TONI-KARRI PAKARINEN

The Management and Clinical Outcome of the Charcot Foot

ACADEMIC DISSERTATION
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ABSTRACT

Diabetes mellitus is an endemic disease affecting up to six percent of population worldwide. In Finland, over 300,000 patients have a diagnosis of diabetes and the number is exponentially increasing. Diabetic foot problems; such as ulceration, infection, gangrene, Charcot foot and amputation are a major source of morbidity and a leading cause of hospitalization for patients with diabetes. A non-infectious destruction of bones and joints in a neuropathic extremity was first described more than 100 years ago and has since come to be known by eponym *Charcot foot.* Today diabetes is the most common cause of Charcot foot, which is recognised as one of the most devastating and disabling complication of diabetes and among the most important risk factors for plantar ulcer formation and subsequent amputation. The understanding of the basic pathophysiological mechanisms of Charcot foot has gradually led to the development of new treatment strategies and the purpose of the present study was to investigate the effect of zoledronic acid (bisphosphonate) on the treatment of acute Charcot foot in a prospective, randomized controlled trial. In addition, the long-term effects of chronic Charcot foot on patient's clinical outcome and quality of life were investigated and a comprehensive analysis of historical patient series was conducted.

The study population consisted of Charcot foot patients treated at the Tampere University Hospital Diabetic Foot Clinic during period 1994-2007. The first retrospective data was obtained from the patient records of the Diabetic Foot Clinic and was collated with the Hospital Discharge Register in order to assess the patient demographics and management details of a historical patient series with Charcot foot. The second data set consisted of prospectively enrolled patients (2002-2007) with acute midfoot Charcot foot and compared clinical resolution and bone mineral density changes during the treatment of acute Charcot foot with and without zoledronic acid. The fourth set data was also identified from the patient register of the Diabetic Foot Clinic and was a cross-sectional descriptive study assessing long-term clinical outcome and quality of life in patients with Charcot foot and at least five years of follow-up.

The diagnosis of acute Charcot foot is demanding and significant delays in diagnosis were common. The average delay was 29 weeks and the most frequent incorrect diagnoses were erysipelas, deep venous thrombosis, gout, arthritis, fracture or osteomyelitis. The prospective study failed to show any clinical benefit (reduced immobilisation time) with zoledronic acid as an adjuvant in the treatment of acute midfoot Charcot foot. The median immobilisation time in the placebo group was 20 weeks, but this lengthy immobilisation did not lead to an obvious disuse osteoporosis of the hip in the Charcot foot affected side after six months of treatment. Management with zoledronic acid

led to a significant increase of the hip bone mineral density in both sides compared to placebo, but the clinical significance of this was uncertain. In the long-term follow-up study 67% of patients had ulceration during follow-up and 40% were ulcerated more than once. Fifty percent of patients were managed surgically with an increase in surgery 4 years post diagnosis. Chronic Charcot foot was found to impair patient's physical functioning and general health but did not affect mental health. Long-term functional outcome of patients with Charcot foot is usually relatively good, mainly due to the absence of pain and if the correct diagnosis is reached early.

TIIVISTELMÄ

Diabeteksen esiintyvyys kasvaa kaikkialla maailmassa ja tällä hetkellä jopa 6% maailman väestöstä sairastaa diabetesta. Vuonna 2010 lääkehoitoa saavia diabetesta sairastavia suomalaisia oli jo yli 300 000. Diabetekseen liittyvät jalkaongelmat (haavaumat, infektiot, kuoliot, Charcot'n jalka ja amputaatiot) ovat yksi merkittävimmistä diabetespotilaiden sairaalahoitoa aiheuttavista syistä. Charcot'n neuroartropatia (CN) on yleistyvä ja usein erittäin invalidisoiva pitkäkestoisen diabeteksen vaikeahoitoinen nivel- ja luukomplikaatio. Taudin patofysiologia on monitekijäinen, eikä sitä kaikilta osin vielä täysin tunneta. Tyypillistä CN:n kehittymiselle on laajamittainen perifeerinen neuropatia ja suhteettoman suuri inflammatorinen reaktio jollekin ulkoiselle ärsykkeelle (trauma, kirurgia, infektio jne.). Inflammatorinen prosessi johtaa osteoklastiaktiviteetin lisääntymiseen ja luun paikalliseen resorptioon altistaen luun vaurioitumiseen. Nykyään CN kehittyy lähes yksinomaan komplisoituneen diabeteksen seurauksena ja affisioi pääasiassa nilkan sekä jalkaterän aluetta (Charcot'n jalka).

Tämän väitöskirjan tarkoituksena oli selvittää zoledronaattihoidon kliinistä hyötyä akuutin Charcot'n jalan hoidossa sekä selvittää hoidon aikana tapahtuvia luuntiheyden muutoksia. Lisäksi tutkimuksessa selvitettiin Charcot'n jalan pitkäaikaisennustetta, diagnostisia haasteita sekä taudin vaikutusta potilaiden elämänlaatuun.

Tutkimusmateriaali koostui Tampereen yliopistollisen sairaalan jalkatyöryhmässä vuosina 1994-2007 hoidetuista Charcot'n jalka- potilaista. Ensimmäisen tutkimuksen aineisto kerättiin retrospektiivisesti jalkatyöryhmässä ennen vuotta 2001 hoidetuista potilaista tarkoituksena selvittää historiallisen potilaskohortin diagnostiikan ja hoidon toteutuminen. Toisena aineistona oli prospektiivisesti kerätty potilaskohortti (2002-2007) akuutteja Charcot'n jalka- potilaita, joiden konventionaaliseen hoitoon liitettiin zoledronaatti- lääkitys tai lumelääke satunnaistetussa tutkimusasetelmassa. Tutkimuksen tarkoituksena oli selvittää lyhentääkö lääkehoito akuutin Charcot'n jalan kokonaisimmobilisaation kestoa ja millainen vaikutus pitkällä immobilisaatiolla on luuntiheyteen kuuden kuukauden seurannan aikana. Lisäksi Charcot'n jalan pitkäaikaisennustetta ja vaikutusta potilaiden elämänlaatuun selvitettiin ennen vuotta 2003 diagnosoidun potilaskohortin poikkileikkaustutkimuksessa.

Retrospektiivinen tutkimuksemme osoitti Charcot'n jalan diagnostiikan olevan hankalaa ja diagnostiikassa todettiin merkittäviä viiveitä. Keskimääräinen viive oikeaan diagnoosiin oli 29 viikkoa ja yleisimpinä virhediagnooseina olivat ruusu/selluliitti, syvä laskimotukos, kihti, artroosi, murtuma ja osteomyeliitti. Prospektiivinen tutkimuksemme osoitti, ettei zoledronaattihoito lyhentänyt Charcot'n jalan hoidon kokonaisimmobilisaation kestoa. Lumelääkeryhmän

keskimääräinen immobilisaatioaika oli 20 viikkoa, jonka ei kuitenkaan todettu johtavan kliinisesti merkittävän immobilisaatio-osteoporoosiin (“disuse osteoporosis”) kehittymiseen kuuden kuukauden seurannan aikana. Zoledronaatti-hoito lisäsi reiden yläosan luuntiehyttä merkittävästi enemmän verrattuna lumelääkeryhmään, mutta tämän lisäyksen kliininen merkitys on vähäinen. Charcot’n jalka- potilaiden pitkäaikaisennuste on kohtuullisen hyvä, jos diagnoosiin päästään varhain. Keskimäärin kahdeksan vuoden seurannan aikana 67%: lla potilaista todettiin jalkahaavauma jossain taudin vaiheessa ja 50% potilaista vaati jonkinlaista kirurgista hoitoa Charcot’n jalan tai haavaumia seuranneiden ongelmien vuoksi. Kirurgisen hoidon tarve havaittiin lisääntyvän neljä vuotta diagnoosin jälkeen. Elämänlaatumittareista krooninen Charcot’n jalka heikensi fyysistä toimintakykyä ja yleistä terveydentilaa, mutta mielenterveyden osalta vastaavaa heikkenemistä ei todettu.

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II Pakarinen TK, Laine HJ, Mäenpää H, Mattila P and Lahtela J (2011) The effect of zoledronic acid on the clinical resolution of Charcot neuroarthropathy: a pilot randomized controlled trial. Diabetes Care 34: 1514-6

III Pakarinen TK, Laine HJ, Mäenpää H, Kähönen M, Mattila P and Lahtela J The effect of zoledronic acid on bone mineral density in patients with acute Charcot foot. A prospective randomized trial. Submitted

IV Pakarinen TK, Laine HJ, Mäenpää H, Mattila P and Lahtela J (2009) Long-term outcome and quality of life in patients with Charcot foot. Foot Ankle Surg 15:187-9

ABBREVIATIONS

18F-FDG	fluorodeoxyglucose
1CTP	urinary pyridinoline cross-linked carboxy-terminal telopeptide domain of type 1 collagen
AFOS/ALP	alkaline phosphatase
AOFAS	American Orthopaedic Foot and Ankle Society score
BMD	bone mineral density
CF	Charcot foot
CN	Charcot neuropathic osteoarthropathy
CRP	c-reactive protein
CT	computed tomography
DEXA	dual energy x-ray absorptiometry
DVT	deep venous thrombosis
ESR	erythrocyte sedimentation rate
FFP	farnesyl diphosphatase
$HbA1_c$	glycosylated haemoglobin
IGF-1	insulin-like growth factor-1
IL-1β	interleukin 1-beta
MRI	magnetic resonance imaging
NF-κB	nuclear factor kappa-B
NTx	serum N-telopeptides of type 1 collagen
OM	osteomyelitis
OPG	osteoprotegerin
P1CP	carboxy-terminal propeptide of type 1 collagen
PET	positron emission tomography
PTH	parathormone
QUS	quantitative ultrasound
RANK	receptor activator of nuclear factor-kappa-B

RANKL	receptor activator of nuclear factor-kappa-B ligand
S&F	Sanders and Frykberg classification system of Charcot foot
SF-36	Short-Form 36
SUV	standard uptake value
TNF-α	tumour necrosis factor – alpha
WBC	white blood cell count

1. INTRODUCTION

Diabetes mellitus is an endemic disease affecting up to 6.4% of general adult population worldwide (Wild et al. 2004, Shaw et al. 2010). The number of patients with diabetes, especially type 2, is increasing rapidly due to population growth, aging and increasing prevalence of obesity and physical inactivity. In 2010, approximately 300,000 patients in Finland had a diagnosis of diabetes (prevalence of 5.6%) according to the National Institute for Health and Welfare and approximately 200,000 more patients are estimated to have a type 2 diabetes without knowing it (Peltonen et al. 2006). The incidence of type 1 diabetes in Finland is the highest in the world (64 new cases /100,000/ year in children under the age of 15) and is increasing exponentially (Harjutsalo et al. 2008). Eventually this greater number of patients will also face an increased number of late complications, i.e. stroke, cardiovascular disease, nephropathy, neuropathy, micro- and macroangiopathy and diabetic foot problems.

Non-infectious destruction of bones and joints in a neuropathic extremity (neurogenic osteoarthropathy) was first described more than 100 years ago in patients with tertiary syphilis (Charcot and Féré 1883). Since then neurogenic osteoarthropathy has been known by the eponym *"Charcot's disease"*. Some decisive breakthroughs in medicine also changed the occurrence of neurogenic osteoarthropathy. Penicillin cured syphilis and today in the western world tertiary syphilis is responsible for only a few cases of osteoarthropathy annually (Viens et al. 2010). In the early 1920's insulin was isolated and the lifespan of patients with diabetes started to increase eventually leading to higher frequency of late complications. In 1936 Jordan (Jordan 1936) reported the first cases of *diabetic Charcot's disease,* which usually affected the area around the foot and ankle (*i.e. Charcot foot*).

Today diabetes is the most common cause of Charcot foot (Frykberg and Kozak 1978, Gupta 1993). It is recognised as one of the most devastating and disabling complications of diabetes and as a single most important risk factor for plantar ulcer formation and subsequent amputation (Boyko et al. 1999). However, the long-term impact of Charcot foot on a patient's clinical outcome and quality of life is not known. The association between diabetes and Charcot foot has been known for over 75 years, but most of the pathophysiological mechanisms are still unidentified, likewise the optimal management strategies. It seems that the interactions of various component factors result in an acute and localized inflammatory process that leads to osteolysis and various degrees and

patterns of bone and joint destruction and deformity around the foot and/or ankle (Jeffcoate et al. 2005). The mainstay of the treatment has traditionally been off-loading and immobilization in a cast until the acute inflammatory phase subsides, which may take as long as 12 months (Armstrong et al. 1997, Petrova and Edmonds 2010, Rogers et al. 2011). The increase of bone turnover and osteoclastic activity in patients with acute Charcot foot led to a conjecture that antiresorptive drugs (e.g. bisphosphonates) might be beneficial in the management of acute Charcot foot. Preliminary patient series have yielded promising results but the clinical efficacy of these drug remains to be determined (Selby et al. 1994, Jude et al. 2001, Anderson et al. 2004, Pitocco et al. 2005, Bem et al. 2006).

The purpose of the present study was to investigate the effects of an intravenous bisphosphonate (zoledronic acid) treatment on the management of acute Charcot foot in a prospective, randomized controlled trial. In addition, the long-term effects of chronic Charcot foot on patient's clinical outcome and quality of life were investigated and a comprehensive analysis of a historical patient series was conducted.

2. REVIEW OF THE LITERATURE

Diabetic foot problems, such as ulceration, infection, gangrene, Charcot foot and amputation are a major source of morbidity and a leading cause of hospitalization for patients with diabetes. According to the American Diabetes Association diabetes and its complications cost the United States $174 billion annually ($7,300 / person with diabetes / year) and it is estimated that at least 33% of these costs are linked to the treatment of diabetic foot disorders (American Diabetes Association 2008). An estimated 15% of patients with diabetes develop lower extremity ulcer during the course of their disease and the annual cumulative incidence of diabetic foot ulcers is 0.5-3% (Moss et al. 1992, Kumar et al. 1994, Moss et al. 1999, Ramsey et al. 1999). Charcot foot is the single most important risk factor for foot ulceration in patients with diabetes (Boyko et al. 1999). Other risk factors include peripheral neuropathy, atherosclerotic vascular disease, impaired joint mobility, other foot deformities, abnormal plantar foot pressures, trauma, history of ulceration/amputation and impaired visual acuity (Frykberg et al. 1998, Boyko et al. 1999, Reiber et al. 1999, Frykberg and Armstrong 2002). Seven to 25% of patients with diabetes and foot ulceration will subsequently require amputation and more than 60% of all lower extremity amputations occur in patients with diabetes (Pecoraro et al. 1990, Larsson et al. 1998, American Diabetes Association 1999, Margolis et al. 2005, Singh et al. 2005). Foot ulceration is the most common precursor to lower extremity amputation among patients with diabetes (precursor to approximately 85% of amputations) with annual risk of 5% for major lower extremity amputation (Pecoraro et al. 1990, Larsson et al. 1998, American Diabetes Association 1999, Prompers et al. 2008). Healing of an ulcer without amputation costs on average of 7,722€, whereas healing by amputation averaged 25,222€ (Apelqvist et al. 1994, Prompers et al. 2008). The implementation of a multidisciplinary programme for the management of patients with diabetic foot disorders decreases the rate of major amputations up to 83% (Larsson et al. 1995, Van Gils et al. 1999, Driver et al. 2005, Driver et al. 2010).

