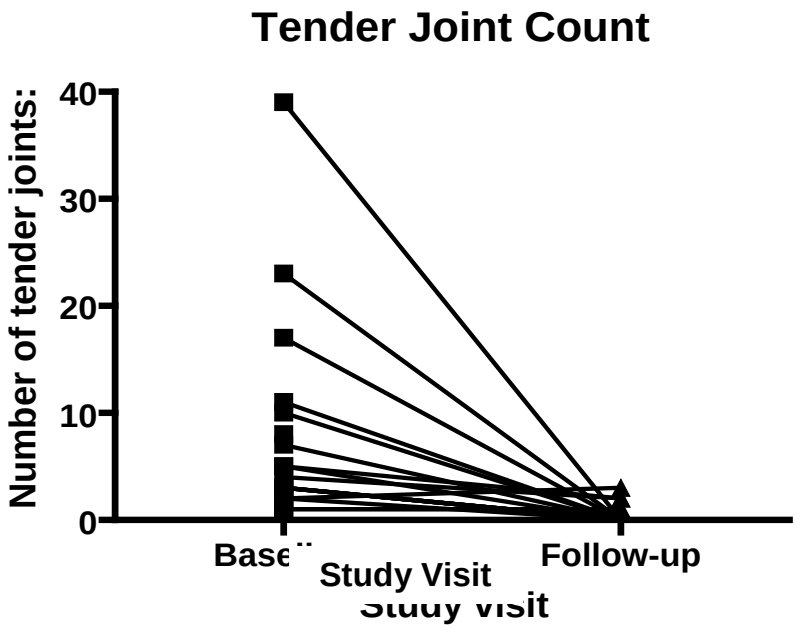

Figure 5.2: Changes in tender joint count scores during and after an acute flare.

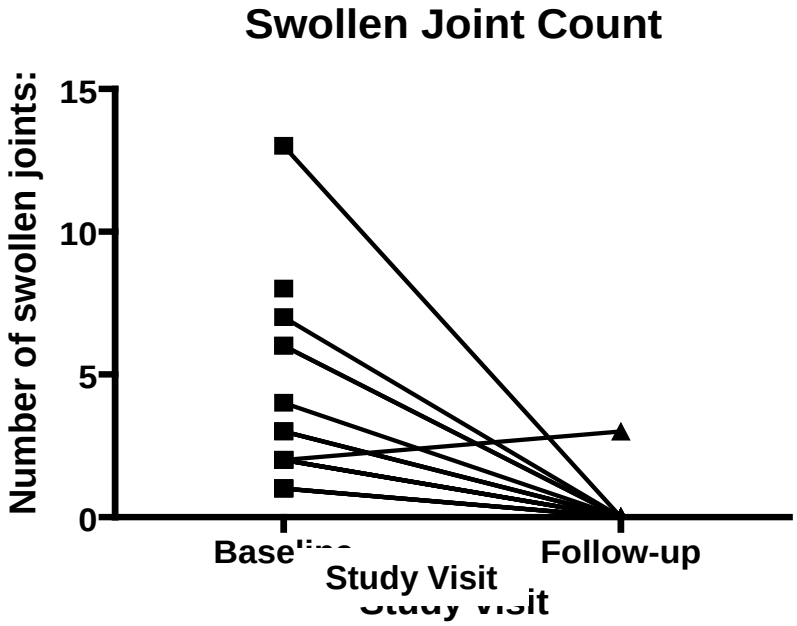

Figure 5.3: Changes in swollen joint count scores during and after an acute flare.

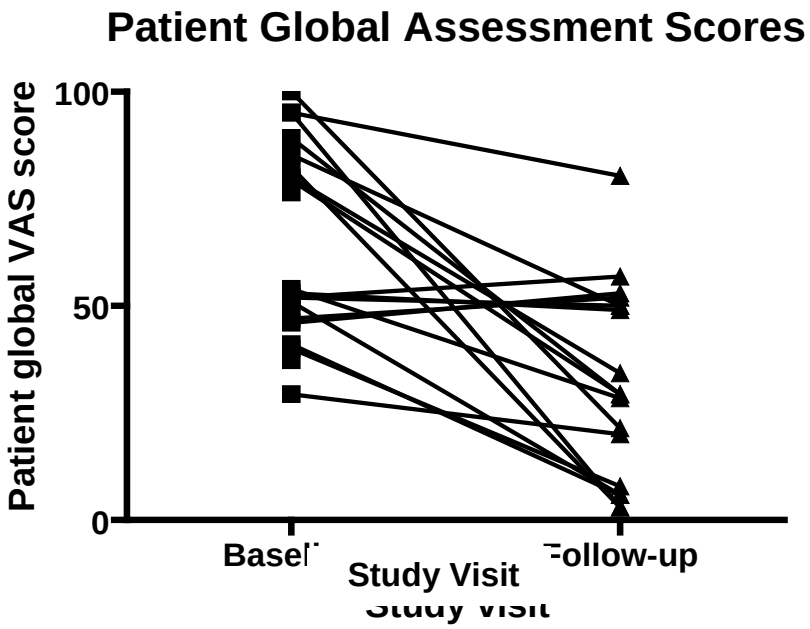

Figure 5.4: Changes in patient global scores during and after an acute flare

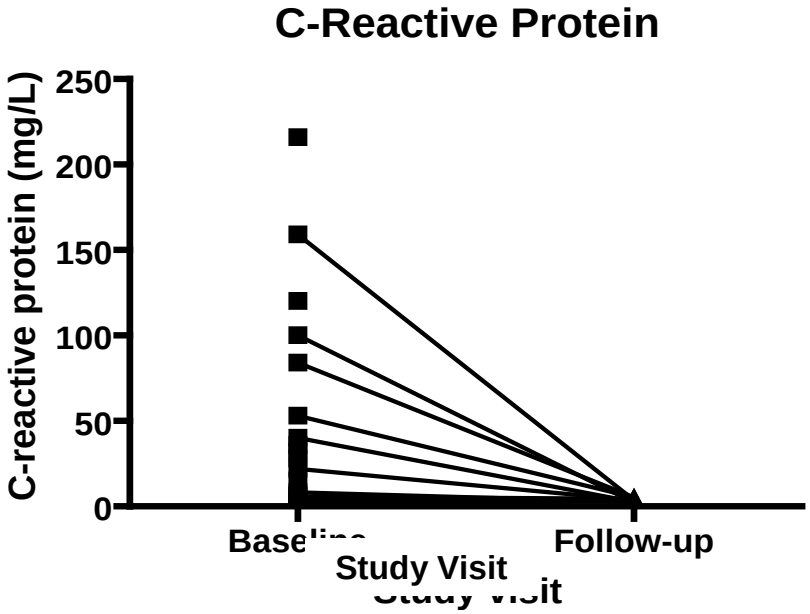

Figure 5.5: Changes in C-reactive protein levels during and after an acute flare.

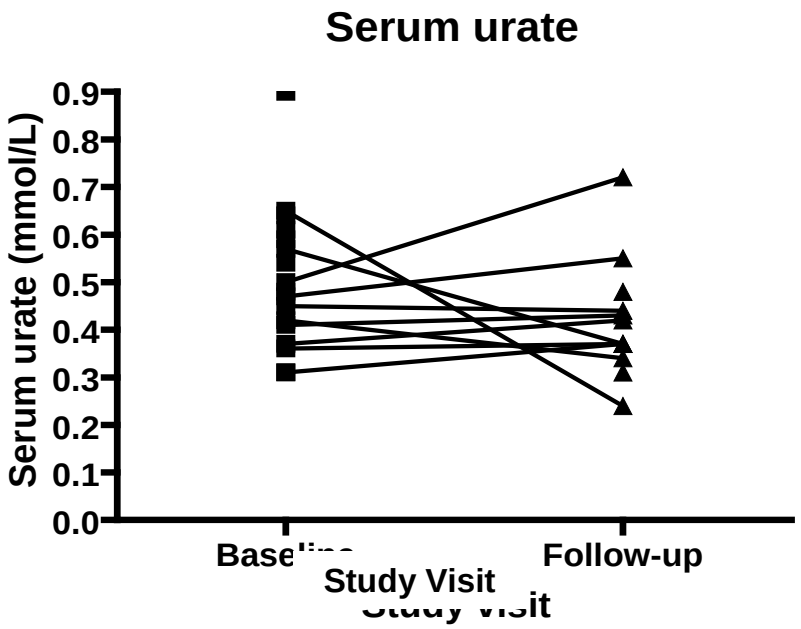

Figure 5.6: Changes in serum urate levels during and after an acute flare.