2.1 History of Charcot foot

2.1.1 Jean-Martin Charcot and *pied tabétique*

In 1831 John Kearsley Mitchell (1798-1858) was the first to describe denervation-induced bone and joint destruction due to tuberculous spinal cord damage (Mitchell 1831). More than 30 years later, in 1868, Jean-Martin Charcot (1825-1893), a French neurologist at Salpêtriere Hospital in Paris published his early observations of tabetic arthropathies (Charcot 1868). Tabes dorsalis is a slow degeneration of the dorsal columns of the spinal cord caused by demyelinisation secondary to untreated syphilis (Allali et al. 2006). This leads to episodes of intense pain, unsteady gait and loss of sensation and in some patients subsequent destruction of the periarticular bones and large joints (Scheck and Hook 1994, Allali et al. 2006). It was not until 1881 that Charcot received international recognition for his research on tabetic arthropathies and Sir James Paget suggested that the condition of denervation-induced destruction of bones and joints should be called *"Charcot's disease"* (Sanders 2004). In 1883 Charcot and Féré published a case of extensive bone and joint destruction of the tarsal bones claiming that it was analogous to the tabetic arthropathies of the larger joints (Charcot and Féré 1883). They called the process *pied tabétique*, foot tabes, which would later come to be known as Charcot foot.

The association between diabetes and Charcot foot was first described in 1936 by William Reliy Jordan (Jordan 1936). While the number of neurosyphilis cases has steadily decreased, diabetes is now recognized to be the most common cause of Charcot foot worldwide (Gupta 1993).

2.1.2 Terminology of neuropathic osteoarthropathies

There is still a lack of consensus on the nomenclature of the neuropathic bone and joint destruction of the foot in the absence of infection. Numerous names have been used to describe it, such as neurogenic arthropathy, diabetic neuroarthropathy, neuropathic arthropathy, Charcot neuroarthropathy, Charcot osteoarthropathy, Charcot's joint, Charcot's disease, Charcot arthropathy, Charcot neuro-osteoarthropathy etc. In this dissertation the most frequently used terms *Charcot neuropathic osteoarthropathy* (CN; referring to disease of the bones and joints not defining

the body region) and *Charcot foot* (CF; when Charcot osteoarthropathy affects the foot or ankle) are used (Rogers et al. 2011).

2.2 Pathophysiology of Charcot foot

The exact pathogenesis of CF remains unclear. The basic mechanisms leading to the development of CF have been a subject of a long debate mainly due to the lack of a clear definition of CF and the fact that the present scientific evidence is mostly circumstantial at best. Historically two theories, neurotraumatic and neurovascular, were initially considered as competing but are now considered to overlap to some extent, even though these theories could not conclusively explain the whole clinical picture of CF (e.g. why CF is usually unilateral while neuropathy is most often bilateral and why CF is so rare while neuropathy is a common diabetic complication). Recent studies show that there seems to be no single cause for the development of CF but rather a number of possible precipitating events (trauma, surgery, infection etc.) as well as factors that predispose to its development (Jeffcoate et al. 2005, Rogers et al. 2011). Once a process of inflammation is triggered in a susceptible individual, the uncontrolled inflammation leads to osteolysis and local osteopenia and the subsequent progressive destruction of bones and joints due to the lack of protective sensation (Jeffcoate et al. 2005).

For decades acute CF was considered to be a simple result of continuing damage to bones and joints caused by a lack of protective sensation due to the peripheral neuropathy, i.e. *neurotraumatic theory* (Eloesser 1917, Salo et al. 1997). According to this theory repetitive trauma to the insensate foot causes microfractures of the periarticular bones and results in progressive bone and joint destruction if the affected area is not properly immobilized. *Neurovascular theory* was based on the assumption that the autonomic neuropathy (loss of trophic nerves, (Charcot 1868)) would lead to an increase in local blood flow to the lower extremities and to arteriovenous shunting causing subsequent osteoclastic activation and local bone resorption (Edmonds et al. 1982, Edmonds et al. 1985, Baker et al. 2007). Three separate groups also found that patients with CF had normal blood flow in the lower extremities and retained normal vasomotor regulation of blood flow compared to diabetic control subjects with neuropathy alone (Shapiro et al. 1998, Veves et al. 1998, Baker et al. 2007). The assumption of bone resorption due to sympathetic denervation also proved to be erroneous and

sympathetic activity has been shown to increase (not decrease) the osteoclastic activity and bone loss (Kondo et al. 2005, Kondo and Togari 2011).

2.2.1 Peripheral neuropathy

Peripheral neuropathy is associated with all disorders that can produce CF. The prevalence of peripheral neuropathy in patients with diabetes is estimated to vary between 7.5 and 45% depending on the duration of the diabetes (Dyck et al. 1993, Young et al. 1993, Toeller et al. 1999, Charles et al. 2011). Peripheral neuropathy is thought to be an essential prerequisite for the development of CF and radiological signs of CF will develop in up to 13-37% of diabetic patients with neuropathy (Cofield et al. 1983, Tawn et al. 1988, Fabrin et al. 2000, Armstrong et al. 2001, McIntyre et al. 2007). The retention of autonomic vasodilatory reflexes in patients with CF has been reported in contrast to patients with diabetes and peripheral neuropathy without CF (Shapiro et al. 1998, Veves et al. 1998, Baker et al. 2007). If the foot is not properly immobilized after the initiation of inflammation and the patient has loss of pain perception and continues to bear weight normally, further trauma leads to further inflammation and subsequent progressive local osteolysis and fragmentation (Jirkovska et al. 2001, Hastings et al. 2005, Petrova et al. 2005, Petrova and Edmonds 2010). Initial microfractures may also be more likely in case of osteopenia and there is some evidence that both diabetes and neuropathy are associated with osteopenia (Rix et al. 1999) and that local osteopenia may predispose to the development of the CF (Sinacore et al. 2008).

2.2.2 Inflammation

The single most obvious clinical sign of acute CF is the occurrence of local inflammation (rubor - redness, tumour - swelling, calor - warmness and dolor - pain; absent in the case of peripheral neuropathy). During the last decade the role of the local exaggerated inflammatory reaction in the development of acute CF has received more attention (Jeffcoate et al. 2005). The current belief is that the development of acute CF needs some form of initial insult (whether noticed by the patient or not), which is sufficient to trigger an inflammatory cascade through activated proinflammatory mediators (e.g. tumour necrosis factor alpha (TNF-α) and interleukin 1-beta (IL-1β)). Fractures in general are associated with acute release of TNF-α and IL-1β and activation of these cytokines leads to the activation of macrophages, activated T-cells and bone marrow stromal cells which start

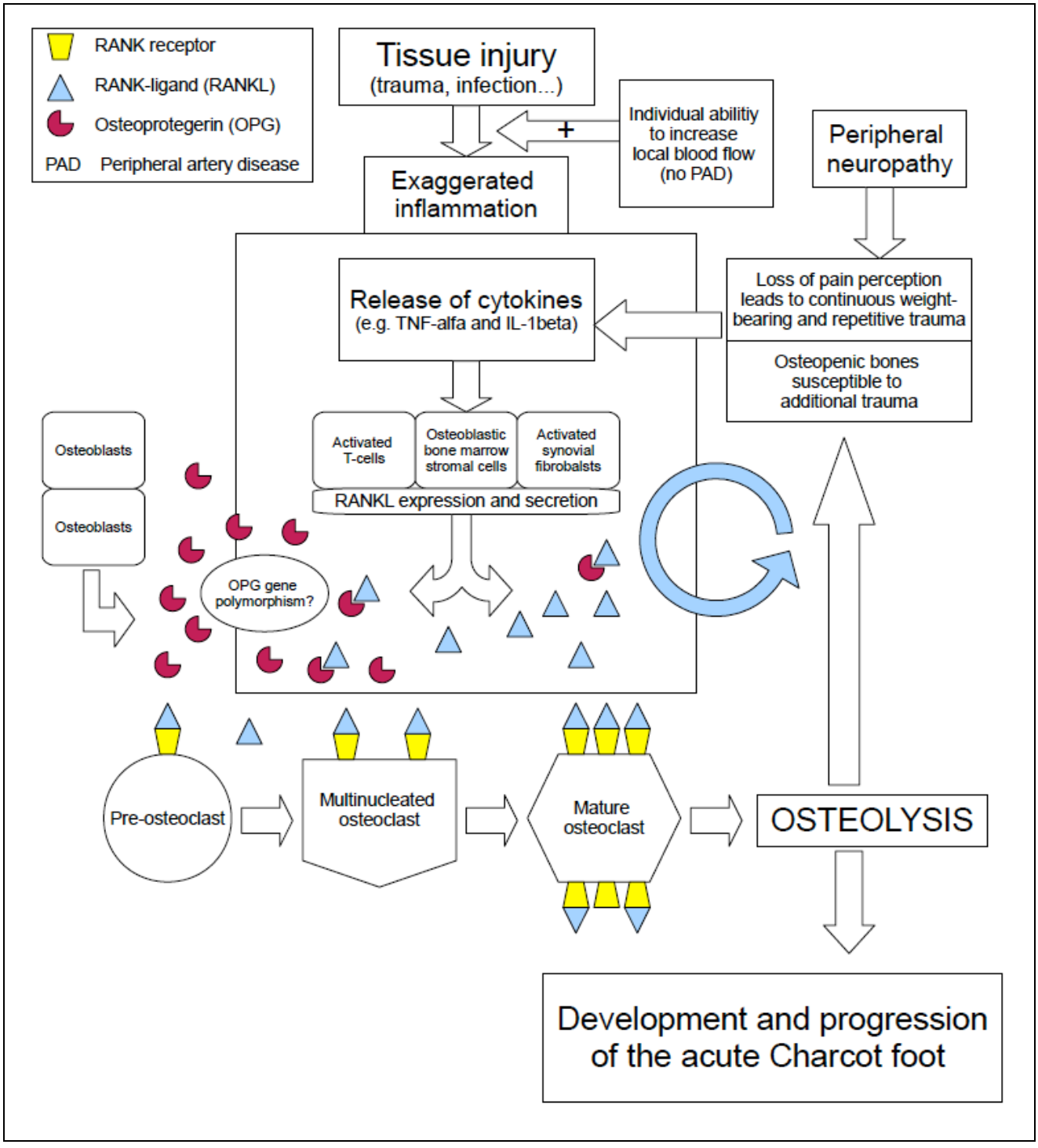
producing receptor activator of nuclear factor-kappaB ligand (RANKL) (Kon et al. 2001). RANKL is the ligand for RANK receptor in osteoclast precursor cells and its expression increases at the onset of inflammation in acute CF (Mabilleau et al. 2008). RANK receptor activation leads to the expression of nuclear transcription factor-κB (NF-κB) and subsequent osteoclast maturation and osteoclast activation as well as the production of osteoprotegerin (OPG) from osteoblasts (Boyle et al. 2003). OPG is a decoy receptor for RANKL and effectively antagonizes the effect of RANKL. Expression of RANKL and OPG is coordinated to regulate bone resorption and density by controlling the activation state of RANK on osteoclasts (Boyle et al. 2003, Boyce and Xing 2008).
In a recent survey, preceding trauma was identified in over one third of CF cases, even in those patients with no history of trauma as many as 35% had had a preceding ulcer, surgery or osteomyelitis (Game et al. 2007). Whatever the initial trigger is, it is sufficient to induce, in certain susceptible patients, an excessive and persistent inflammatory reaction which eventually leads to increased NF-kB-receptor activation and subsequent increase in osteoclastogenesis and local osteopenia (Griffith et al. 1995, Baumhauer et al. 2006, Mabilleau et al. 2008).
RANKL/RANK/OPG-pathway may also be responsible for other diabetic complications, such as media sclerosis of arteries (Schoppet et al. 2004, Ndip et al. 2011), arterial occlusive disease (Avignon et al. 2005, Anand et al. 2006), neuropathy (Jeffcoate 2005), retinopathy (Knudsen et al. 2003), nephropathy (Knudsen et al. 2003) and osteopenia/osteoporosis (Knudsen et al. 2003, Galluzzi et al. 2005).

2.2.3 Individual predisposition to Charcot foot

Due to the rarity of CF in general diabetic population and even in patients with neuropathy, there must be individual or genetic factors e.g. OPG polymorphism, that constitute a small group of patients with diabetes at greater risk than others for CF compared with others (Pitocco et al. 2009). Maybe patients with diabetic neuropathy who are unable to control the intensity and length of the local inflammatory response and who retain the capacity to increase distal limb blood flow even further could be exposed to increased and continuous local expression of TNF-α and IL-1β after trauma (Stevens et al. 1992, Shapiro et al. 1998, Veves et al. 1998, Baker et al. 2007). This increased blood flow and ongoing inflammation would then lead to the expression of RANKL, leading to the maturation of osteoclasts and subsequent osteolysis (Hofbauer et al. 2000, Lam et al. 2002, Boyle et al. 2003). This is supported by the increased number of proinflammatory phenotypes of macrophages detected in patients with acute CF when compared with diabetic control subjects

(Uccioli et al. 2010). Figure 1 presents the modern pathophysiological concept of the development of acute CF.

Figure 1. Modern pathophysiology of the Charcot foot



2.3 Epidemiology of Charcot foot

2.3.1 Disorders producing Charcot neuropathic osteoarthropathy

Diabetes mellitus is today recognized as the most common cause of Charcot neuropathic osteoarthropathy (CN) worldwide (Frykberg and Kozak 1978). There are also several other disorders causing neuropathy or nerve dysfunction, which may lead to development of CN (Table 1). Chronic alcohol consumption or exposure to other potentially toxic agents (i.e. steroids) are reported as risk factors for CN (Pereda et al. 1974, Vera and Nixon 1995) and in endemic areas leprosy and tertiary syphilis (tabes dorsalis) are still common causes of CN (Fishel et al. 1985, Horibe et al. 1988). Less common causes include surgery (Fishco 2001, Zgonis et al. 2007), amyloidosis (Shiraishi et al. 1997), Charcot-Marie-Tooth- disease (Parks and Benstead 2010), hereditary sensory neuropathy (Ahmed et al. 1990), multiple sclerosis (Rosenthal 1965), myelomeningocele (Zimmermann et al. 2007), spina bifida (Nagarkatti et al. 2000), peripheral or spinal nerve injury (Kopec et al. 2009) or rheumatoid arthritis (Alarcon Segovia and Ward 1965).