5.5 Foot pain

Based on the VAS, mean (SD) pain was significantly reduced from 60 (28) at baseline to 16 (16) at the follow-up visit, a 73% reduction, as shown in Table 5.4. Foot pain was also measured using the pain subscale of the Foot Function Index (FFI (pain). FFI (pain) was significantly reduced from 75 (19) to 34 (25), as shown in Figure 5.7.

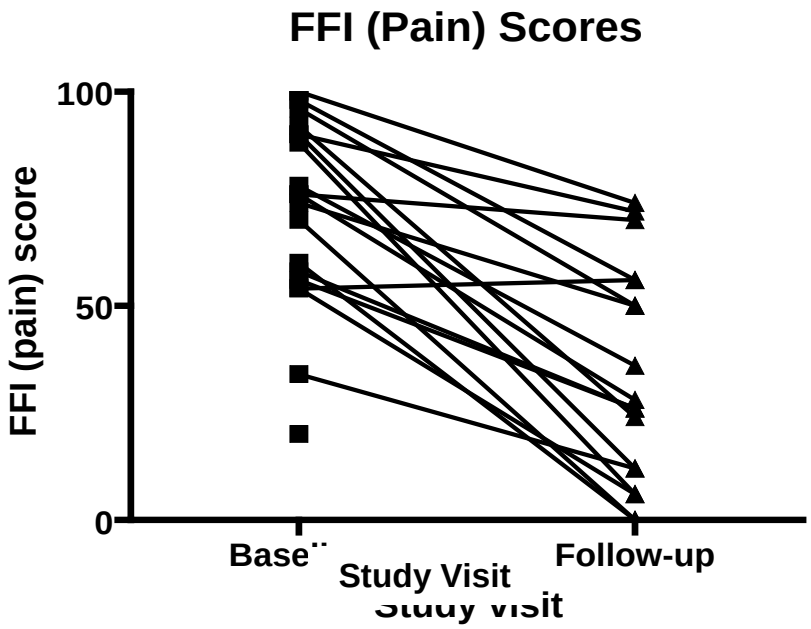

Figure 5.7: Changes in FFI pain scores during and after an acute flare.

5.6 Foot impairment

The results for the Foot Posture Index (FPI) showed no significant differences between baseline and follow-up visit (p = 0.132). Structural Index demonstrated no significant differences (p = 0.245). However, the $LFIS_{IF}$ showed significant differences between baseline and follow-up visit (p = <0.001). Figure 5.8 illustrates the changes in $LFIS_{IF}$ scores between the two study visits.

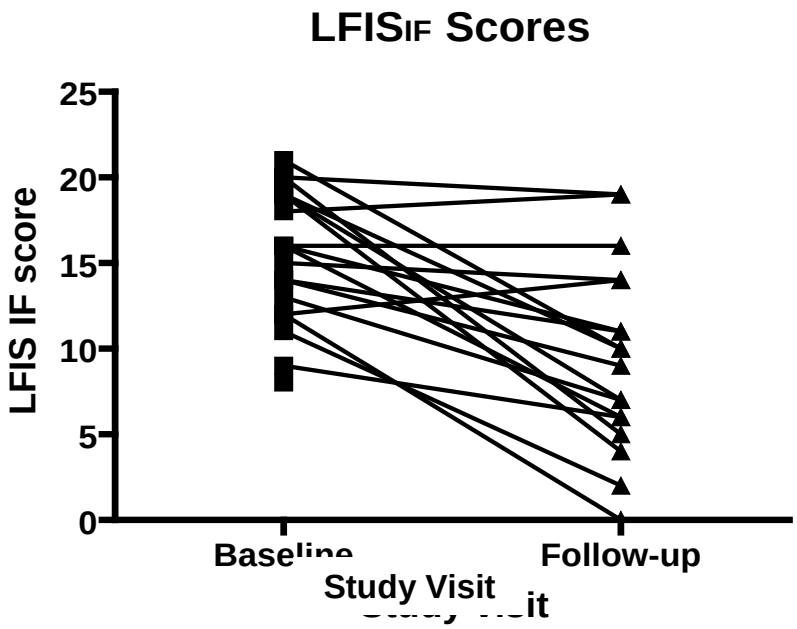

Figure 5.8: Changes in $LFIS_{IF}$ scores during and after an acute flare.

5.7 Foot function

The results for the HAQ-II scores were significantly reduced between the two study visits ($p = <0.001$). Significant differences were also found between the ADL and recreational domains of the LLTQ ($p = <0.001$). Figure 5.9 illustrates the HAQ-II changes between baseline and follow-up visits. Figures 5.10 and 5.11 illustrate the changes between the baseline and follow-up visits for the LLTQ ADL and LLTQ recreation domains, respectively.

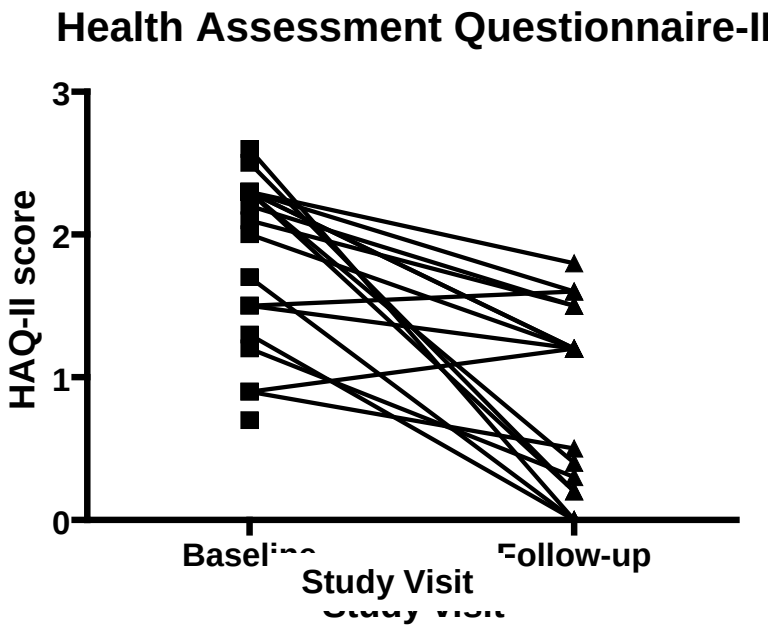

Figure 5.9: Changes in HAQ-II scores during and after an acute flare.

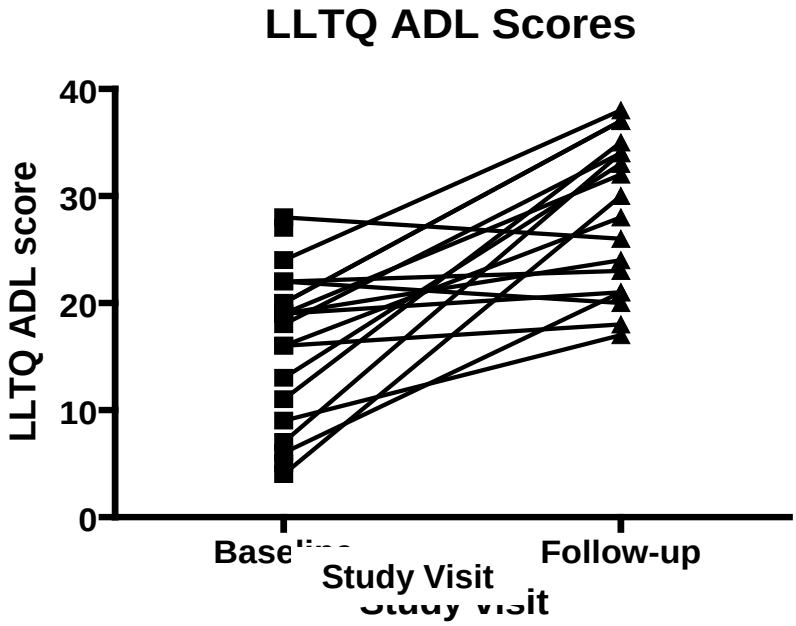

Figure 5.10: Changes in LLTQ ADL scores during and after an acute flare.