Table 1. Diseases/disorders that can lead to the development of Charcot neuropathic osteoarthropathy

Disease / disorder	Reference(s)
Amyloidosis	(Shiraishi et al. 1997)
Alcoholism	(Vera and Nixon 1995)
Charcot-Marie-Tooth	(Parks and Benstead 2010)
Hereditary sensory neuropathy	(Ahmed et al. 1990)
Diabetes mellitus (type 1 and type 2)	(Jordan 1936)
Leprosy	(Horibe et al. 1988)
Multiple sclerosis	(Rosenthal 1965)
Myelomeningocele	(Zimmermann et al. 2007)
Parkinson's disease	(Singh and Kelly 2009)
Steroids	(Pereda et al. 1974)
Syphilis	(Fishel et al. 1985)
Surgery	(Fishco 2001, Zgonis et al. 2007)
Syringomyelia	(Hendrikx et al. 2007)
Spina bifida	(Nagarkatti et al. 2000)
Spinal or peripheral nerve injury	(Kopec et al. 2009)
Rheumatoid arthritis	(Alarcon Segovia and Ward 1965)

2.3.2 Localization of Charcot neuropathic osteoarthropathy

Jean-Martin Charcot's original series included neuropathic osteoarthropathies of the large bones and joints, which was a typical distribution of the disease for tabetic osteoarthropathy (Charcot 1868). Today, while CN is mainly caused by diabetes, it almost exclusively affects the small bones and joints of the foot and ankle (Sanders and Frykberg 1991). There are a few case reports of CN affecting other sites including wrist (Lambert and Close 2005, Wrobel et al. 2007), elbow (Ruette et al. 2007, Garg and Chaurasia 2010), knee (Bae et al. 2009, Kucera et al. 2011), hip (Viens et al. 2010), spine (Barrey et al. 2010, David et al. 2010) and shoulder (Clayton et al. 2010).

2.3.3 Incidence and prevalence of Charcot foot

There are no high-quality studies on the epidemiology of CF. However, there are a few population-based studies reporting its incidence and estimated prevalence. The incidence of newly diagnosed CF cases (acute and chronic CF cases combined) among all diabetic patients is 0.1-0.9% / year (Bailey and Root 1947, Sinha et al. 1972, Fabrin et al. 2000, Lavery et al. 2003). The prevalence of CF (usually chronic deformity in these studies) is 0.1-37.0% (Pogonowska et al. 1967, Sinha et al. 1972, Cofield et al. 1983, Tawn et al. 1988, Cavanagh et al. 1994, Klenerman 1996, Smith et al. 1997, Armstrong and Peters 2002, McIntyre et al. 2007). The reported prevalence varies considerably between studies due to differences in diagnostic criteria of CF and whether the study cohort included only patients with neuropathy or all patients with any kind of diabetes. The epidemiological data of these studies is summarized in Table 2. The exact prevalence of CF in diabetic population is still not known, mainly because most studies present patient series from specialized referral centres with highly selected study populations.

Table 2. Summary of epidemiological data of the Charcot foot.

Reference	**Study population**	**Incidence**
Bailey and Root 1947	All DM patients	0.3% / yr
Sinha et al. 1972	All DM patients	0.9 % / yr
Fabrin et al. 2000	All DM patients	0.1% / yr
Lavery et al. 2003	All DM patients	0.1% / yr
	Average	**0.4% / yr**
		Prevalence
Pogonowska et al. 1967	Not reported	7.0%
Sinha et al. 1972	All DM patients	0.1%
Cofield et al. 1983	All DM patients DM + neuropathy	7.5% 29.0%
Tawn et al. 1988	DM + neuropathy	37.0%
Cavanagh et al. 1994	DM + neuropathy	17.0%
Klenerman 1996	All DM patients	0.4%
Smith et al. 1997	All DM patients	1.4%
McIntyre et al. 2007	DM + haemodialysis	19.5%
	Average **All DM patients** **DM + neuropathy**	**13.2%** **3.3%** **25.6%**

2.3.4 Distribution of Charcot foot

CF may affect all areas of the foot and ankle but the midtarsal area is the most frequent with 50-82% of so affected (Sinha et al. 1972, Armstrong et al. 1997, Schon et al. 1998, Fabrin et al. 2000, Frykberg and Mendeszoon 2000, Herbst 2004). The most widely used classification system was developed by (Sanders and Frykberg 1991) and describes anatomical areas of bone and joint involvement in patients with CF. It describes five patterns (Figure 2) of disease distribution which may occur independently or in combination with each other. S&F classification is described as follows: S&F I – forefoot, S&F II - tarsometatarsal joints, S&F III - midtarsal and

naviculocuneiform joints, S&F IV – ankle and subtalar joints, S&F V – calcaneus (Figure 2). Another classification system was developed by (Brodsky 1999). Brodsky type 1 involves the tarsometatarsal and naviculocuneiforme joints. Type 2 involves subtalar, talonavicular and calcaneocuboid joints. Type 3A involves the ankle joint and type 3B tuberosity of the calcaneus. Both classifications are based on the anatomical localization of the disease process and existing classifications do not provide prognostic value or direct treatment recommendations for CF. Table 3 presents reported distributions of CF involvement from the recent literature according to Sanders and Frykberg classification.

Figure 2. Distribution of Charcot foot involvement (according to the Sanders and Frykberg classification).

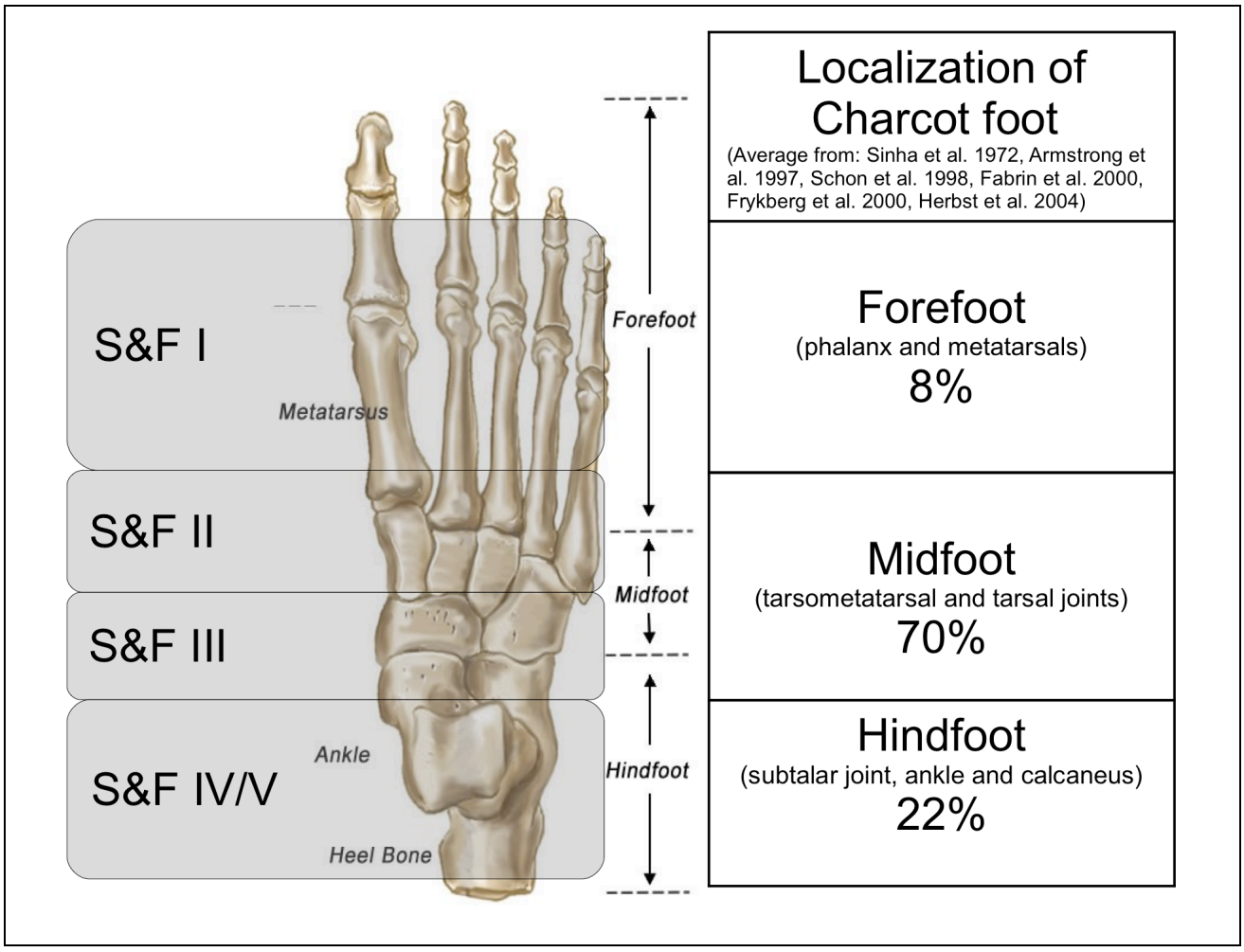


Table 3. Distribution of Charcot foot involvement.

Reference	S&F I	S&F II	S&F III	S&F IV-V
Sinha et al. 1972	7%	34%	47%	12%
Armstrong et al. 1997	2/55 3%	26/55 48%	19/55 34%	8/55 15%
Schon et al.1998	8%	59%		33%
Fabrin et al. 2000	26/140 19%	104/140 74%		10/140 7%
Frykberg 2000	10%	40%	30%	15%
Herbst et al. 2004	3%	50%		47%
Average	**8%**	**69%**		**22%**
Myerson et al. 1994	N/R	73%	27%	N/R
Sella et al. 1999	N/R	14/51 27%	37/51 73%	N/R
S&F II-III average		**44%**	**56%**	

N/R, not reported; S&F, classification according to Sanders and Frykberg (1991).

2.4 Diagnosis of Charcot foot

There are no uniform diagnostic criteria or any specific diagnostic markers for CF. This lack of criteria means that diagnosis of CF depends primarily on recognizing typical patterns of non-specific signs and symptoms of the disease. CF is often easily recognisable by those with a high index of suspicion and experience of the disease. To reach the correct CF diagnosis one should: 1. Identify high-risk patients, 2. Combine typical clinical features of CF with certain radiological findings and 3. Exclude disorders (e.g. acute gout, erysipelas, cellulitis, DVT, trauma, osteomyelitis) that cause clinical signs or symptoms similar to those seen in CF (Gill et al. 2004). This problematic diagnostic pathway often leads to significant diagnostic delays and makes it difficult to compare different patient series with each other. The diagnosis may be delayed for up to 6 months or missed in as many as 25-79% of cases (Myerson et al. 1994, Marks 2001, Gill et al. 2004, Chantelau 2005).

2.4.1 General characteristics of patients with Charcot foot

CF usually affects diabetic patients in their fifth or sixth decades of life (Sinha et al. 1972, Cofield et al. 1983, Armstrong et al. 1997, Fabrin et al. 2000, Petrova and Edmonds 2010). A review of 85 cases of CF revealed that patients with type 1 diabetes are often younger (42 yrs vs. 59 years) and

have longer history of diabetes (19 yrs vs. 8 yrs) than patients with type 2 diabetes (Petrova et al. 2004). Gender does not appear to be associated with the occurrence of CF (Sinha et al. 1972, Armstrong et al. 1997, Fabrin et al. 2000). A slight preponderance of type 1 diabetes to type 2 has been reported (Fabrin et al. 2000, Petrova et al. 2004) but in other series type 2 diabetes predominates (Armstrong et al. 1997, Herbst et al. 2004). Many patients may recall a precipitating traumatic event (Foltz et al. 2004). However, it is nowadays conceded that different causes may trigger the local inflammatory process leading to acute CF, such as previous surgery, osteomyelitis, previous ulceration or infection (Rogers et al. 2011). Pain is usually absent or mild due to the peripheral neuropathy usually present in all CF patients (Fabrin et al. 2000). Reported bilateral involvement of CF has varied between 9-75% depending on the method of assessment (clinical or radiological) but usually acute CF presents as a unilateral condition (Clohisy and Thompson 1988, Griffith et al. 1995, Armstrong et al. 1997).

2.4.2 Clinical features of acute Charcot foot

The clinical course of CF can be divided into four different stages (stage 0-3, Table 4 and Table 5), all of which have their distinctive clinical and radiographical features (Eichenholtz 1966, Sella and Barrette 1999). CF may present as an acute or chronic disease and clinical features vary depending on the stage of the disease process. Often these two phases (acute and chronic) and different stages seem to overlap (Jeffcoate et al. 2000).

Stage 0 (Pre-destruction). Stage 0 was not included in the original staging system of CF developed by Eichenholtz (1966). Sella and Barrette (1999) identified the pre-destruction phase of acute CF and named it stage 0. Stage 0 has the same clinical signs of acute inflammation as stage 1 but without any radiological abnormalities in plain radiographs.

Stage 1 (Development/fragmentation). Acute CF (stages 0 and 1) is characterized by unilateral erythema, swelling and an increase in skin temperature of at least 2°C (usually 2-10°C) compared to the contralateral foot (Armstrong and Lavery 1997, McGill et al. 2000). Stage 1 also includes radiological abnormalities in x-rays (demineralization of regional bone, periarticular fragmentation and acute fractures or joint dislocations).

Stage 2 (Coalescence, "transitional phase"). The erythema, swelling and temperature difference are decreased from stage 1. Fractures and dislocations present early healing and organization in plain radiographs and some new bone formation is seen.

Stage 3 (Reconstruction/consolidation, chronic CF). The erythema, swelling and temperature difference subside. Fixed or non-fixed deformities may be observed in clinical examination. Radiographs may reveal osseous or fibrous ankylosis, smoothing of bone edges and sometimes extensive destruction of the tarsal bones.

Table 4. Staging of Charcot foot (Eichenholtz 1966, Sella and Barrette 1999).

Stage	Eichenholtz (1966)	Sella and Barrette (1999)	Modern staging
0	-	Swelling, erythema, and warmth without changes in plain X-ray MRI: bone marrow oedema	Acute phase
1	Development / fragmentation	Swelling, erythema, and warmth with subtle X-ray changes	
2	Coalescence	Joint subluxation, early healing of fractures, periosteal bone formation	Transitional phase
3	Reconstruction / consolidation	Smoothing on edges of bone fragments, sclerosis, ankylosis, joint collapse, fixed deformities	Chronic phase

Table 5. Stages of Charcot foot in clinical practise (Eichenholtz 1966, Johnson 1997, Sella and Barrette 1999).