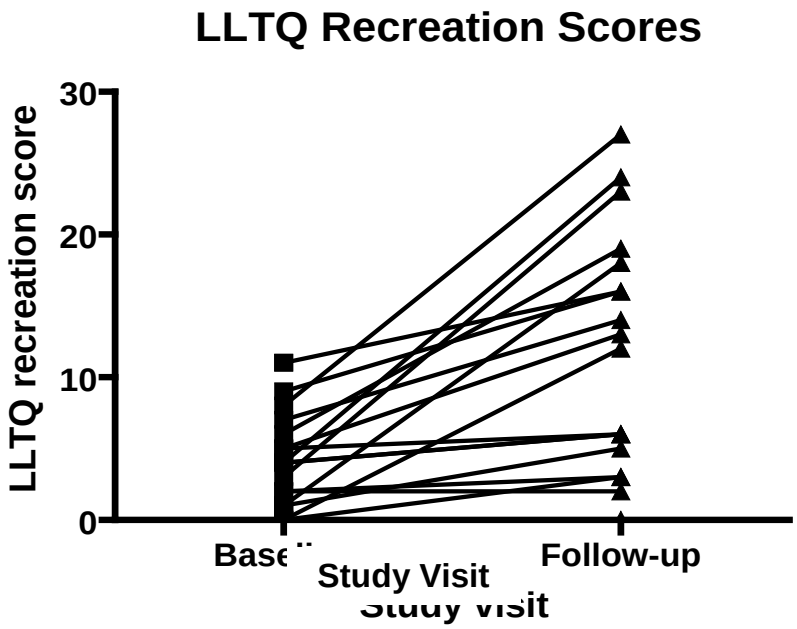

Figure 5.11: Changes in LLTQ recreation scores during and after an acute flare.

5.8 Foot disability

The results (Table 5.4) showed significant differences between baseline and follow-up visit with all foot disability scores ($LFIS_{AP}$, FFI (disability), FFI (activity limitation), LFIS (total score) and FFI (total score). Figure 5.12 illustrates changes in $LFIS_{AP}$ scores during and after an acute flare. Figures 5.13 and 5.14 illustrate the changes between the baseline and follow-up visits for the FFI (disability) and FFI (activity limitation) domains, respectively.

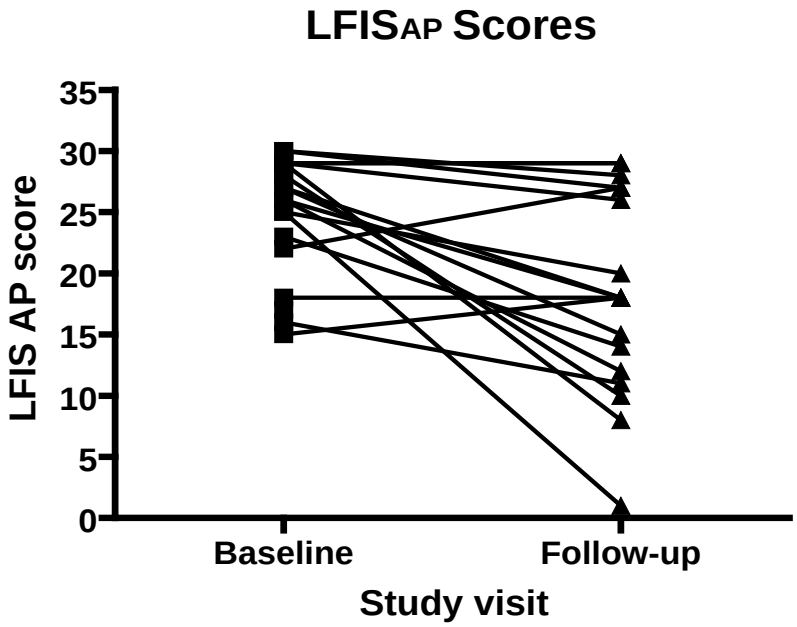

Figure 5.12: Changes in $LFIS_{AP}$ scores during and after an acute flare.

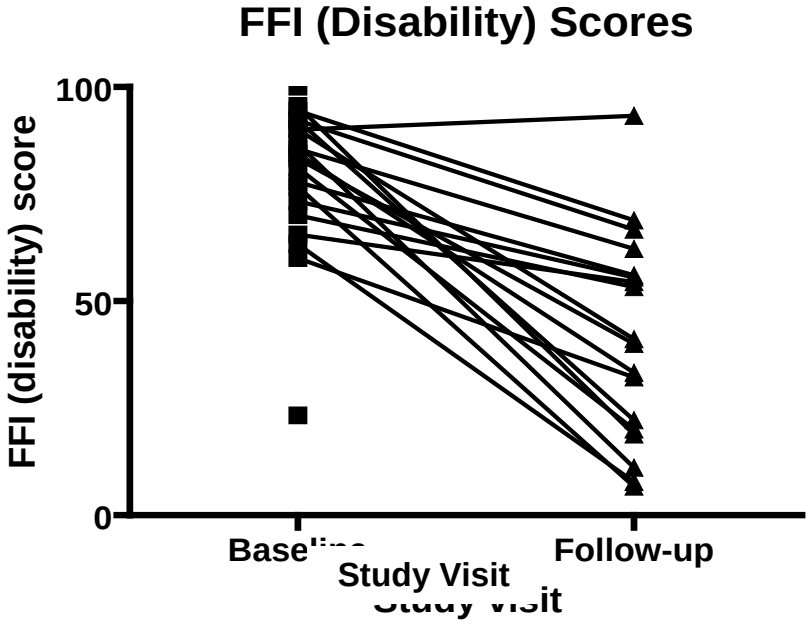

Figure 5.13: Changes in FFI (disability) scores during and after an acute flare.

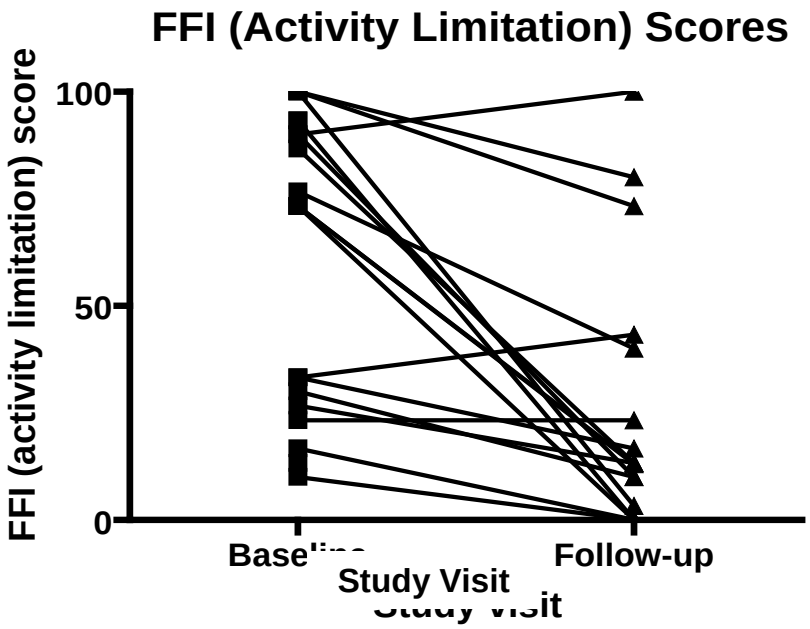

Figure 5.14: Changes in FFI (activity limitation) scores during and after an acute flare.

5.9 Summary

Significant differences were found in all flare characteristics measured, except for serum urate between the two assessment points. Acute gout flares were associated with high levels of pain, impairment and disability. Reduced function with every day and recreational tasks was also reported during acute flares. Significant differences in foot pain, impairment, function, and disability scores were observed between the baseline and follow-up study visits.

Chapter 6: Discussion

6.1 Introduction

The aims of the current study were (a) to describe the prevalence of foot involvement in patients with acute gout; (b) to examine the changes over time of clinical features associated with acute gout, and (c) to determine the impact of acute gout on foot pain, impairment, function and disability. It was hypothesised that significant differences in foot pain, impairment, function and disability would be found between the baseline and follow-up visit. It was also hypothesised that there would be significant differences in the clinical features associated with acute flares between the baseline and follow-up visit. The first section of the discussion describes the demographic and clinical information of the patients. The following sections address the above mentioned aims. Finally, study limitations and future direction are presented.

6.2 Clinical Characteristics

The current study was an observational follow-up design, assessing patients with acute gout flares and again several weeks later once the symptoms of the flare were absent. Twenty patients were assessed at baseline and eighteen of those were assessed again at the follow-up visit. The findings suggested that the sample could be classified as obese. BMI scores were consistent with previous work investigating acute gout (Terkeltaub et al., 2010).

The ethnic make-up of the sample was 35% Pacific Island, 30% Maori, 35% New Zealand European. These numbers are similar to those reported in a previous gout study with high numbers of Maori and Pacific Island participants (Dalbeth et al., 2007). However, the ethnic make-up of the current study may not be representative of gout outside of Auckland where the majority of these ethnic groups live in New Zealand (Statistics New Zealand, 2006; Statistics New Zealand and Ministry of Pacific Island Affairs, 2010).

Co-morbidities were a common feature with 65% of patients having at least one, and they included hypertension, diabetes mellitus or cardiovascular disease, with 55% having two or more coexisting conditions. Hollis-Moffat et al. (2009) reported co-morbidities in 256 gout patients of

various ethnic groups in New Zealand. Type II diabetes was present in 18-25% of patients, hypertension was reported in 56-67% of patients and cardiovascular disease was reported in 30-56% of patients. Halpern et al. (2009a) reported similar rates of co-morbidities in a sample of 18,243 patients from America.

Co-morbidities such as obesity, hypertension, diabetes, cardiovascular disease and renal disease have been suggested as risk factors in the development of gout (Choi, Atkinson, Karlson & Curhan, 2005; Facchini, Chen, Hollenbeck & Reaven, 1991; Singh, Reddy & Kundukulam, 2011). Patients who are hospitalised due to acute flares have higher rates of co-morbidities such as hypertension and diabetes (Hutton, Gamble, Gow & Dalbeth, 2009). Wu et al. (2011) reported that patients with ≥6 acute flares per year had significantly higher rates of emergency department admissions, hospitalisations and use of other healthcare services compared to those who experienced between 3 and 5 flares per annum. The authors stated that their patient's appointments were often related to co-morbidities associated with gout such as hypertension, cardiovascular disease, diabetes and obesity.

6.3 Gout History

Family history was higher than most other reported studies with 65% of patients having another family member with gout. Other studies undertaken outside of New Zealand have reported a family history being evident between 35-37% (Chou & Lai, 1998; Grahame & Scott, 1970; Lee et al., 2009). A possible reason for the differences between the current study and previous work may be due to the large number of Maori and Pacific Island patients involved in the current study. Maori have higher serum urate levels than their European counterparts (Prior, 1981). Maori are also reported to develop gout earlier (Klemp et al., 1997). Several studies (Hollis-Moffatt et al., 2009; Merriman & Dalbeth, 2011) have also reported genetic factors which may influence the prevalence and severity of gout in these populations.

Current medications were recorded at both study visits. Colchicine was used by 65% of patients at baseline, with 50% of patients using the drug at the follow-up visit. Colchicine is used for the treatment and prophylaxis of acute flares and is often continued for several months after a

flare to help prevent subsequent gout flares associated with the commencement of urate lowering therapy such as allopurinol (Borstad et al., 2004). Allopurinol use at baseline was significantly lower than that recorded at the follow-up visit. The allopurinol use in the current study was lower than that reported in other research undertaken in New Zealand (Dalbeth et al., 2007; Rome et al., 2010). Sub-optimal allopurinol use has been described in several studies (Harrold et al., 2009; Roddy et al., 2010). The commencement of urate-lowering therapy is associated with more acute flares (Shoji, Yamanaka & Kamatani, 2004; Wortmann, MacDonald, Hunt & Jackson, 2010). Several studies have also reported issues surrounding patient compliance with urate-lowering therapy (Halpern, Mody, Fuldeore, Patel & Mikuls, 2009b; Harrold et al., 2009). The changes observed may also be due to the fact that some patients in the current study were experiencing their first acute flare at baseline. There is evidence (Becker et al., 2005; Shoji et al., 2004) supporting the use of urate-lowering therapy to reduce the risk of recurrent gout flares long term. Baseline prednisone use was 50% compared to 27.8% of patients at the follow-up visit. Non-steroidal anti-inflammatory drugs (NSAIDs) were used by 80% of patients at baseline and 27.8% of patients at the follow-up visit. The use of colchicine, NSAIDS and corticosteroids (prednisone) is considered first line treatment for gout (Schlesinger, Schumacher, Catton & Maxwell, 2006; Zhang et al., 2006b).

6.4 Prevalence of acute gout in the foot

Acute flares affected the ankle joint (50%) and the 1st MPJ (30%) primarily. Flares affecting a joint within the foot and ankle were seen in 70% of patients, with 85% of patients experiencing an acute flare in a lower limb joint at the baseline assessment. Several studies investigating acute gout have reported the sites at which flares were occurring (Garcia et al., 1997; Grahame & Scott, 1970, Janssens et al., 2008; Park et al., 2000; Puig et al., 1991; Roddy et al., 2007a). Of the patients in the current study, 60% experienced their first gout attack at the 1st MPJ, with 75% having suffered at least one attack at the 1st MPJ during their disease duration. Table 6.1 compares the prevalence of gout affecting the 1st MPJ in the current study to previous studies.

Table 6.1: Prevalence of 1st MPJ involvement in patients with acute gout

Authors	Country	Nos	Initial presentation at the 1st MPJ	Previous attacks at the 1st MPJ
Grahame & Scott, (1970)	UK	354	Not reported	76%
Puig et al., (1991)	Spain	257	70%	79%
Garcia et al., (1997)	Guatemala	148	23%	73%
Park et al., (2000)	Korea	108	55%	62%
Roddy et al., (2007a)	UK	164	Not reported	66%
Janssens et al., (2008)	Netherlands	120	63%	Not reported
Current study	New Zealand	20	60%	75%

The prevalence of gout affecting the 1st MPJ has previously been reported throughout Europe (Grahame & Scott, 1970; Janssens et al., 2008; Puig et al., 1991; Roddy et al., 2007a), Asia (Park et al., 200) and Central America (Garcia et al., 1997). These data suggests that the initial presentation of gout typically occurs at the 1st MPJ, with between 60-79% of patients experiencing a flare at this site during the course of the disease. The findings from the current study in relation to 1st MPJ involvement are similar to previous studies, which may suggest that gout has a 'typical' initial presentation in the foot, regardless of ethnicity or country of origin.

The mean number of flares reported by patients in the current study over the previous 3 months was 3.4. Previous studies have reported the mean number of flares experienced by patients annually ranging from 3.1 to 3.5 (Janssens et al., 2008; Rome et al., 2010). Yu (1984) investigated 1,800 patients with gout and found that 70% of patients experienced less than 4 acute flares each year. It is also well recognised that recurrent acute flares can lead to radiographic damage and tophus formation (Dalbeth et al., 2009; Kumar & Gow, 2002). Tophi are also known to cause mechanical problems at various sites in the body, including the foot (Kumar & Gow, 2002). Several authors have reported that gout patients who experience recurrent gout flares have the poorest quality of life (Becker et al., 2009; Lee et al., 2009).

6.5 Flare Characteristics

It was hypothesised that there would be changes in flare characteristics between the two study visits. Polyarticular flares were a common occurrence with 45% of patients experiencing multiple joints affected at the baseline assessment. Other studies have reported the prevalence of polyarticular flares as being 11% (Grahame & Scott, 1970), 24% (Rubin et al., 2004) and 20% (Willburger et al., 2007). The higher level noted in the current study might be due to the high number of Maori and Pacific Island patients within the study sample. In the current study all patients were taking at least one of; NSAIDs, colchicine or prednisone at baseline. The mean duration of the flares in the current study was 13 days, measured from the initial onset of symptoms to the first study visit. This appears longer than the duration of flares reported in previous work (Borstad et al., 2004; Doherty, 2009; Douglas & Thompson, 1970; Garcia et al., 1997), however, it is not always clear as to how these time periods were measured. Lindsay et al. (2011) described patients with severe gout who experienced flare symptoms lasting over six months. The extended duration of flares and high occurrence of polyarticular flares in the current study may suggest a sample with severe gout.

6.5.1 Joint tenderness and joint swelling

Mean scores for tender and swollen joint counts at baseline were both significantly higher than those from the follow-up visit. Changes in joint count scores may to be due to the remission of ‘typical’ flare symptoms (pain, swelling, redness and erythema) over time and the effects of pharmacological interventions. Reductions in joint tenderness and swelling following acute flares have also been reported in previous studies investigating the use of NSAIDs and COX-2 inhibitors (Rubin et al., 2004; Schumacher et al., 2002). Tender joint scores at the follow-up visit may also be indicative of other joint pathology such as tophi or osteoarthritis. One patient displayed an increase in swollen joints although this was believed to be a side-effect of medication causing oedema-like symptoms around the ankles. The higher number of tender joints compared to swollen joints reported at baseline may be related to the impact of acute flares on neighbouring joints and the high prevalence of polyarticular involvement reported in the current study.