Stage	**Clinical signs** (Johnson 1997)	**Radiological findings** (Eichenholtz 1966, Sella and Barrette 1999)
Acute	Acute inflammation: swelling, erythema, and warmth. Temperature difference > 2°C compared to contralateral foot	Plain X-ray: from normal to demineralization, periarticular fractures and joint dislocations MRI: significant bone marrow oedema
Transitional	Less inflammation and swelling. Decreased temperature difference. Increased stability of the fractures.	Plain X-ray: joint subluxation, early healing of fractures, periosteal bone formation. MRI: diminishing bone marrow oedema
Chronic	No swelling, erythema or warmth. No temperature difference. Fixed deformities.	Plain X-ray: smoothing on edges of bone fragments, sclerosis and ankylosis on plain X-ray. MRI: no (or minimal) bone marrow oedema.

2.4.3 Imaging of Charcot foot

2.4.3.1 Plain radiography

The staging system described by the American orthopaedic surgeon Sidney Eichenholtz (Eichenholtz 1966) is still a widely used classification system for sequential changes observed in the clinical course of CF. The Eichenholtz classification is only a radiographical classification and originally had no clinical correlation (symptoms and signs of inflammation). Later Johnson (1997) added the typical clinical features of each stage to Eichenholtz's radiographical stages. In addition to the original Eichenholtz classification Sella and Barrette (1999) described stage 0, in which there are no radiographic changes, but clinically the inflammatory process is obvious (swelling, warmth, increased temperature difference). Thus, normal plain radiograph does not rule out the possibility of early phase of CF. Today the role of plain radiographs is mainly to detect the anatomic pattern of involvement at the time of initial diagnosis and later in the course of the treatment to monitor possible CF progression (Armstrong and Peters 2002).

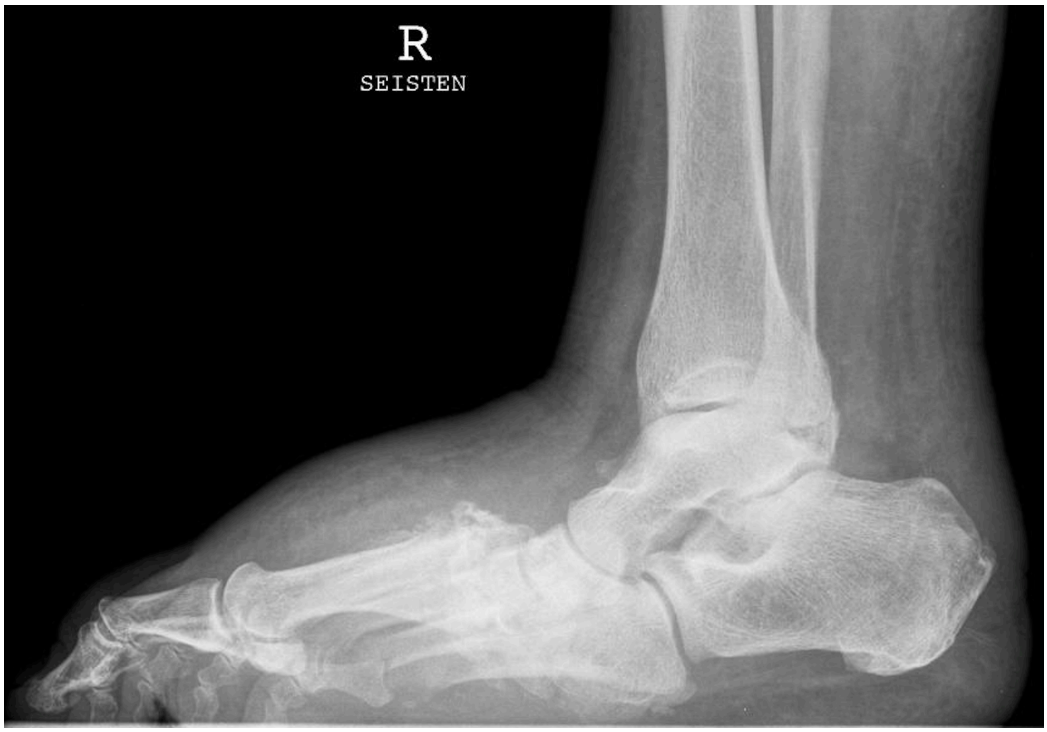


Figure 3. Lateral plain radiography of acute Charcot foot (Eichenholtz Stage I). Note the marked soft tissue swelling on the dorsum of the foot and extensive bone and joint destruction of the midfoot (S&F- classification II).

2.4.3.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is increasingly used for the diagnosis of CF due to its accuracy in detecting early changes of CF when clinical suspicion is high and plain radiographs are still normal (stage 0) or when changes in plain radiographs are minimal or equivocal (Chantelau and Poll 2006, Chantelau et al. 2006, Tan and Teh 2007, Schlossbauer et al. 2008) (Figure 4).

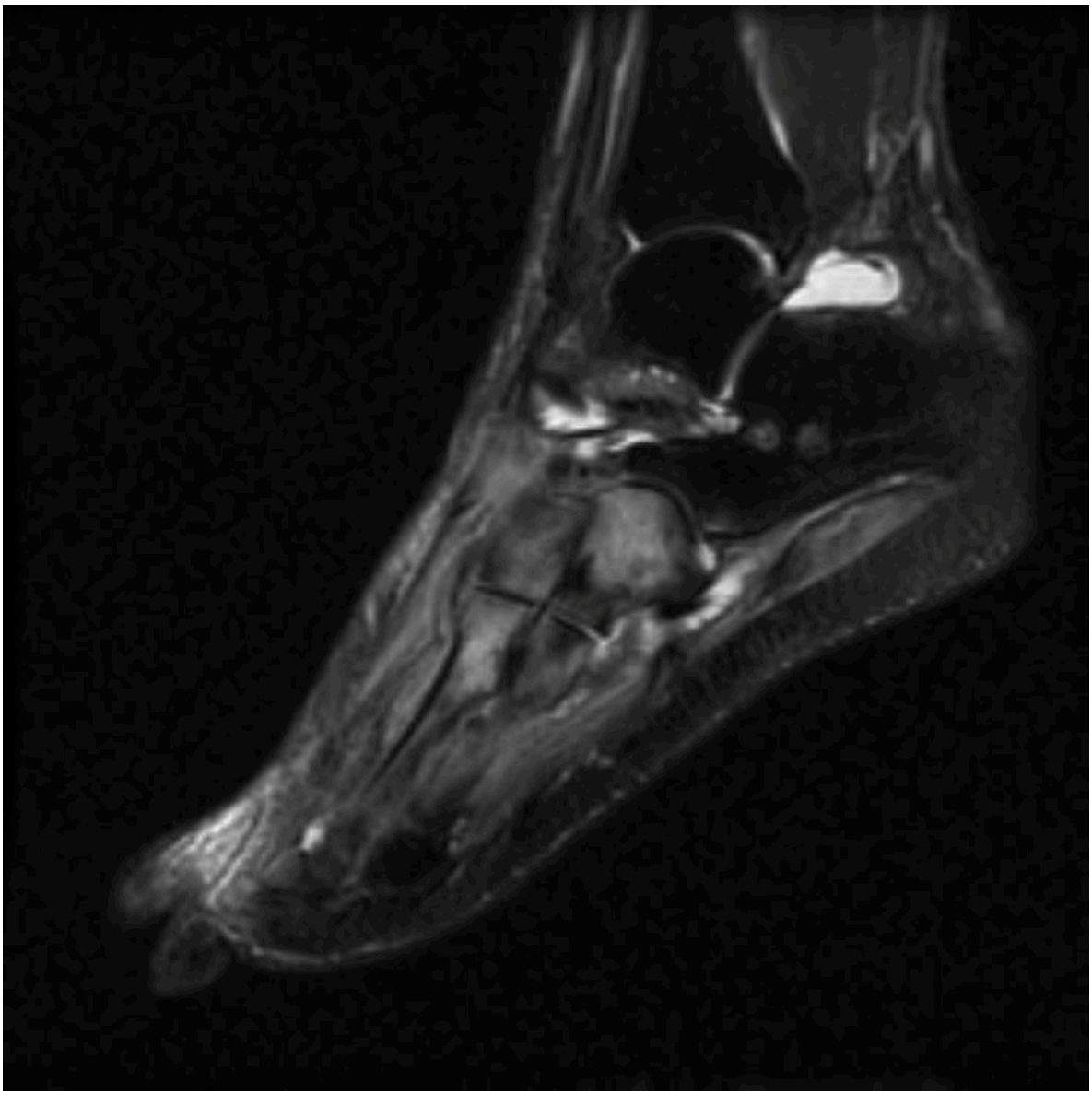


Figure 4. T2-weighted sagittal MRI image of acute (stage 0) Charcot foot. Note the significant bone marrow oedema (os cuboideum, lateral cuneiform and third metatarsal) with no destruction of bones or joints.

In the interpretation of MRI, a common problem is to distinguish osteomyelitis (OM) from CF. CF and OM are both characterized by a decrease in intensity in the marrow on T1-weighted images and increased signal intensity on T2-weighted images (Ledermann and Morrison 2005). Usually the diagnosis of CF is reached by combining MRI findings with the clinical presentation of the disease (Ledermann et al. 2002, Ledermann and Morrison 2005). Over 90% of OM is caused by the direct spread of infection from the skin, so OM often results from tissue defects, abscesses or sinus tracts extending from surface of the skin to the bone (Ledermann et al. 2002). Other MRI findings used to distinguish CF from OM include: localisation (OM: forefoot and toes; CF: midfoot), involvement of one or several bones (OM usually involves one bone; CF often involves multiple bones), presence of a deformity (uncommonly in OM; common in CF) (Ledermann and Morrison 2005, Chantelau and Poll 2006). From a clinical standpoint, MRI has proven an extremely useful method to detect subtle and early changes in CF (i.e. stage 0) before any bone and joint destruction has occurred (Morrison et al. 2001, Greenstein et al. 2002, Chantelau and Poll 2006). However, sometimes the MRI may be over-sensitive in detecting subtle and transient bone marrow changes which do not predict future CF development (Thorning et al. 2010). Therefore MRI findings must always be in accordance with the clinical picture of the disease.

2.4.3.3 Bone scintigraphy, CT and PET-CT

Bone scintigraphy is still widely used in diagnosing acute CF. There are several different bone scintigraphies (”bone scans”) available in which radiolabelling is used to detect increased areas of bone turnover (e.g. 99-technetium, 111-indium and 99m-technetium leukocyte labelled (HMPAO) scans) (Schauwecker et al. 1984, Keenan et al. 1989, Devillers et al. 1998, Palestro et al. 1998, Poirier et al. 2002). The 99-technetium and 111-indium scans are highly sensitive for the diagnosis of CF but not specific enough to differentiate CF from OM (Schauwecker et al. 1984, Palestro et al. 1998). 99m-techentium leukocyte labelled (HMPAO) scan is fairly good in the diagnostics of diabetic foot infection with sensitivity and specificity of 88-93% and 97-98% respectively (Devillers et al. 1998, Poirier et al. 2002). However, diminished circulation (arterial occlusive disease) can result in false negative results and distinguishing soft tissue uptake from bone may be difficult (Palestro et al. 1998).

Computed tomography (CT) has not traditionally been used in the diagnostics of acute CF. It provides better visualization of fragmentation than plain x-rays but is unable to detect subtle

changes in bones and joints at stage 0. Soft tissue resolution is also poor compared to MRI. It may be useful for planning corrective surgery but its role in diagnostics of CF is minimal.

Positron emission tomography CT (PET-CT) is increasingly used in the diagnosis of diseases that increase local cellular metabolism and glucose uptake. Radiolabelled glucose (18F-FDG, fluorodeoxyglucose) is injected intravenously and positron emission tomography (PET) pictures are combined with CT images to detect areas of increased glucose uptake. The intensity of glucose uptake is reported as the Standard Uptake Value (SUV). There are some preliminary reports on PET-CT in the diagnosis of OM and CF (Hopfner et al. 2004, Keidar et al. 2005, Pickwell et al. 2011). CF usually presents with lower SUVs than OM but the role of PET-CT in the diagnosis of CF remains still unclear.

2.4.4 Differential diagnosis

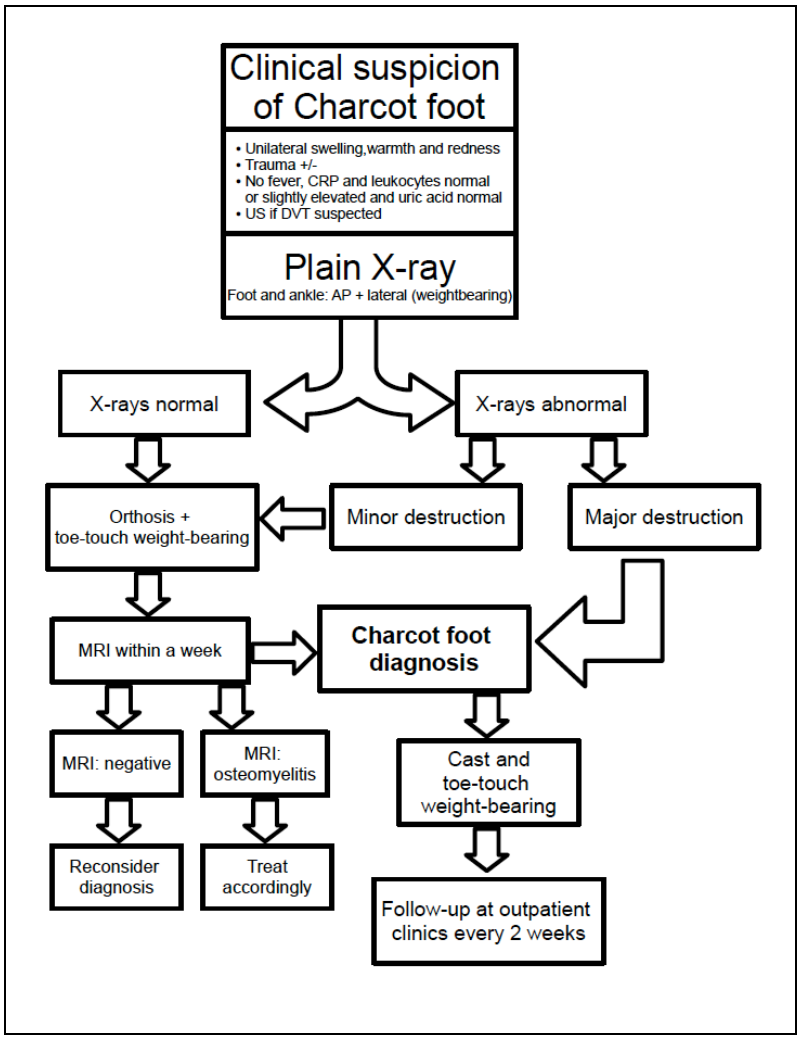
There are several different conditions that may present with clinical signs and symptoms similar to those of acute CF (Table 6).

Table 6. Differential diagnosis of the Charcot foot.

Differential diagnosis	**Characteristics + diagnostic tests**
Erysipelas/cellulitis	Fever, leukocytosis, frequently markedly elevated CRP
Deep venous thrombosis	History, Homans' sign, elevated D-Dimer, doppler ultrasonography
Osteomyelitis	Ulceration, elevated ESR and/or CRP, lytic bone areas on plain X-ray, bone biopsy for bacterial culture
Trauma	History, clinical examination, radiology (x-ray, CT or MRI when appropriate)
Acute gout	History, clinical examination, synovial fluid (or tophus) analysis for monosodium urate crystals, hyperuricaemia, frequently elevated ESR, CRP and leukocytes
Complex regional pain syndrome 1 (CRPS-1)	History of oedema, skin blood flow abnormality, or abnormal sweating in the region of pain since the inciting event. Patchy osteoporosis on plain X-ray
Tibialis posterior tendon dysfunction / rupture	Pes calcaneoplanovalgus, "too many toes" sign. Only subtle inflammatory changes.

Cellulitis/erysipelas causes red, hot and swollen foot similar to CF but is usually accompanied by ulcer, elevated temperature and markedly elevated infection parameters (e.g. C-reactive protein, CRP). CRP value in patients with acute CF remains within normal range (CRP 0-10 g/l) in almost 50% of patients or is only slightly elevated (Jude et al. 2001, Petrova et al. 2007, Judge 2008). White blood cell count (WBC), CRP and erythrocyte sedimentation rate (ESR) will often be elevated in osteomyelitis and markedly elevated in erysipelas. However, in acute CF, WBC, CRP and ESR vary considerably from normal to slightly elevated, mainly due to local tissue damage. Deep venous thrombosis and acute gout may resemble the clinical signs of CF but are often fairly easily excluded by duplex vein scan and measurement of serum uric acid. Acute trauma is usually differentiated from acute CF by detailed history (energy of the trauma in accordance with findings) and radiographic investigations (plain x-rays, CT or MRI). If a neuropathic foot in a patient with diabetes sustains trauma or infection (or any other insult) it may trigger the development of CF and a proper clinical follow-up must be arranged.

Figure 5. Diagnostic pathway of acute Charcot foot.



2.5 Management of the Charcot foot

The rarity of CF and the lack of uniform diagnostic criteria as well as the inability to accurately measure the efficacy of the treatment have made it difficult to design and conduct high-quality studies on the management of CF. Various treatment protocols have been proposed by experts with no single regimen emerging as the most effective (Schon and Marks 1995, Pinzur et al 2000, Jude et al 2001, deSouza 2008). There are only a few randomized controlled trials (RCT) with CF and all of these address only the medical management of acute CF (Jude et al. 2001, Pitocco et al. 2005, Bem et al. 2006). The management of CF can be divided into two phases: the management of the acute CF and chronic (inactive) CF.

2.5.1 Management of acute Charcot foot

2.5.1.1 Immobilization and off-loading

Elimination of continuous stress on the affected areas of the foot is essential to stop the vicious circle of repeated trauma and inflammation in the early phase of acute CF. Thus, the mainstay of the initial management of acute CF has traditionally been total off-loading of the affected foot and a non-removable plaster cast until subsidence of the acute inflammation (Schon and Marks 1995, Armstrong et al. 1997, Johnson 1998, Pinzur et al. 2000). The cast is changed and clinical signs of inflammation (swelling, redness and temperature difference) are checked every two weeks. The casting is continued until the temperature difference between the affected and not-affected foot is less than 2°C and the other signs of inflammation have disappeared (transitional stage). Usually this takes 12-18 weeks (Armstrong et al. 1997, Jude et al. 2001). After this, partial weight-bearing may be started and the cast is replaced by a removable ankle-foot orthosis. Some studies report benefit from specialized footwear (e.g. Charcot restraint orthotic walker and patellar tendon-bearing brace) after cast treatment in acute CF (Morgan et al. 1993, Guse and Alvine 1997, Mehta et al. 1998). Orthosis and partial weightbearing are continued until the chronic stage (no temperature difference between feet, no erythema or abnormal swelling) is reached and custom made shoes or orthotic devices are prescribed. It is difficult for patients with complicated diabetes to be completely non-

weight-bearing due to numerous co-morbidities and absolute adherence to non-weight-bearing in different patient series is not known. However, in two studies (Pinzur et al. 2006, de Souza 2008) no deleterious effects were observed of weight-bearing on the clinical outcome of acute CF. The ultimate goal of the treatment of acute CF is to arrest the acute process of inflammation and to prevent the development of permanent deformities.

2.5.1.2 Medical management

Radiographically evident bone resorption and detection of elevated levels of bone turnover markers in circulation led to the logical assumption that osteoclasts and increased bone turnover play a decisive role in the pathogenesis and natural clinical course of acute CF. Increased levels in markers of bone resorption (serum N-telopeptides of type 1 collagen, NTx and urinary pyridinoline cross-linked carboxy-terminal telopeptide domain of type 1 collagen, 1CTP) were observed, which was not matched by an increase in markers indicating bone formation (carboxy-terminal propeptide of type 1 collagen, P1CP) (Edelson et al. 1996, Gough et al. 1997). This led to the hypothesis that osteoclast inhibitors could be beneficial in the management of acute CF.

Bisphosphonates have been used in clinical medicine since 1968. Since then, various indications for their use have been introduced including osteoporosis, Paget's disease, bone metastases, multiple myeloma, primary hyperparathyroidism and osteogenesis imperfecta. (Fleisch 1998) Bisphosphonates are pyrophosphate analogues in which the oxygen atom of the pyrophosphate molecule (P-O-P) is replaced by a carbon atom (P-C-P) (Green 2004). Bisphosphonates accumulate in the mineralized bone matrix and are released during bone resorption. First generation bisphosphonates (etidronate and clodronate) have non-nitrogen containing side chains and during bone resorption these molecules accumulate inside activated osteoclasts and are metabolized to cytotoxic ATP-analogues that induce osteoclast apoptosis (Selander et al. 1996, Lehenkari et al. 2002). Nitrogen-containing bisphosphonates (e.g. zoledronic acid, alendronate, pamidronate, ibadronate and risedronate, i.e. second generation bisphosphonates) carry nitrogen containing side chains which increase their antiresorptive potency (Fleisch 1998). After internalization to osteoclasts, nitrogen-containing bisphosphonates inhibit farnesyl diphosphonate (FFP) synthase in the biosynthetic mevalonate pathway (Rogers et al. 1997, Luckman et al. 1998). As a result osteoclasts are not able to form the tight-sealing zone or ruffled borders required for bone resorption. The potency of the FFP synthase inhibition of various nitrogen-containing

bisphosphonates also correlates with their potency to inhibit bone resorption *in vitro* (Dunford et al. 2001). The bone resorption inhibiting capacity (*in vitro*) of zoledronic acid is x25 and x100 that of alendronate and pamidronate, respectively (Green et al. 1994, Dunford et al. 2001).

After the pilot study on the effect of pamidronate in the resolution of the acute CF by Selby et al. (1994), a larger randomized prospective placebo-controlled trial by Jude et al. (2001) compared the effect of a single infusion of 90mg of pamidronate to placebo in addition to standard foot care (immobilization and off-loading). Thirty-nine patients were recruited and randomized. The temperature difference between the affected and not-affected feet fell significantly in both groups at two weeks with further decrease at four weeks in the treatment group reaching statistical significance. Also, a significant reduction in patient's symptom scores (pain, discomfort and swelling) was observed in the treatment group throughout the study period. There was also an effect of a single pamidronate infusion on bone turnover markers but the reduction was not long-lasting. Authors suggested that repeated doses of bisphosphonates might be more effective.

Pitocco et al. (2005) randomized 20 patients to standard foot care and alendronate (70mg by mouth once a week for six months) therapy or standard foot care only. They measured bone turnover markers, local bone mineral density (local BMD), pain and temperature difference at baseline and at six months. A significant fall was noticed in some bone turnover markers (hydroxyprolin and 1CTP). The local BMD increased and pain decreased significantly in the treatment group at six months. The reduction in the temperature difference between groups did not reach statistical significance.

Anderson et al. (2004) published a retrospective study on 23 patients comparing a single pamidronate (60-90mg, dose depending on renal function) infusion to standard foot care (off-loading and immobilization). They measured temperature difference reduction between feet at two days and two weeks and serum alkaline phosphatase (AFOS) levels at two weeks. The authors found that the reduction in temperature differences and the fall in AFOS were significantly more pronounced in the pamidronate group, suggesting a possible effect of the medication to halt the acute Charcot process.

Calcitonin is a physiological endogenous inhibitor of bone resorption. It decreases osteoclast formation, osteoclast attachment and bone resorption in organ cultures and animal models (Kallio et al. 1972, Holtrop et al. 1974, Azria 2003). Only one randomized controlled trial of the effect of calcitonin on the management of acute CF has been reported (Bem et al. 2006). The randomized controlled trial on 32 patients investigated the effect of calcitonin (200IU daily for six months with calcium supplementation) in the management of acute CF. A small but statistically significant

difference was observed in the reduction of the temperature differences and also on the bone turnover markers between the groups.

There is still no conclusive evidence to support the use of bisphosphonates or calcitonin in the treatment of the acute CF. However, although there are no scientific evidence of the effect of calcium and vitamin D supplementation in the treatment of acute CF, it might be beneficial to ensure the adequate supply of calcium and vitamin D during the management of acute CF. Table 7 summarizes clinical trials in the medical management of acute Charcot foot.

Table 7. Clinical trials of medical management of the acute Charcot foot.

Reference	**N**	**Intervention**	**Patient demographics**	**Primary outcome measures**	**Results**
Jude et al. 2001	39	Single intravenous infusion of 90mg of pamidronate vs. placebo (RCT, double-blind) Standard foot care in both groups	F/M: 13/26 Mean age 56 yrs DM type 1/2: 13/26 Mean DM duration 18 yrs.	Disease activity (temperature difference between feet) Symptom score (pain, swelling and subjective discomfort)	At 4 weeks, a significantly greater reduction in the temperature difference in the treatment group A significant reduction in symptom score in the treatment group over the whole 12 months of treatment
Pitocco et al 2005	20	70mg of alendronate / week per os + standard foot care vs. standard foot care (RCT)	N/R	Markers of bone metabolism Pain Foot (BMD)	Significant reduction in bone resorption markers and pain at 6 months in the treatment group Foot BMD increased in the treatment group
Anderson et al. 2004	23	Single infusion of 60-90 mg of pamidronate and standard foot care vs. standard foot care (retrospective study)	N/R	Temperature reduction Changes in AFOS	Significant reduction in temperature difference in the treatment group at 2 days and 2 weeks Significant reduction in AFOS at 2 weeks in the treatment group
Bem et al. 2006	32	200 IU calcitonin, (nasal spray) + calcium supplementation vs. calcium supplementation (RCT) Standard foot care in both groups	F/M: 21/11 Mean age 54 yrs Type 1/2: 22/11	Disease activity (temperature and bone turnover markers)	Significantly greater reduction in bone turnover markers in the first 3 months in the treatment group No significant difference in the reduction in temperature difference between groups

RCT, randomized controlled trial; BMD, bone mineral density; AFOS, alkaline phosphatase; N/R, not reported

2.5.1.3 Surgical management of acute Charcot foot.

Surgical management of CF is primarily based on small, uncontrolled retrospective case series and expert opinions. Surgical site infections around the foot and ankle in patients with diabetes are more common than in patients without diabetes (Wukich et al. 2010, Wukich et al. 2011a). It seems that it is peripheral neuropathy that is most strongly associated with postoperative infectious complications and patients with complicated diabetes with peripheral neuropathy are six times more likely to experience a postoperative complication compared to non-neuropathic diabetic patients (Armstrong et al. 1996, Wukich et al. 2010).

In patients presenting with acute CF with no apparent foot deformity (stage 0), conservative management is the mainstay of the treatment (Chantelau 2005, Wukich et al. 2011b). Surgery has generally been avoided during the acute inflammatory stage of CF due to the potentially increased risk of wound infection or mechanical failure of the fixation in the acute stage of the disease (Trepman et al. 2005, Pinzur 2007b).

Reconstructive surgery of an acute CF may be considered if the deformity or instability cannot be effectively controlled or accommodated by immobilization and off-loading (Sella and Barrette 1999, Pinzur 2004, Trepman et al. 2005). Patients with unstable foot or ankle deformities at the acute stage of the disease process comprise this ”high risk” sub-group of acute CF patients. Unstable hind- or midfoot deformities may be difficult to accommodate with casts or orthoses and these patients carry a markedly increased future risk for development of plantar foot ulcerations and subsequent amputation (Saltzman et al. 2005). In these patients early realignment surgery may be indicated and acceptable complication rates have recently been reported in such cases (Simon et al. 2000, Mittlmeier et al. 2010).

The ultimate goal of early realignment surgery is to restore a stable, plantigrade foot with ulcer healing and elimination of infection. Different techniques of realignment and osseous fixation have been proposed with no single method emerging as the most effective (Farber et al. 2002, Fabrin et al. 2007, Pinzur 2007a, Pinzur and Sostak 2007, Wukich et al. 2008, Assal and Stern 2009, Mittlmeier et al. 2010). Due to the poor bone quality in acute CF most authors agree that a postoperatively extended period of non-weightbearing is necessary to ensure bone healing (Simon et al. 2000, Pinzur 2007b, Mittlmeier et al. 2010). It should be noted that even after a successful surgical reconstruction of CF, accommodative footwear will be necessary as loading of the sole of the foot is still likely to be abnormal. There is some preliminary data on electrical bone stimulation as an adjuvant therapy after surgical reconstruction to promote healing of arthrodeses (Strauss and Gonya 1998, Petrisor and Lau 2005, Hockenbury et al. 2007).

2.5.2 Management of chronic Charcot foot

2.5.2.1 Accommodative footwear

The goals of the management of chronic CF are to eliminate areas of increased plantar pressures with prescription shoes, boots or braces, preserve the integrity of the skin with continuous foot care and provide a stable and plantigrade foot with surgery if necessary. Most patients need adaptation of footwear to accommodate their deformity in addition to custom-made insoles and regular renewal of the footwear.

The time required to reach the chronic stage of CF has been reported to be 3-12 months from the initial application of total contact cast (Armstrong et al. 1997, Fabrin et al. 2000, Saltzman et al. 2005, de Souza 2008, Petrova and Edmonds 2010). Presence of chronic Charcot deformity is the most important risk factor for ulcerations and increases the relative risk of foot ulceration 3.5-fold (Boyko et al. 1999). Fabrin et al. (2000) reported an ulceration incidence of 37% after a median of three years of follow-up and Saltzman et al. (2005) reported the incidence of 47% after a median of 3.8 years of follow-up in patients with CF. Prevention of subsequent ulcerations in the deformed CF is challenging and requires continuous monitoring of multiple risk factors (Boyko et al. 1999).