6.5.2 Patient global assessment

A significant reduction in patient global assessment scores was found between the two study visits. Maccagno et al. (1991) measured patient global assessment using a 5-point Likert scale and reported a 59% and 47% improvement in two groups of patients with acute flares over a 7 day period. This finding is similar to the 51% improvement observed in the current study. Baseline patient global scores in the current study were higher than those reported in RA (Parekh & Taylor, 2010; Wolfe et al., 2005), although follow-up scores were similar to those reported in RA. Changes in patient global scores may be due to flare symptoms and their subsequent impact on an individual's everyday life. Qualitative research exploring gout has reported themes of pain, isolation, debilitation, dependency and work disability in patients suffering from acute flares (Lindsay et al., 2011). The presence of co-morbidities may also influence gout patient's perceptions of their health.

6.5.3 Acute-phase marker

CRP levels, a marker of acute flares, were significantly higher at baseline compared to the follow-up visit. Elevations in CRP during acute flares have been reported in other studies (Janssens et al., 2008; Urano et al., 2002; Woolf et al., 1985). The higher levels of serum CRP found in the current study may be due to the high number of polyarticular flares. Woolf et al. (1985) reported a significant correlation (r=0.62) between peak serum urate and the number of joints affected by flares. Mean CRP at the follow-up visit was within normal limits, suggesting that the flare symptoms had reduced. Differences in CRP may be due to the remission of flare symptoms and the effects of pharmacological interventions. The use of NSAIDS reduces CRP levels following acute flares (Woolf et al., 1985). In the current study 90% of patients were taking at least one of a NSAID or corticosteroids at the time of their acute flare.

6.5.4 Serum urate

Mean serum urate values were higher at baseline compared to the post visit, although the difference was not statistically significant. Other studies have reported mixed results in regards to differences in urate levels during acute flares compared to intermittent/chronic stages. Urano et al. (2002) reported a significant reduction in serum urate levels during acute flares. Contrary to this, Ruotsi and Vainio (1978) reported higher serum urate levels during acute flares, in two groups, one of which was a significant difference. Wang et al. (2009) also reported a decrease serum urate pre and post-intervention, however, the time between assessments was 28.9 (3.6) months and changes may be related to urate lowering therapy. Reasons for changes in serum urate may be attributed to a number of factors. Urano et al. (2002) reported that an increase in urinary excretion of uric acid was associated with lower serum urate levels during flares. The authors also suggested that part of the inflammatory process of acute flares may influence the reduction in serum urate during flares. Pharmacological interventions, such as urate lowering therapy are also prescribed for acute flares.

6.6 Foot Pain

Baseline pain in the current study can be classified as moderate to severe based on scoring systems used in previous studies measuring pain with a 100mm VAS (Collins, Moore & McQuay, 1997; Kelly, 2001). Pain levels reported at baseline were higher than those previously reported in RA (Ritter, González, Laurent & Lorig, 2006; Wolfe et al., 2005; Wolfe & Michaud, 2007), but consistent with other studies investigating acute gout (Janssens et al., 2008). Overall, there was over a 70% significant reduction in general pain on VAS from baseline to the follow-up visit, with a mean difference of 44.1. These results are similar to previous work by Janssens et al. (2008) who reported a mean reduction in pain of 44.7 on a 100mm VAS over a 90 hour period in patients with acute gout. Rubin et al. (2004) reported pain in two groups using a 5-point Likert scale, with scores of 2.9 and 3.0 at the initial assessment to 0.9 and 1.0 after 8 days. This indicates a 70% and 68% reduction in pain suffered by the two groups over that 8 day period. Maccargno et al. (1991) reported a 62% and 59% reduction in pain over a 7 day period.

Previous studies have measured pain using generic tools such as 100mm VAS (Janssens et al., 2008) and Likert scales (Rubin et al., 2004) but in the current study a more specific tool measuring foot pain was used. No previous studies have reported foot pain in acute gout using a foot specific measure. A significant difference was seen in foot pain between the baseline and follow-up visits with a 55% reduction in pain. Baseline and follow-up visit FFI (pain) scores were higher than those reported by Rome et al. (2010) in patients with chronic gout. The high levels of foot pain found at both study visits may be attributed to obesity. Obesity is associated with an increased risk of plantar heel pain (Wearing, Hennig, Byrne, Steele & Hills, 2006). We can speculate that the foot pain described by the gout patients in the current study may have not always been attributed to gout alone and that other coexisting musculoskeletal conditions (plantar heel pain) may also be present in the foot. Changes in pain levels may also be attributed to pharmacological interventions (Janssens et al., 2008; Rubin et al., 2004) and the time between the two assessments. The priority of acute gout flares is to address the primary symptoms (pain, swelling, inflammation), which is typically achieved using a combination of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and/or colchicine (Eggebeen, 2007; Hoskison & Wortmann, 2006).

At the follow-up assessment, pain levels on both VAS and the FFI (pain) subscale had not reduced back to zero, suggesting that general and foot-related pain may be a constant feature in patients with recurrent flares. This depiction of pain has been reported by Lindsay et al. (2011) where patients with severe gout described living with constant pain. These constant levels of pain may influence some of the trends relating to function, impairment and disability found in the current study.

6.7 Foot Impairment

No changes were found between forefoot SI scores between baseline and follow-up. This is possibly to be due to fixed digital deformities (HAV, claw toes, Tailor's bunion) that once present, will not change over time. However, changes in rearfoot SI scores were likely to be attributed to flare symptoms (pain, swelling) which in turn prevented standardised assessment of patients at baseline. These factors would have an effect on the measurement of calcaneal joint position, assessing total ankle joint range of motion and classification of foot type (pes planus). Maccagno et al. (1991) reported reduced ROM in joints affected by acute flares. Platto et al. (1991) stated that rearfoot deformity was associated with greater levels of impairment to gait compared to forefoot deformity in RA. Rearfoot SI scores in the current study were similar to those reported in RA (Silvester et al., 2010). Although the rearfoot aspects of the SI were not always able to be assessed from standardised positions during baseline assessments, this in itself highlights the impact of acute flares on impairment in gout. Helliwell et al. (2005) also stated that the SI is limited in its ability to monitor small changes over time.

The Leeds Foot Impact Scale Impairment/Footwear ($LFIS_{IF}$) subsection was used to assess impairment at both baseline and the follow-up visit. A moderate to high degree foot impairment has been classified as a $LFIS_{IF}$ score >7 (Turner et al., 2006). Based on these figures, all 20 patients from the baseline visit had moderate to high levels of foot impairment, with over 60% of the 18 follow-up visit patients having a moderate to high degree of foot impairment. Follow up scores were higher than those reported by a study on chronic gout (Rome et al. 2010). Impairment scores did not reduce at the follow-up visit. We can suggest that this may be due to the merging of impairment and footwear into a single subsection. Footwear represents over half of the 21 questions, giving it a significant weighting towards the overall score.

6.8 Foot Function

HAQ-II scores were significantly reduced from baseline to the follow-up visit indicating that function is considerably affected by acute flares. HAQ-II scores taken at the follow-up visit were higher than those reported in previous studies investigating chronic gout (Rome et al., 2010; ten Klooster et al., 2011). The HAQ-II scores reported at baseline were also higher than those reported in other joint diseases such as RA, non-inflammatory disorders (osteoarthritis, fibromyalgia) and auto-immune connective tissue disorders (systemic lupus erythematosus, systemic sclerosis) (Parekh & Taylor, 2010). High baseline HAQ-II scores may be due to the high number of polyarticular flares seen at baseline. The items of the HAQ-II include tasks which involve the upper and lower limb. Another reason for the higher HAQ-II scores at the follow-up visit may also be due to presence of tophi. In the current study 40% of patients had tophi, the majority of which were in the upper limb. A higher prevalence of upper limb tophi has been reported in another study (Schumacher et al., 2005). Dalbeth et al. (2007) reported that tophi had a significant impact on hand function in gout patients.