2.5.2.2 Reconstructive surgery

Indications for reconstructive surgery in a chronic CF are the correction of fixed deformities causing recurrent ulcerations and fixation of marked instability not amenable to custom made shoes, orthosis or walkers (Schon et al. 1998). Pinzur (2004) reported that 60% of midfoot CF cases were successfully managed by conservative means and 40% required some surgical procedure at a minimum of 1-year follow-up in accordance with an earlier study by Schon et al. (1998), where one-third of midfoot CF patients needed surgery.

In a consecutive series of 127 initially conservatively managed acute CF cases, Saltzman et al. (2005) found that patients with open ulcers at presentation or patients with recurrent ulcerations were more likely to need transtibial amputation with an annual risk for amputation of 2.7% during median follow-up of 3.8 years. Forty-nine percent of patients developed recurrent ulcers and recurrence was more common in patients with more severe deformities and with those who needed orthoses to accommodate the unstable or deformed foot.

Different techniques for the correction of deformities have been described including: exostectomy (Brodsky and Rouse 1993, Rosenblum et al. 1997, Laurinaviciene et al. 2008), arthrodeses (Papa et al. 1993, Stone and Daniels 2000, Mittlmeier et al. 2010) and Achilles tendon lengthening (Hastings et al. 2000, Holstein et al. 2004, Maluf et al. 2004). Exostectomy is a simple procedure in which the most prominent area of bony prominence is cut away with no attempt to correct the deformity. It is a fast procedure with a low complication rate and at the midfoot area it yields acceptable results in terms of prevention of future ulcerations (Brodsky and Rouse 1993, Pinzur 2004, Laurinaviciene et al. 2008).

If the overlying deformity is severe enough and simple exostectomy will not suffice, a combination of arthrodeses with osteotomies is needed to correct the deformity. There are numerous different techniques to achieve fixation after deformity correction including screws, conventional plates, locked plates, bolts, intramedullary devices and external fixators (Farber et al. 2002, Dalla Paola et al. 2007, Fabrin et al. 2007, Pinzur 2007a, Assal and Stern 2009, Sammarco 2009). The choice of implant(s) is often based on surgeon's preferences and currently there is insufficient scientific evidence to recommend one technique over the other as long as the soft tissue envelope around the foot is handled appropriately (Pinzur 2004, Sammarco 2009). There are no conclusive long-term data on the effect of reconstructive surgery on ulcer prevention, limb preservation or quality of life in the patients with chronic CF (Pinzur and Evans 2003, Dhawan et al. 2005).

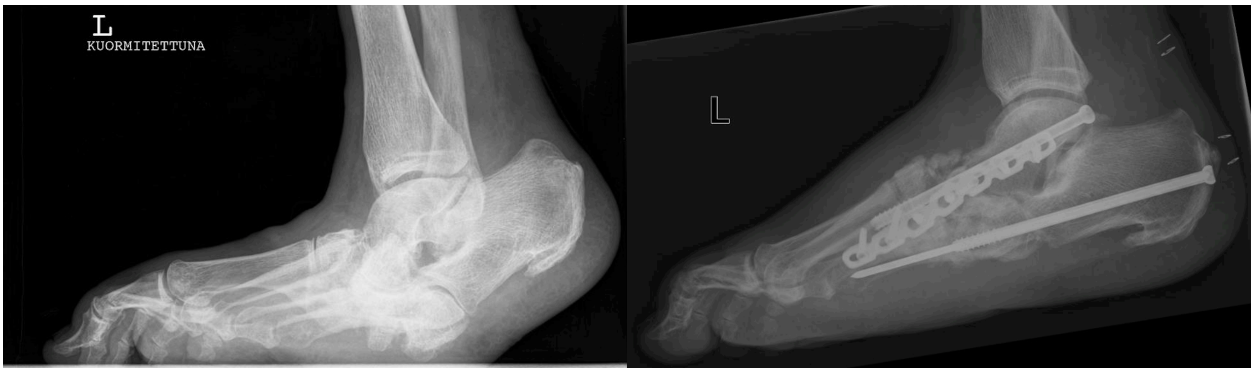


Figure 6. Reconstruction of the chronic midfoot Charcot foot with realignment of the midfoot, Achilles tendon lengthening and fixation with 3.5mm reconstruction plate with locking screws and 6.5mm cannulated screws. Note the typical "rocker-bottom deformity" on the preoperative x-ray.

2.6 Bone mineral density in diabetes and in patients with Charcot foot

It was demonstrated more than 50 years ago that diabetes is associated with decreased bone mass (Albright and Reidfenstein 1948). Since then a number of research groups have assessed the association of type 1 and type 2 diabetes with reduced bone mineral density (BMD) (Kayath et al. 1994, Krakauer et al. 1995, Hampson et al. 1998, Miazgowski and Czekalski 1998, Christensen and Svendsen 1999, Kao et al. 2003, Schwartz 2003, Thrailkill et al. 2005). The majority of recent studies confirm that there appears to be certain differences between the mechanisms responsible for the development of bone loss and the magnitude of bone loss observed in type 1 and type 2 diabetes (Tuominen et al. 1999, Hofbauer et al. 2007). Local osteolysis and osteopenia play a central role during the acute stage of CF, but it is not known whether it is responsible or a prerequisite for the development of acute CF or merely just a consequence of it.

2.6.1 Bone mineral density and diabetes

The association of type 1 diabetes and decreased BMD has been confirmed in several studies and the pathophysiological mechanisms are considered to be multifactorial (Hofbauer et al. 2007, Vestergaard 2007). The reduced peak bone mass detected shortly after the onset of type 1 diabetes in adolescents has led to a hypothesis that insulin and insulin-like growth factor-1 (IGF-1) have an important role in the development of bones during childhood growth (Bouillon et al. 1995, Moyer-Mileur et al. 2004, Thrailkill et al. 2005). Insulin and IGF-1 continue to have an anabolic effect on bones, also in adults (Thrailkill et al. 2005). Administration of exogenous insulin normalizes insulin receptor expression but IGF-1 receptor expression is only partially recovered indicating that patients with type 1 diabetes may have a continuous deficiency of IGF-1's anabolic effect on bone (Einhorn et al. 1988, Maor and Karnieli 1999). Campos Pastor et al. (2000) detected a positive effect of "intensive insulin therapy" on bone metabolism in patients with type 1 diabetes.

There is also a mounting body of evidence that complications of diabetes (micro-and macroangiopathy, retinopathy, nephropathy and neuropathy) may decrease BMD in type 1 diabetes (Wientroub et al. 1980, Lunt et al. 1998, Rix et al. 1999, Campos Pastor et al. 2000, Rigalleau et al. 2007). The role of amylin (osteotrophic amino acid secreted by pancreatic β-cells) and other

pancreatic and enteric hormones in the decrease of BMD in patients with type 1 diabetes remains yet to be determined (Horcajada-Molteni et al. 2001, Clowes et al. 2005).

While low BMD is consistently reported in studies concerning type 1 diabetes, the relationship is less clear in type 2 diabetes, with studies showing unchanged or slightly increased BMD in type 2 diabetes (Hofbauer et al. 2007). Most of the studies reporting increased BMD involve only postmenopausal women (Barrett-Connor and Holbrook 1992, Christensen and Svendsen 1999, Kao et al. 2003, Dennison et al. 2004, Strotmeyer et al. 2004, Schwartz et al. 2005). Patients with type 2 diabetes are often overweight and some studies report that obesity protects against bone loss in type 2 diabetes (Wakasugi et al. 1993, Bridges et al. 2005). This may be associated with increased mechanical loading due to obesity and altered levels of cytokines (leptin, adiponectin and resistin) secreted by adipose tissue (Lenchik et al. 2003). In contrast to patients with type 1 diabetes with deficiency of endogenous insulin (and amylin), patients with type 2 diabetes have peripheral insulin resistance with variable degree of hyperinsulinemia due to the hyperglycaemia. Hyperglycaemia may adversely effect bone mass by leading to nonenzymatic glycosylation of various bone proteins which may impair bone quality (Vashishth et al. 2001), causing hypercalciuria (caused by glucosuria) and impairing parathyroid hormone and vitamin D response to hypocalcemia (Okazaki et al. 1997, D'Erasmo et al. 1999). However, the adverse effects of hyperglycaemia on the skeleton are thought to be counteracted by the positive effects of obesity on bone mass.

2.6.2 Bone mineral density in patients with Charcot foot

There are only few studies investigating BMD in patients with acute or chronic CF. The appendicular (lumbar spine and hips) BMD of patients with acute or chronic CF has been reported in three trials (Young et al. 1995, Jirkovska et al. 2001, Christensen et al. 2010). In these studies the BMD of CF patients was compared to that of diabetic patients with neuropathy and the CF-affected side hip BMD was compared with to the non-affected side. The BMD of the lumbar spine in patients with CF has been reported to be similar to that of control population and T-scores are usually within normal limits (Young et al. 1995, Jirkovska et al. 2001, Christensen et al. 2010). The BMD of the hip is reported to be lower in patients with acute CF compared to control patients with diabetes and neuropathy (Young et al. 1995, Jirkovska et al. 2001), although Christensen et al. (2010) did not find any difference between acute or chronic CF patients and control population. Reduced BMD of the hip in the CF-affected side was reported by Young et al. (1995).

Calcaneal BMD (measured by quantitative ultrasound, QUS) is used to assess the local BMD in CF (Jirkovska et al. 2001, Petrova et al. 2005, Sinacore et al. 2008, Christensen et al. 2010, Petrova and Edmonds 2010). Most of the studies are cross-sectional studies and show a significant reduction of the calcaneal BMD on the CF-affected side compared to the non-affected side (Jirkovska et al. 2001, Petrova et al. 2005), but Christensen et al. (2010) observed no difference between the BMD of the affected and non-affected side. Petrova and Edmonds (2010) measured calcaneal BMD at presentation, after three months and at the time of clinical resolution. The BMD of the affected side CF was significantly reduced compared with the non-affected side CF at all measurements in patients with type 1 and type 2 diabetes. There was no change in the BMD of the non-affected side during the study period. Studies on BMD in Charcot foot are presented in Table 8.

Table 8. Results of prior studies on bone mineral density (BMD) in patients with Charcot foot.

Reference	**Number of cases**	**Site and method of BMD measurements**	**Lumbar spine and proximal femur BMD**	**Calcaneal BMD**
Young et al. 1995	17	Lumbar spine and proximal femur, DEXA	LS: no difference PF: affected side decreased BMD	N/R
Jirkovska et al. 2001	16	Calcaneus, QUS Lumbar spine and proximal femur, DEXA	LS: no difference PF: increased frequency of osteoporotic BMD in CF patients	Affected foot decreased BMD
Petrova et al. 2005	35	Calcaneus, QUS	N/R	Type 1 DM: decreased BMD in affected and non-affected foot Type 2 DM: decreased BMD in affected foot
Sinacore et al. 2008	32	Calcaneus, QUS	N/R	Affected foot < non-affected foot < healthy control patients
Petrova and Edmonds 2010	36	Calcaneus, QUS	N/R	Affected foot decreased BMD compared with non-affected foot
Christensen et al. 2010	24	Calcaneus, lumbar spine and proximal femur, DEXA	LS: no difference PF: no difference	Calcaneal BMD lower in patients with chronic CF

DEXA, dual X-ray absorptiometry; QUS, quantitative ultrasound; BMD, bone mineral density; LS, lumbar spine; PF, proximal femur; N/R, not reported

2.7 Long-term outcome of Charcot foot

There are only a few studies reporting long-term consequences (major amputation, mortality and quality of life) of CF with a significant follow-up time.

Major amputations (above ankle joint)**.** Saltzman et al. (2005) presented an annual risk of 2.7% for major amputation after the development of CF (median follow-up 3.8 years), whereas Fabrin et al. (2000) reported a 1.7% rate for major amputation after a median of 4 years (minimum follow-up 6 months). Pinzur et al. (1993) followed 47 patients for an average of 3.6 years with no major amputations performed during follow-up, but later Pinzur (1999) reported a 9% major amputation rate (21 amputations for 237 patients) during a ten-year period.

Mortality. Two earlier studies describe a very low mortality rate after diagnosis of CF. Armstrong et al. (1997) reported no deaths in 55 patients followed up for 1.8 years and Fabrin et al. (2000) published two deaths in 115 patients (1.7%) followed for 4 years. On the contrary, three recent reports from the U.K. and U.S. showed a markedly incresed mortality risk for patients with CF. Gazis et al. (2004) found that 44.7% of patients with CF died after an average follow-up of 3.7 years. Sohn et al. (2009) suggested that CF was associated with a significantly increased mortality risk (28% mortality rate in 5-year follow-up) independent of neuropathic foot ulcers and other comorbidities. van Baal et al. (2010) reported a median survival of 8 years in patients with acute CF and life expectancy of these patients was reduced by 14 years (when compared with normative U.K. population data).

Quality of life. Pinzur and Evans (2003) investigated the effect of CF on individuals' general health and health-related quality of life in 18 CF patients. The general health was rated fair or poor and all component scores of SF-36 were inferior compared with population controls.

3. AIMS OF THE STUDY

The aim of the present study was to investigate the effects of zoledronic acid in the management of acute Charcot foot. In addition, the long-term consequences of chronic Charcot foot were determined and a comprehensive analysis conducted on a historical patient series. The specific aims of this study were the following:

I To describe patient demographics and management details of a historical patient series with Charcot foot.

II To investigate the clinical efficacy of zoledronic acid on the clinical resolution of the acute Charcot foot.

III To assess bone mineral density in patients with acute Charcot foot and to investigate the effect of zoledronic acid on bone mineral density changes during the management of acute Charcot foot.

IV To evaluate the long-term functional and clinical outcome and the quality of life of patients with chronic Charcot foot

4. MATERIALS AND METHODS

4.1 Study population and study design

Table 9 presents the study population in studies I-IV.

Table 9. Study population in Studies I-IV.