There were significant differences in scores between the baseline and follow-up visit for both the activities of daily living (ADL) and recreational activities domains of the LLTQ. These changes in scores indicate that lower limb function is significantly reduced during an acute flare. Despite this, the scores recorded at the follow-up visit, showed that patients were still experiencing deficits in lower limb function. The mean ADL score from the follow-up visit in the current study was similar to studies on chronic gout (Survepalli, 2009) and knee OA (Reid & McNair, 2011). However, the mean score for the recreational domain in the current study was much lower. Qualitative work by Lindsay et al. (2011) described patients having to give up sporting activities because of gout. Overall, this suggests that recurrent acute flares play a significant role in patient's lower limb function, particularly with recreational activities. Brown, Dare, Smith and Meyers (1987) reported that the inability to undertake everyday tasks as the most commonly reported problem identified by gout patients. Difficulties with functional tasks may also be related to co-morbidities such as obesity. Lazzer et al. (2003) reported that obese

individuals expend more energy when walking and were also less likely to partake in sporting activities.

6.9 Foot Disability

Disability was measured using the activity limitation/participation restriction subsection of the Leeds Foot Impact Scale ($LFIS_{AP}$) and the disability and activity limitation subscales of the Foot Function Index (FFI). Based on these figures described by Turner et al. (2006), all patients in the current study had moderate to high levels of disability at baseline, with 89% of the follow-up patients having moderate to high levels of disability. A significant reduction in $LFIS_{AP}$ scores was also found between the two study visits. Changes in scores may be attributed to the ethnic make-up of the study sample. Several questions in the $LFIS_{AP}$ subsection mention family and interaction with others who are close to the individual. Both Maori and Pacific Island communities are strongly family orientated, with management of medical conditions often not limited to the individual (Gibbs, Dawson, Forsyth, Mullen & Tonu Tanga, 2004). Qualitative work by Lindsay et al. (2011) described the massive burden of acute gout on the individual's ability to support their family. Scores from the follow-up assessment were higher than those reported by Rome et al. (2010) in patients with chronic gout. This may further emphasise the impact of an acute flare on gout patient's life.

Mean baseline scores for the FFI disability and activity limitation subsections were significantly higher than those at the follow-up visit. Follow-up visit scores were also higher than those reported in chronic gout (Survepalli, 2009). FFI disability and activity limitation scores were also higher than those reported in patients requiring foot and ankle surgery (SooHoo et al., 2006). The differences between baseline and follow-up visit scores may be due to the similar changes observed in impairment and functional scores, from baseline to the follow-up visit. Impairments lead to reduced function, which lead to disability.

6.10 Limitations

The following section discusses the limitations associated with the current study. The current study included a small sample of participants, with 20 being assessed at baseline and 18 of those being assessed at the follow-up visit. Recruiting patients for the current study was difficult as patients were often reluctant to participate as the pain they were experiencing was so severe. Significant differences were reported across the majority of outcome measures. Many of the information recorded under clinical characteristics shared similarities to other studies undertaken in New Zealand (Dalbeth et al., 2007; Hollis-Moffat et al., 2009; Rome et al., 2010).

Currently, there are no specific outcome measures related to gout in the foot. Many of the measures used in the current study were originally designed for the assessment of patients with RA. Despite there being some similarities in pain, function and disability between the two different populations, capturing an accurate account of the impact of gout was difficult. Foot pain, impairment and disability exist during both the acute and chronic stages of the disease with some patients experiencing rapid fluctuations between the two, which may be due to recurrent acute flares. Questionnaires which ask for an account of the previous week may in fact capture both acute and chronic symptoms. Others which record information at a single, specific time may not provide a broad enough representation of the patient, as patients often expressed having ‘good’ and ‘bad’ days. It also appears that priorities of patients during the acute and chronic are different. Typically the patient goals during acute flares are focused on reducing pain and swelling, whereas during the intermittent/chronic stage patient goals may be more variable.

Another limitation regarding the questionnaires used is that some of these measured multiple domains within a single subsection. For example, the $LFIS_{IF}$ subscale grouped impairment and footwear into a single section. Thus it was difficult to appreciate the scores associated with separate constructs. The aim of the current study was to examine the impact of gout on the foot, however, some questionnaires such as the HAQ-II assess both upper and lower limb function. Isolation of particular body parts or outcome domains may not always be suitable in gout as involvement may be widespread and the prevalence of co-morbidities is extremely

common. Future work that may investigate specific body parts such as the foot should investigate the validity of foot-specific measures in a gout sample.

6.11 Future directions

The following section will discuss potential areas for future research, derived from the findings of the current study. It is recognised that gout is extremely prevalent within New Zealand compared to other parts of the world. Over the past 30 years, the prevalence of gout in New Zealand has increased significantly (Winnard et al., 2008). Future work could investigate the incidence of gout patients developing foot problems. The study could examine gout patients of all ages, gender and ethnicity from various geographical areas of New Zealand, ranging from rural to urban communities.

The flares seen in the current study displayed 'typical' clinical characteristics, with a high number affecting the 1st MPJ and ankle joint. Future work could investigate the biomechanics of these joints in gout patients during everyday activities such as walking. Rome et al. (2010) reported abnormalities in several gait parameters in patients with chronic gout. Improved understanding of foot function may help to describe some of the trends related to foot pain, impairment and disability in gout patients.

The current study found that acute flares were associated with high levels of foot pain, impairment, and disability. Future work could be directed towards investigating foot problems commonly seen in gout patients by developing a gout specific tool. These could include the presence of digital deformities, tophi and range of motion at the 1st MPJ, subtalar and ankle joints. This may further lead to the development of a scoring system for foot impairments in gout patients. This could then be validated against pre-existing tools designed for other rheumatological conditions. Improved knowledge of foot-related impairments in gout patients may lead to more conclusive reasons surrounding the reduced function and high levels of disability found in the current study.

Several outcome tools originally designed for different groups were used in the current study, measuring a range of different constructs. Further research into gout within the foot will dictate whether or not new measures are needed, or for the suitability of other tools used in the gout population to be tested. Significant differences were found between the two stages in pain, function/impairment and disability. This suggests that the needs of gout patients may change dependent on the 'stage' of their disease. Further research would need to be undertaken to determine the suitability of current available tools in the assessment of the feet of gout patients, both during the acute and chronic/intermittent phases.

6.12 Conclusion

Acute gout is characterised by excruciating pain, swelling and erythema of the affected joint. A critical review of the impact of gout on foot pain, impairment, function and disability was undertaken to identify gaps in the literature. The acute flares experienced by patients in the current study demonstrated clinical characteristics that are often observed with acute gout. The foot and ankle were the most common sites of involvement for acute flares which is consistent with previous studies on acute gout. Other typical features include elevated CRP at the time of the reported flares. Despite having 'classic' signs of acute flares, the current observed flares appeared to occur more frequently and lasted for greater periods of time. There was also a higher number of polyarticular flares reported in the current study compared to the figures reported in previous work. These findings may further emphasise the severity of gout within New Zealand.

Acute gout flares were associated with high levels of foot pain, impairment and disability. Significant differences in foot pain, impairment, function and disability was observed between the two study visits. Pain and disability scores did not return to normative levels after the acute flares had subsided, suggesting that gout patients suffer constant levels of foot pain. Limitations of the current study demonstrate the lack of reliable and validated outcome tools to assess the feet of gout patients. Future work could be directed towards further investigating the reasons for the high levels of foot pain, impairment and disability associated with acute gout. The incidence of foot related problems is also another area that needs to be explored. The current

work is novel and has identified that there is a growing need to address the impact of gout on foot pain, impairment, function and disability.

Declaration of conflict of interest

There is no conflict of interest. The researcher has no affiliation with or financial involvement in any organisation or entity with any direct commercial interest and it is a non-profitable research.

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Appendices

Appendix 1: American College of Rheumatology Criteria for the Classification of Acute Arthritis for Primary Gout (Wallace et al., 1977)

American College of Rheumatology criteria for the classification of acute arthritis of primary gout.
Clinical diagnosis requires A, B or C to be met:
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. At least six of the following findings:
1. More than one attack of acute arthritis 2. Maximum inflammation develops within 1 day 3. Monoarthritis attack 4. Redness over joints 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. Asymptomatic swelling within a joint on radiography 11. Subcortical cysts without erosions on radiography 12. Monosodium urate monohydrate crystals in joint fluid during attack 13. Joint fluid culture negative for organisms during attack

Appendix 2: Patient Information Sheet

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TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Participant Information Sheet

Foot health problems in acute gout

An Invitation

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. This is part of a master's study being undertaken at AUT University by Michael Frecklington (researcher).

What is the purpose of this research?