Study	Number of patients (feet)	Male / female	Data collection	Type 1 / Type 2 DM	Follow-up
I	32 (36)	22/10	1994-2000	13/19	21 (1-81) months
II	35	29/6	2002-2007	13/22	52 months
IV	35	29/6	2002-2007	13/22	6 months
III	41 (42)	12/17*	1991-2002	12/17	8 (5-16) years

* 12 patients deceased

4.1.1 Patient cohort for determining demographics and management details of a historical patient series of Charcot foot (Study I)

From 1 May 1994 to 31 October 2000 a total of 36 cases (32 patients) of CF were diagnosed at the Departments of Surgery and Internal Medicine at Tampere University Hospital. Manual list of all these patients were maintained throughout the study period and study data was obtained from patient records and radiographs for this descriptive retrospective study. Demographic data was recorded at the time of the initial diagnosis of CF. The type (WHO 1999) and duration of diabetes, presence of neuropathy (insensitivity to 5.07 Semmes-Weinstein monofilament and vibratory stimulus (128Hz), retinopathy and nephropathy (defined as albumin levels > 30 µg/minute in an overnight urine sample) and $HbA1_c$ percentage of glycosylated haemoglobin values were also recorded. Disease-specific data were collected: the presence or absence of instigating trauma and temperature differences between the feet at the time of the diagnosis. The duration of symptoms

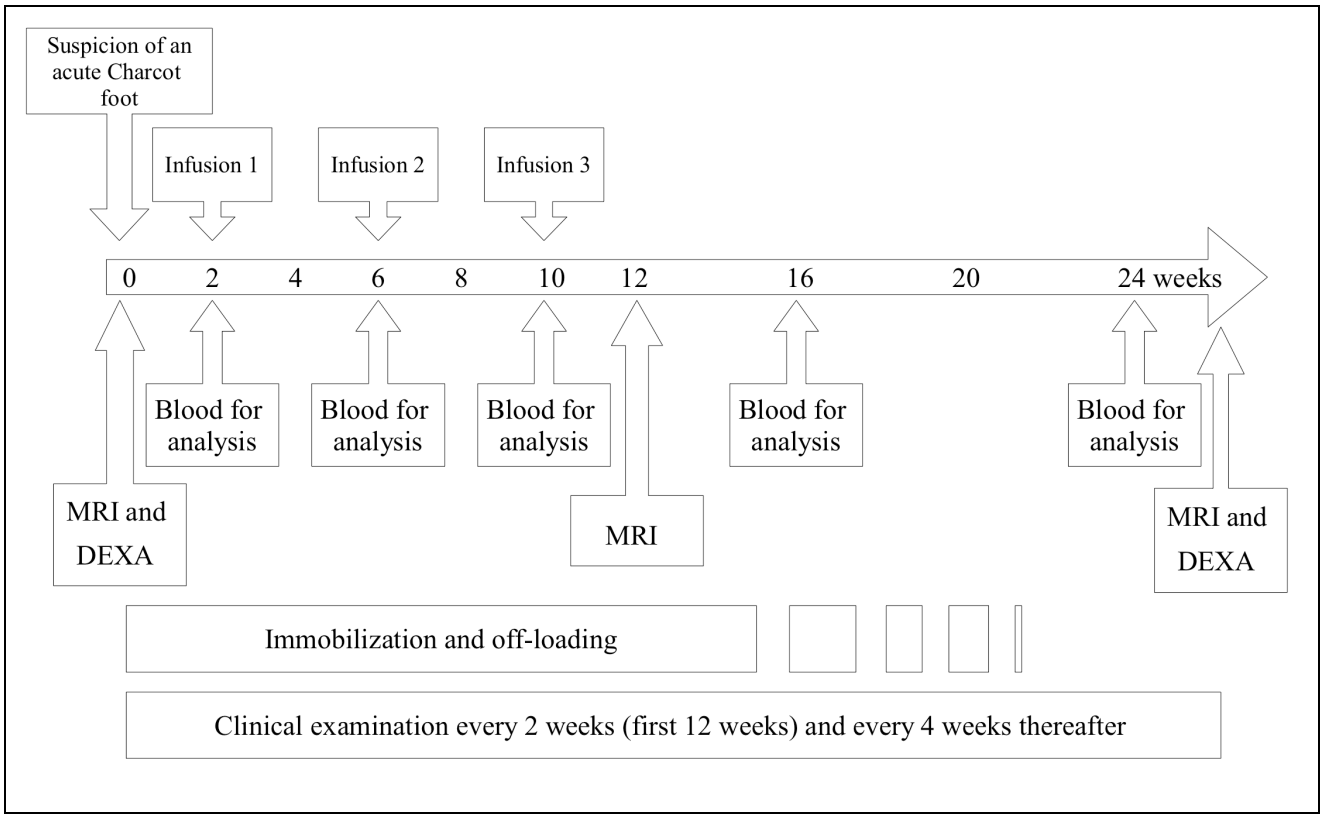
prior to diagnosis was evaluated likewise diagnostic delay and possible preceding erroneous diagnoses were assessed. Radiological findings were classified according to Eichenholtz (1966) and with clinical findings the stage of the disease process was determined as dissolution (acute, stage 1), coalescence (transitional, stage 2) or resolution (chronic, stage 3). The involvement of hindfoot, midfoot or forefoot distribution of CF was classified according to Sanders and Frykberg (1991). Weight-bearing radiographs and MRI were analysed. The treatment regimen was recorded: duration of casting and use of any kind of orthoses, duration of non-weightbearing and partial weightbearing, need for custom-made insoles and possible bisphosphonate medication. All surgical procedures were recorded, indication, type, timing, complications and outcome of each procedure included.

4.1.2 Prospective cohort of patients with acute Charcot foot: a prospective randomized study of management with zoledronic acid or placebo (Studies II-III)

The study was primarily designed to ascertain whether three infusions (administered at one month intervals) of 4mg zoledronic acid (Zometa™) could accelerate the clinical resolution of the acute CF process. The study was carried out at the Department of Internal Medicine in Tampere University Hospital. The local ethics committee approved the protocol developed by the investigators. The trial was conducted in accordance with the Declaration of Helsinki and all patients gave their written informed consent prior to the initiation of treatment. Patients were assessed at baseline, at 2 to 4-week intervals for the first 3 months and at 6, 9 and 12 months thereafter.

Patients were recruited from the Internal Medicine Diabetic Foot Clinic between April 2002 and October 2007. All patients with acute midfoot CF (S&F classification II and III) were asked to participate and were given written information concerning the study. Patients with severe renal insufficiency (serum creatinine > 400μmol/l) were excluded from the study.

Figure 7. Study design for Studies II and III.



The diagnosis of CF was made on the basis of clinical examination, radiological findings and laboratory tests. The clinical criteria included the presence of a warm, swollen foot with erythema over the warmest area of the foot. Temperature was measured from both feet using an infrared thermometer at the site of the maximum deformity or erythema and from three standard sites (foot sole, dorsum of the foot and anterior to the ankle joint). An increase of 2˚C or more compared to the same site on the contralateral foot was taken to indicate active CF. Measurements were performed at a minimum of 30 minutes of stabilization (supine) after removal of socks, shoes, casts or orthoses. All patients with suspicion of CF by clinical findings had plain radiographs and MRI of the affected foot within 2 weeks after initial assessment. From plain X-rays collapse of bony architecture, osteolysis and bone fragmentation were analysed. The main MRI criteria for Charcot neuroarthropathy were periarticular focal bone marrow oedema, absent sinus tracts and soft-tissue fluid collections and preservation of periarticular subcutaneous fat (Tan and Teh 2007). Peripheral neuropathy was ascertained by insensitivity to 5.07 Semmes-Weinstein monofilament and vibratory stimulus (128Hz). Nephropathy was defined as nightly urine albumin excretion of >30µg/minute.

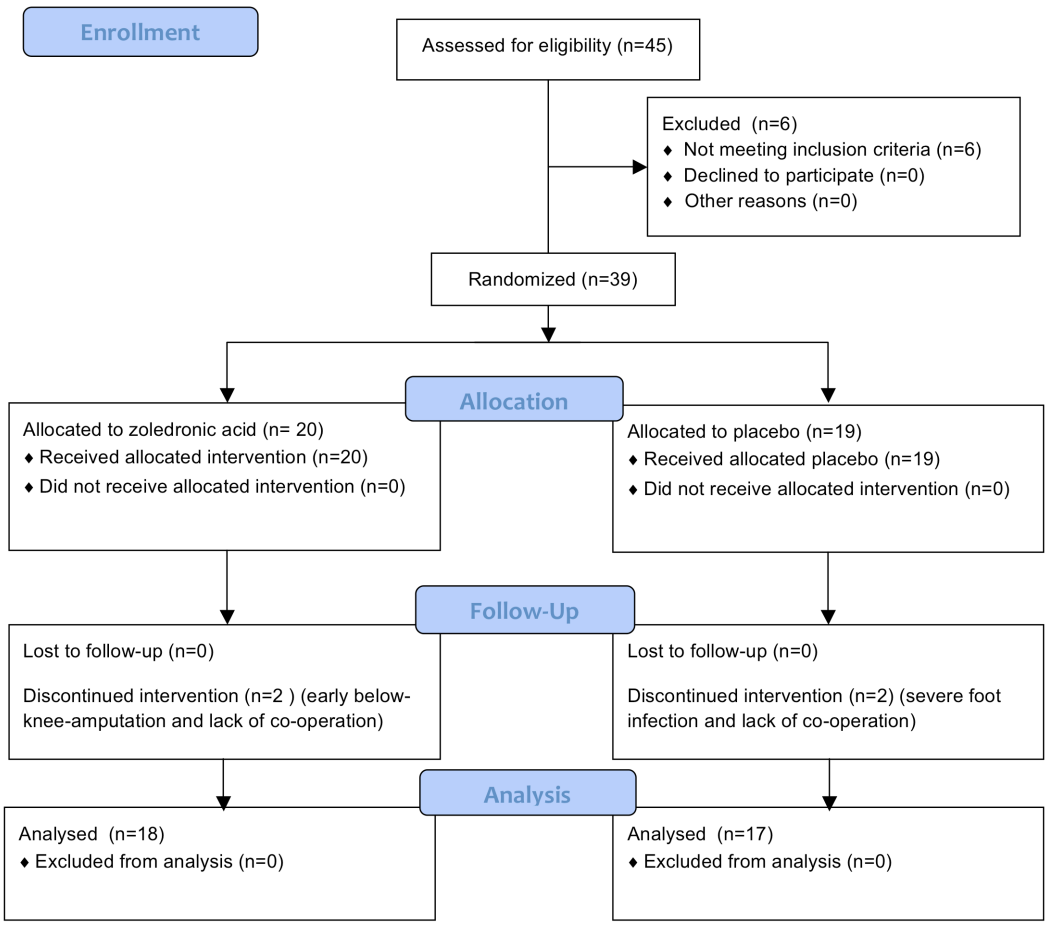
Patients were randomly assigned treatment with three infusions of zoledronic acid (Zometa™ 4mg in 50ml of physiological saline) or placebo (physiological saline) administered at one month

intervals. Investigators, physicians and nurses and all patients were blinded to the randomization. Zoledronic acid and placebo infusions were prepared by the hospital pharmacy. The computer-generated randomization list was provided in advance to the study pharmacist and was followed throughout the study. Infusions were made and delivered by the study pharmacist on the morning of the infusion. All adverse effects related to infusions were registered.

Patients were initially treated conservatively with a non-weight-bearing below the knee cast. The casting with non-weight-bearing was continued until the clinical signs of active Charcot process (absence of swelling, erythema and temperature difference > 2˚C) subsided. When the skin temperature difference between the feet was 1-2˚C and no other clinical signs of an active Charcot process (swelling or erythema) were present, partial weightbearing was allowed and a fixed ankle-foot orthosis applied. The temperature differences and clinical signs of re-activation of the Charcot process were evaluated at 2-4 week intervals in the outpatient clinic until the resolution stage (skin temperature differences between feet less than 1˚C during the last 30-day period and no evidence of marked erythema or oedema) was reached. At this point immobilization was discontinued and full weightbearing was allowed when prescribed accommodative shoe wear (total contact insoles or custom made shoes with rocker soles) was available.

BMD was measured by dual energy x-ray absorptiometry (DEXA, GE Lunar Prodigy, GE, Madison, WI, USA using software version enCORE 10.51.006). The lumbar spine and both hips (femoral neck, trochanter and total hip BMD) were scanned at baseline and at six months after the initiation of the treatment. The absolute bone mineral density values (g/cm^2), T-scores and Z-scores were registered. The WHO definitions of osteopenia (-2.5 < T-score < -1.0) and osteoporosis (T-score < -2.5) were used (WHO-Study-Group 1994). The Z-score was calculated according to a normal reference (incorporated in the scanner) for age, weight, sex and ethnic matched material. Our DEXA scanner's predetermined precision error for longitudinal measurements was 0.009 g/cm^2. All patients (n=35) completed two DEXA measurements and were included in the analysis.
The aim of Study II was to investigate the effect of zoledronic acid on the clinical resolution of Charcot foot as determined by total immobilization time (casting + orthosis). The aims of Study III were to assess the effect of immobilization and off-loading on BMD in patients with acute CF and to determine the efficacy of zoledronic acid in BMD changes during the management of acute CF.

Figure 8. Flowchart of the patients in the study (Studies II-III).



4.1.3 Patient cohort and outcome measures for evaluating the long-term outcome of Charcot foot (Study IV)

Forty-one patients diagnosed with CF were identified at the Departments of Surgery and Internal Medicine in Tampere University Hospital before 31 December 2001 and constitute the study population for this cross-sectional descriptive study. This study was carried out in autumn 2007 and analysed data on patients with at least 5 years of follow-up. The study population of this study (Study IV) included all patients in Study I and additionally 9 patients diagnosed between 1 November 2000 and 31 December 2001. Patients were re-examined in a study focused follow-up visit in autumn 2007. The medical records of the patients were examined for all data related to the study (especially history of previous surgery or ulcerations). A thorough physical examination was

carried out and patients' ambulatory status was evaluated. Each patient completed the American Orthopaedic Foot and Ankle Society (AOFAS) ankle and hindfoot scores (Kitaoka et al. 1994) and patients independently completed the Short-Form Health Survey (Hays and Morales 2001). The Finnish version of the SF-36 for general and chronically ill Finnish population has been validated and is an accepted method for assessing physical and mental health as perceived by the individual (Aalto et al. 1999). The physical functioning component measures the individuals' capacity to perform the activities of daily living. The role-physical component measures the magnitude of disruption in the individuals' work or daily activities due to their disease. It also measures pain, vitality, general health, social functioning, and emotional and mental health.

The main outcome measures for this study were the following: functional outcome determined by AOFAS, clinical outcome determined by number of preceding ulcerations and surgical procedures and health-related quality of life determined by SF-36.

4.2 Statistical analysis (Studies I-IV)

Study I and Study IV. Continuous and normally distributed variables were analysed with Student's t-test and continuous variables without normal distribution with Mann-Whitney U-test. Pearson's chi-square test was used to compare discrete variables. Alpha level for all analyses was set at 0.05.

Study II. Prior to the study, a power calculation for the total sample size was calculated as the number of patients needed to detect a 25% difference in the total immobilization (cast + orthosis) time with a significance level of 0.05 and a power of 80% (n = 22 patients in each group). The results from Study I were used to determine expected average immobilization time and calculate the difference of 25%. Continuous variables are expressed as means with 95% confidence intervals unless otherwise stated; score variables are expressed as median and range. Between-group comparisons of continuous variables at each time point were analysed with Mann-Whitney U test, and within-group comparisons between baseline values were made by Wilcoxon signed-rank test. Categorical data were analysed with chi-square test and Fisher's exact test as appropriate. All tests were two-tailed and the critical value was 0.05.