We are interested in finding out how acute gout affects your life. There has been a lot of work done studying how other types of arthritis affect the lives of patients. However, there have been very few research studies examining how gout influences people's ability to manage with day to day activities associated with your feet. Because of the problems with acute gout we would like to look at your feet.

What will happen in this research?

The study involves asking you questions about your everyday foot health problems at the time that you have a gout attack. The research team will also ask questions about your footwear and any problems with pain and disability. The researcher will then invite you back in about 6 weeks and ask the same questions.

The researcher will also ask that you agree to have a blood test taken as part of the research study. We will study some your blood for factors that may cause joint inflammation or damage. The researcher may freeze small amounts of your blood and keep this stored for up to ten years. The blood collections will be kept for ten years and then destroyed, according to the usual medical regulations. You may wish to discuss this process with your whanau before agreeing to take part in this research study.

Your participation is entirely voluntary (your choice). If you change your mind about participating after your study visit, you can withdraw your data up to one month after the study visit without giving a reason. If you wish to withdraw your data, please contact Professor Rome (contact details above). You do not have to take part in this research study, and if you decide not to take part or withdraw from the study, this will not affect your normal medical care in any way. The assessment will take about 30 minutes to complete.

The researcher would like to ask you to consider taking part in our research study. This will involve an assessment at the time of your clinic visit or hospital admission with a gout attack. During this assessment, we will do a number of tests with you:
1. Ask questions about your gout and your general health.
2. Examine the joints in your foot.
3. Ask you to fill in forms to understand how gout affects your life.
4. Take photographs of your feet.
6. Look at your footwear.
7. Take a blood test of up to 4 teaspoons of blood [blood specimens can be returned on request].

The researcher will then invite you back to the clinic six weeks later to repeat these tests. This will allow us to compare your results at the time of your gout attack with your usual function.

What are the benefits?

The research team will be happy to give you information about the progress of the project and about future projects at your request at any time. The researcher will keep you informed of the results of the study. Please note that there may be a delay between your study visit and when the results are made public.

What are the costs of participating in this research?

The team will provide you with ASICS footwear as we believe finding adequate footwear is a major problem with acute gout patients. No payments are being made to any doctors or researchers for including patients in this study.

Will I receive feedback on the results of this research?

The team plan to publish results from this study in scientific journals so that the information is freely available to other doctors, scientists and the public. Patients will not be identified in any report or publication and indeed all information about your identity will be kept strictly confidential. Although no names will be used in the publication, age, sex, ethnicity, diagnosis and medications will be reported. If you agree, we will tell your GP and rheumatologist that you are involved in the study, and provide them with the results of your tests.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

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

If you have any questions or medical problems during this study, you should call the study doctor Professor Keith Rome who is in charge of this research or one of the study staff. The study doctor or

study staff will also answer any questions you have about this research study or your participation in the study. You have the right to ask questions about this study at any time.

Study Doctor: Professor Keith Rome
Telephone Number: 921 9999 extension 7688

If you have any queries or concerns regarding your rights as a participant in this study you may wish to contact an independent Health and Disability Advocate

Telephone: 0800 555 050

Free Fax: 0800 2787 7678 (0800 2 SUPPORT)

Email: advocacy@hdc.org.nz

For Auckland District Health Board Maori health support, please contact Mata Forbes, RGON; Coordinator / Advisor, Maori Health Services, Auckland Hospital, Grafton, Mobile 021 348432, Tel: (09) 307 4949 extension 7292.

How do I agree to participate in this research?

If you choose to help us with our research we ask you to sign a consent form to show that you agree to the above. Thank you for reading this.

This study has ethical approval from the Northern X Regional Ethics Committee.

Appendix 3: Participant Consent Form

Professor Keith Rome
Department of Podiatry
School of Rehabilitation & Occupation Studies
Telephone: 64 9 921 9999 extn 7688
Facsimile: 64 9 921 9839
Email: krome@aut.ac.nz

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TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Participant Consent Form

FOOT HEALTH PROBLEMS IN ACUTE GOUT

English	**I wish to have an interpreter.**	**Yes**	**No**
Maori	**E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.**	**Ae**	**Kao**
Samoan	**Ou te mana'o ia i ai se fa'amatala upu.**	**Ioe**	**Leai**
Tongan	**Oku ou fiema'u ha fakatonulea.**	**Io**	**Ikai**
Cook Island	**Ka inangaro au i tetai tangata uri reo.**	**Ae**	**Kare**
Niuean	**Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.**	**E**	**Nakai**

I have read the study information sheet (date 18/11/10) for gout patients taking part in the study to understand foot health problems in gout

The study has been explained to me by: Prof/Dr/Mr/Mrs/Ms_____

I have been given the opportunity to ask questions and discuss this study with the investigator and my whanau/family, and I have received satisfactory answers to all my questions.

I have received enough information about the study and have had enough time to think about it.

I understand that taking part in this study is voluntary (my choice). If I change my mind after I have attended a study visit, I understand that I can withdraw my data up to one month after this visit, without having to give a reason for withdrawing and without affecting my future medical care.

I know who to contact if I have any questions about the study.

I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

I consent to the researchers storing a specimen of my blood for its later use as part of this study.

I agree to take part in this study.

I wish to receive a copy of the results YES/NO

Signed.....Date.....

(NAME IN BLOCK CAPITALS).....

Investigator's signature.....Date: .....

(NAME AND ROLE IN BLOCK CAPITALS).....

Whanau/family member signature……Date.....

(NAME IN BLOCK CAPITALS).....

Appendix 4: ARA 66/68 Joint Count for Tender and Swollen Joints

Joint Evaluation – Upper Extremities

RIGHT SIDE	LEFT SIDE

Not Evaluable	Tenderness		Swelling		JOINTS	Not Evaluable	Tenderness		Swelling	
Yes	Yes	No	Yes	No		Yes	Yes	No	Yes	No
☐	☐	☐	☐	☐	**Tempromandibular**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Sternoclavicular**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Acromioclavicular**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Shoulder**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Elbow**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Wrist**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MCP1**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MCP2**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MCP3**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MCP4**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MCP5**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**IP1**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP2**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP3**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP4**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP5**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP2**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP3**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP4**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP5**	☐	☐	☐	☐	☐

Joint Evaluation – Lower Extremities

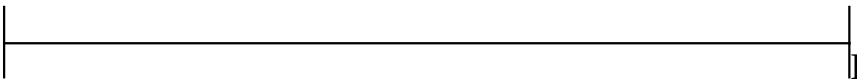
RIGHT SIDE	LEFT SIDE

Not Evaluable	Tenderness		Swelling		JOINTS	Not Evaluable	Tenderness		Swelling	
Yes	Yes	No	Yes	No		Yes	Yes	No	Yes	No
☐	☐	☐			**Hip**	☐	☐	☐		
☐	☐	☐	☐	☐	**Knee**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Ankle**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Subtalar**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**Mid tarsal**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MTP1**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MTP2**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MTP3**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MTP4**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**MTP5**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP1**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP2**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP3**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP4**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**PIP5**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP2**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP3**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP4**	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	**DIP5**	☐	☐	☐	☐	☐

Appendix 5: Pain 100mm Visual Analogue Scale

Patient Pain VAS:

Please indicate the amount of pain recently experienced by marking an (X) through the line:



Appendix 6: Modified Foot Function Index

Foot Function Index

Section 1: To be completed by patient Name:_____ Age:____ Date:_____

Occupation:_____ Number of days of foot pain:_____(this episode)

Section 2: To be completed by patient

This questionnaire has been designed to give your therapist information as to how your foot pain has affected your ability to manage in every day life. For the following questions, we would like you to score each question on a scale from 0 (no pain) to 10 (worst pain imaginable) that best describes your foot **over the past WEEK**. Please read each question and place a number from 0-10 in the corresponding box.

No Pain 0 1 2 3 4 5 6 7 8 9 10 **Worst Pain Imaginable**

	1.	In the morning upon taking your first step?		
	2.	When walking?		
	3.	When standing?		
	4.	How is your pain at the end of the day?		
	5.	How severe is your pain at its worst?		

Answer all of the following questions related to your pain and activities **over the past WEEK**, how much difficulty did you have? ***Disability Scale***

No Difficulty 0 1 2 3 4 5 6 7 8 9 10 ***So Difficult unable to do***

	6.	When walking in the house?		
	7.	When walking outside?		
	8.	When walking four blocks?		
	9.	When climbing stairs?		
	10.	When descending stairs?		
	11.	When standing tip toe?		
	12.	When getting up from a chair?		
	13.	When climbing curbs?		
	14.	When running or fast walking?		

Answer all the following questions related to your pain and activities **over the past WEEK**. How much of the time did you: ***Disability Scale:***

None of the time 0 1 2 3 4 5 6 7 8 9 10 ***All of the time***

	15.	Use an assistive device (cane, walker, crutches, etc) indoors?		
	16.	Use an assistive device (cane, walker, crutches, etc) outdoors?		
	17.	Limit physical activities?		

Section 3: To be completed by physical therapist/provider SCORE:_____/170 x100= _____% (SEM 5, MDC 7)

SCORE: Initial_____ Subsequent_____ Subsequent_____ Discharge_____

Number of treatment sessions:_____

Diagnosis/ICD-9 Code:_____

[1] Adapted from Budiman-Mak E, Conrad KJ, Roach K. The foot function index: A measure of foot pain and disability. J Clin Epidemiology. 4(6): 561-70, 91.

Appendix 7: Structural Indices for Forefoot and Hindfoot Deformities

STRUCTURAL INDICES FOR FOREFOOT AND HINDFOOT DEFORMITIES

FOREFOOT SCORE

DEFORMITY	**RIGHT**	**LEFT**
Hallux Valgus (Yes = 1; No = 0)		
5^{th} MTP Exostosis (Yes = 1; No = 0)		
Claw Toes present number (0-5)		
MTP subluxed number (0-5)		
Total Score	/12	/12

Structural Index Forefoot = Right + Left

REARFOOT SCORE

DEFORMITY	**RIGHT**	**LEFT**
Calcaneus valgus/varus: 0-5 = 0 6-10 = 1 11-15 = 2 >15 = 3		
Ankle total ROM: 46-60 = 0 31-45 = 1 15-30 = 2 < 15 = 3		
Pes Planus (Yes = 1; No = 0)		
Total Score	/12	/12

Structural Index Rearfoot = Right + Left

Appendix 8: Foot Posture Index

	COMPONENT	PLANE	SCORE 1 Date_____ Comment_____		SCORE 2 Date_____ Comment_____		SCORE 3 Date_____ Comment_____	
			Left *(-2 to +2)*	***Right*** *(-2 to +2)*	***Left*** *(-2 to +2)*	***Right*** *(-2 to +2)*	***Left*** *(-2 to +2)*	***Right*** *(-2 to +2)*
Rearfoot	Talar head palpation	*Transverse*						
	Curves above and below lateral malleoli.	*Frontal/ trans*						
	Inversion/eversion of the calcaneus	*Frontal*						
Forefoot	Bulge in the region of the TNJ	*Transverse*						
	Congruence of the medial longitudinal arch	*Sagittal*						
	Abduction/adduction of the forefoot on the rear foot (too-many-toes).	*Transverse*						
	TOTAL							

Appendix 9: Leeds Foot Impact Scale

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
1.	My feet get painful when I'm standing……	☐	☐
2.	My feet hurt me……	☐	☐
3.	I find the pain in my feet frustrating……	☐	☐
4.	The pain is worse when I've been on my feet all day……	☐	☐
5.	At the end of the day there is pain and tension in my feet……	☐	☐
6.	I never get rid of the stiffness in the background…….	☐	☐

Please remember to read each statement thinking about your feet.

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
7.	My feet throb at night……..	☐	☐
8.	My feet wake me up at night……	☐	☐
9.	I feel as though I've got pebbles in my shoes……	☐	☐
10.	I get pain every time I put my foot down……	☐	☐
11.	I get a burning sensation all the time……	☐	☐
12.	I cry with pain……	☐	☐

Please check you have ticked a box for every statement on this page

Please remember to read each statement thinking about your feet.

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
13.	I can only walk in certain shoes……..	☐	☐
14.	I need shoes with plenty of room in them……	☐	☐
15.	I am limited in my choice of shoes……	☐	☐
16.	I need a wider fit of shoes……	☐	☐
17.	I feel I need a lot of padding under my feet……	☐	☐
18.	My footwear always feels heavy……	☐	☐
19.	I have to keep swapping and changing my shoes…..	☐	☐
20.	I can't get any shoes on……	☐	☐
21.	I walk bare foot all the time……	☐	☐

Please remember to read each statement thinking about your feet.

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
22.	I feel unsafe on my feet……	☐	☐
23.	I have to walk for a bit and sit for a bit……	☐	☐
24.	I can’t run……	☐	☐
25.	I find I shuffle around……	☐	☐
26.	I am limping about all the time……	☐	☐
27.	I have to use a walking stick or walking frame……	☐	☐

Please check you have ticked a box for every statement on this page

Please remember to read each statement thinking about your feet.

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
28.	It takes me all my time to climb the stairs……	☐	☐
29.	I need help to climb stairs……	☐	☐
30.	I can't walk on cobbles……	☐	☐
31.	I am unsteady on uneven surfaces……	☐	☐
32.	I can't walk as far as I would like to……	☐	☐
33.	It takes me longer to do things……	☐	☐
34.	My whole life has been adapted……	☐	☐

Please remember to read each statement thinking about your feet.

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
35.	My feet restrict my movement……	☐	☐
36.	I get annoyed because I'm slower……	☐	☐
37.	I get frustrated because I can't do things so quickly…	☐	☐
38.	My whole life has slowed down……	☐	☐
39.	It's reduced the range of things I can do……..	☐	☐
40.	I have to plan everything out……	☐	☐
41.	I can't keep up like I used to……	☐	☐
42.	Socially its affected me a lot……	☐	☐
43.	I am ashamed of how I walk……	☐	☐
44.	I'm nervous of missing a curb edge……..	☐	☐

Please remember to read each statement thinking about your feet.

Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
45.	I feel isolated because I can't go very far……	☐	☐
46.	I feel I slow other people down……	☐	☐
47.	I can't do some of the things I take for granted……	☐	☐
48.	I can't go for walks with the people close to me…….	☐	☐
49.	I'm finding it difficult to be independent……	☐	☐
50.	I dread finishing up in a wheelchair……	☐	☐
51.	I get frustrated because I can't do things for myself…	☐	☐

Please check you have ticked a box for every statement on this page

Appendix 10: Health Assessment Questionnaire II

HAQ-II questionnaire

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**	**With some difficulty**	**With much difficulty**	**Unable**
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?				

Appendix 11: Lower Limb Tasks Questionnaire – Activities of Daily Living

Health and Rehabilitation Research Institute
Auckland University of Technology

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):_____

Enquiries concerning this questionnaire: Prof. Peter McNair, Health and Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland; New Zealand. email: peter.mcnair@aut.ac.nz Phone: 921-9999 Ext 7143

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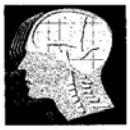
Appendix 12: Lower Limb Tasks Questionnaire – Recreational Activities



Health and Rehabilitation Research
Institute
Auckland University of Technology

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 DIFFICULTY	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

TOTAL (/40):_____

Enquiries concerning this questionnaire: Prof. Peter McNair PhD, Health and Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland; New Zealand. email: peter.mcnair@aut.ac.nz Phone: 921-9999 Ext 7143

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Appendix 13: Bonferroni Correction with Holm and Hochberg Adjustments

Contrast	Obtained P Value	Bonferroni P Value	Holm P Value	Hochberg P Value
1	0.646	0.003	0.05[a](stop)	0.05
2	0.025	0.003	0.025[b]	0.025[b](stop)[c]
3	0.006	0.003	0.017[b]	b
4	0.002	0.003[b]	0.0125[b]	b
5	0.000	0.003 [b]	0.01[b]	b
6	0.000	0.003 [b]	0.0083[b]	b
7	0.000	0.003 [b]	0.0071[b]	b
8	0.000	0.003 [b]	0.0063[b]	b
9	0.000	0.003 [b]	0.0056[b]	b
10	0.000	0.003 [b]	0.005[b]	b
11	0.000	0.003 [b]	0.0045[b]	b
12	0.000	0.003 [b]	0.0042[b]	b
13	0.000	0.003 [b]	0.0038[b]	b
14	0.000	0.003 [b]	0.0036[b]	b
15	0.000	0.003 [b]	0.0033[b]	b
16	0.000	0.003 [b]	0.0031[b]	b

[a]Stop: all individually obtained p values >0.646 are considered statistically not significant

[b]: Statistically significant comparison

[c]Stop: all individually obtained P values <0.025 are considered statistically significant