Study III. Continuous variables are expressed as means with 95% confidence intervals unless otherwise stated; score variables are expressed as mean and standard deviation. Between-group comparisons of continuous variables at each time point were analysed with Student's t-test, and within-group comparisons between baseline and follow-up values were made with Wilcoxon

signed-rank test. Categorical data were analysed with chi-square test and Fisher's exact test as appropriate. All tests were two-tailed and the critical value 0.05. All data was analysed with SPSS 11.0 software (SPSS Inc., Chicago, IL, USA).

5. RESULTS

5.1 Demographic data and management details of a historical patient series (Study I)

Of the 32 patients (with 4 bilateral cases, total of 36 feet), 13 (41%) had type 1 diabetes. Twenty-eight patients (88%) required insulin to control their diabetes, whereas 4 (12%) were managed with oral medication. The average duration of type 1 diabetes was 28 years (range 8-58 years) and of type 2 diabetes 14 years (range 1-28 years). The mean body mass index for male and female patients was 32.9 ± 5.5 kg/m^2 and 34.3 ± 8.5 kg/m^2 respectively. The average of glycosylated haemoglobin ($HbA1_c$) for the whole study group was 9.4%. In 8/36 (22%) cases a triggering traumatic event could be identified and 29 feet (81%) were diagnosed in the dissolution, two in the coalescence, and five in the resolution stage. Midfoot was involved in 31 cases, forefoot in five cases, talocrural joint in three and calcaneus in one. In four cases (11%) more than one area was involved (midfoot together with forefoot or talocrural joint).

In 22 cases (61%), the correct diagnosis was made either by a referring physician or at the initial visit to our institution. The average delay from the first symptoms to the right diagnosis was 29 weeks (range 1-164). Preceding false diagnoses were erysipelas (n=10), deep venous thrombosis (n=5), gout (n=4), osteoarthrosis / arthritis (n=5), fracture (n=2) and unspecific inflammation, osteomyelitis and tumor (n=4). At the initial visit total non-weightbearing and cast or orthosis was prescribed in 16 cases (44%), total non-weightbearing without immobilization in only two (6%) stage 3 cases and 18 cases (50%) were not assigned for treatment (Table 10).

Table 10. The prescribed management at the initial presentation.

Stage (Eichenholtz 1966)	No treatment	Cast or orthosis + total non-weightbearing	Total non-weightbearing
Stage 1 (n = 29)	15	11 cast + 3 orthosis	0
Stage 2 (n = 2)	0	2 cast	0
Stage 3 (n = 5)	3	0	2

At some stage in the treatment 21 cases had a cast with average of 11 weeks (range 4-37). Half (n=18) of the cases had orthosis at some phase of their treatment, average duration 10 weeks (range 3-19). At some point in the treatment 18 patients (50%) received bisphosphonate treatment (pamidronate 30-60 mg infusions once a week for six weeks).

A total of 14 surgical procedures were performed on 10 patients (31%) during an average follow-up time of 21 months (range 1.5-72 months). Two operations were carried out during the acute, one in the transitional and eleven operations in the chronic stage of the disease process (Table 11).

Table 11. Data on 10 surgically managed patients.

Patient	Sex, age	Indication and stage	Intervention	Postoperative course
1	M, 50	Recurrent ulcerations, 3	Exostectomy	Uneventful
2	M, 70	Recurrent ulcerations, 3	Exostectomy	Superficial wound infection managed with antibiotics and local wound care
3	M, 57	Talonavicular destruction, 2	Arthrodesis	Uneventful
4	F, 58	Recurrent ulcerations, 3	Exostectomy	Uneventful
5	M, 63	Talocrural destruction and gross instability, 3	Below-knee amputation	Uneventful
6	F, 44	1. Gross instability, 1 2.-3. Recur. ulcers, 3	1. Triple arthrodesis 2.-3 Exostectomy x 2	1. Nonunion and progression of destruction + recurrent ulcerations 2. Uneventful
7	M, 50	Talocrural destruction, 3	Tibiotalocalcaneal arthrodesis	Uneventful
8	M, 41	Recurrent ulcerations, 3	Exostectomy	Superficial wound infection managed with antibiotics and local wound care
9	F, 51	1. TMT disloc., 1 2. Naviculocuneif. dislocation., 3 3. Gross instability, 3	1. TMT I-V arthrodesis 2. Naviculocuneiform arthrodesis 3. Below-knee amputation	1. Uneventful 2. Nonunion and progression of deformity 3. Uneventful
10	F, 53	TMT I-II dislocation, 3	TMT II-IV and NC-arthrodesis	Uneventful

After six exostectomies two (33%) postoperative wound infections were noted and successfully treated with oral antibiotics. All the exostectomies were performed on feet with healed ulcerations. A total of six arthrodeses (4 midfoot, one tibiocalcaneal and one triple arthrodesis) were performed

and radiological fusion was achieved in four cases. Two postoperative superficial infections (infection rate 33%) were recorded in the arthrodesis group. Immobilization and protective weightbearing after arthrodesis was 12 weeks in five cases and 16 weeks in one case. Two below-knee amputations were performed after a failed arthrodesis and gross instability. One patient (patient 7) with unstable ankle joint was successfully treated with ankle fusion.

Eight of the 18 (44%) patients who were not appropriately immobilized and off-loaded at the initial presentation underwent surgical treatment compared with 2/18 (11%) patients appropriately treated ($p = 0.03$).

5.2 Efficacy of zoledronic acid on the clinical resolution of acute midfoot Charcot foot (Study II).

At baseline there was no significant difference between study groups (Table 12). In the zoledronic acid group (Group Z) the median for total immobilization time was 27 weeks (range 10-62 weeks) and for the placebo group (Group P) 20 weeks (range 10-52 weeks) ($p=0.02$). Feet in Group Z were immobilized in a cast for a median of 15 weeks (range 0-28 weeks) and in Group P for 12 weeks (range 0-20 weeks) ($p=0.13$). Duration of immobilization in orthosis was 15 weeks (7-40 weeks) in Group Z and 10 weeks (range 4-32 weeks) in Group P ($p=0.05$). Total weightbearing with total contact insoles or custom made shoes with rocker soles was permitted after a median of 28 weeks (10-64 weeks) in Group Z and 24 weeks (14-52 weeks) in group P ($p=0.13$). One relapse of CF was diagnosed in each group during the 12-month follow-up period. There was no difference in the median for total immobilization time between randomization groups in patients with type 1 diabetes (Group Z: 28 weeks (range 10-62 weeks), Group P: 22 weeks (range 18-40 weeks), $p=0.36$). In patients with type 2 diabetes management with zoledronic acid led to a significantly longer total immobilization time compared with placebo group (Group Z: 27 weeks (range 12-60 weeks), Group P: 18 weeks (range 12-52 weeks), $p=0.01$). No serious adverse events of zoledronic acid infusions were recorded.

Table 12. Baseline characteristics of the study population (Studies II-III).

Characteristics	**Zoledronic acid group (n=18)**	**Placebo group (n=17)**	**P**
Age (years)	53.8 ± 9.1	56.0 ± 9.2	0.40 §
Sex (F/M)	5/13	1/16	0.18 ¶
Type 1 / Type 2 diabetes (n)	8/10	5/12	0.49 ¶
Duration of diabetes (years)	17.3 ± 14.0	16.9 ± 12.4	0.96 §
Neuropathy (n)	17	15	0.60 ¶
Retinopathy (n)	9	9	1.00 ¶
Nephropathy (n)	15	9	0.08 ¶
Body Mass Index (kg/m²)	29.0 ± 6.4	28.4 ± 6.1	0.94 §
C-reactive protein (mg/l)	12.7 ± 22.1	3.6 ± 4.1	0.07 §
Alkaline phosphatase (U/l) *	156 ± 90	175 ± 153	0.87 §
Ionized calcium (plasma) (mmol/l)	1.26 ± 0.04	1.25 ± 0.05	0.87 §
Phosphate (plasma) (mmol/l)	1.07 ± 0.17	1.04 ± 0.21	0.61 §
HbA1c (%)	8.2 ± 1.4	7.9 ± 1.6	0.64 §
Charcot foot involvement site			
Tarsometatarsal and/or naviculo-cuneiforme joints	14	15	0.66 ¶
Talonavicular and/or calcaneo-cuboideal joints	4	2	
Diagnostic delay (months)	2.5 ± 1.9	2.6 ± 2.0	0.99§
Abnormal foot architecture (n) †	11	7	0.32 ¶
Plantar ulceration (n)	2	1	1.00 ¶
Foot temperature difference (°C)	3.3 ± 1.6	3.2 ± 2.1	0.53 §
Distal pedal pulses present ‡	17	17	1.00 ¶

Data is mean ± SD unless otherwise indicated. * One patient in the zoledronic acid group excluded due to a primary biliary cirrhosis (S-ALP 1250 U/l). † Clinical deformation of the medial longitudinal arch of the foot‡. Arteria dorsalis pedis and arteria tibialis posterior identified. § Mann-Whitney U test. ¶ Fisher's exact test

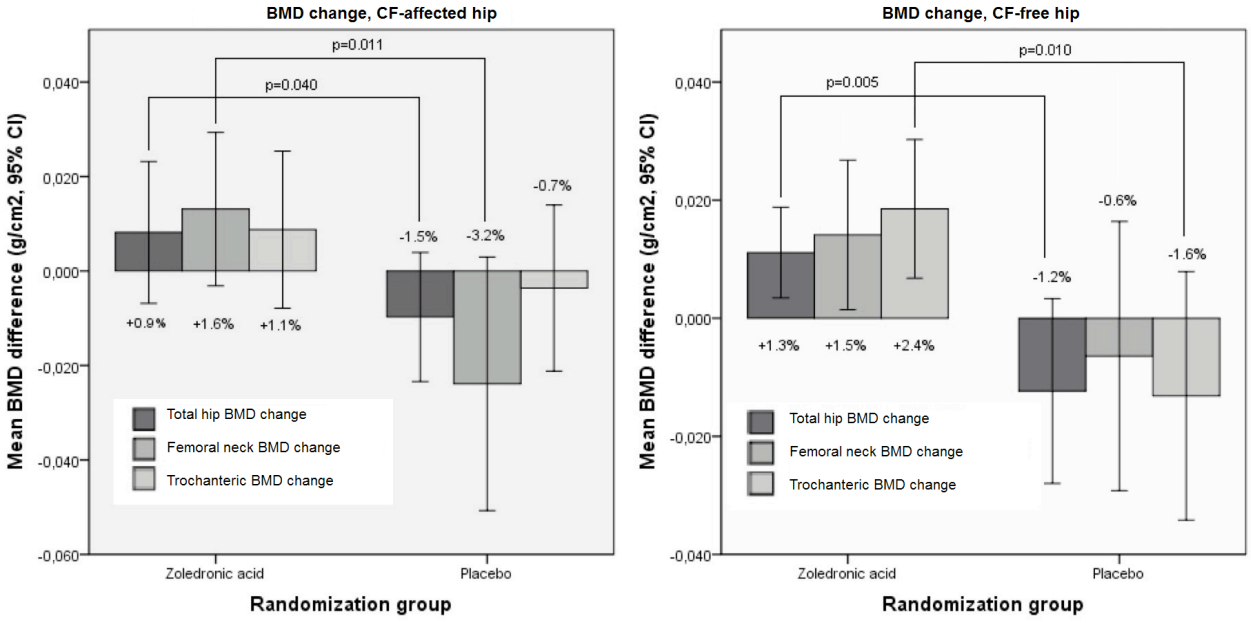
5.3 Effect of immobilization, off-loading and zoledronic acid on bone mineral density in patients with acute Charcot foot (Study III).

At baseline, the mean BMD (for the study group, n=35) of the lumbar spine was 1.21 ± 0.20 g/cm^2 (T-score -0.1 ± 1.6), in the on the CF-affected side 0.98 ± 0.18 g/cm^2 (T-score -0.8 ± 1.4) and in the hip on the CF-free side 0.98 ± 0.18 g/cm^2 (T-score -0.7 ± 1.4) (p=0.63 between hips at baseline). There were no statistically significant differences in the BMD of the lumbar spine or hips between patients with type 1 or type 2 diabetes.

To describe the effect of immobilization on the BMD, a pairwise comparison between BMD at presentation and at six months was performed. In Group P, a significant fall in BMD at the CF-affected femoral neck (-3.2%, p=0.016) and CF-free hip (-1.5%, p=0.026) was observed. However, in Group Z a significant increase of BMD in the CF-free hip (+1.3%, p=0.006), in the trochanteric area (+2.4%, p=0.005) and at the femoral neck (+1.5%, p=0.028) was observed (Wilcoxon signed-rank tests).

To evaluate the effect of zoledronic acid on the change in BMD, the mean change in hip BMD (between baseline and six months) was compared between Group Z and Group P. A significant difference was observed between groups in both hips in favour of Group Z (CF-affected side +0.9% Group Z and -1.5% Group P, p=0.040, CF-free side +1.3% Group Z and -1.2% Group P, p=0.005). There was no difference in the change in lumbar spine BMD between the groups (Group Z +0.7% and Group P +0.0%, p=0.187). Figure 9 presents the differences of BMD changes between groups (Wilcoxon signed-rank tests).

Figure 9. Observed bone mineral density (BMD) changes in the hip between the zoledronic acid and placebo groups.



5.4 Long term outcome of patients with chronic Charcot foot (Study IV).

Mean follow-up time was 8 years (range 5 to 16 years) and mortality rate during the follow-up period was 29% (12/41) leaving 29 patients (30 feet) as our study population. There were 17 females (61%) and 17 patients (61%) with type 2 diabetes. The mean age of patients at presentation was 49 years (range 27-71 years). Mean duration of diabetes was 43 years for type 1 diabetes and 19 years for type 2 diabetes. Two patients (7%) with type 2 diabetes used only oral medication for glucose control, all the others used insulin. $HbA1_c$ averaged 8.9% in patients with type 1 diabetes and 9.0% in patients with type 2 diabetes. All patients had peripheral neuropathy, 59% (17/29) had nephropathy and 69% (20/29) had retinopathy.

Twenty CFs (67%) had at least one ulceration during follow-up and 12 feet (40%) were ulcerated more than once. None of the patients had an open plantar ulcer at the follow-up visit. Fifteen feet (50%) were managed surgically and the mean interval from diagnosis to first operation was 31 months (range 0-67 months). The need for the surgical intervention appeared in two different time periods. The first group of operations were performed during the first year after the diagnosis of CF for gross instability (3/15) or persistent ulceration and ongoing infection (4/15). Then approximately four years after the diagnosis a second series of surgeries was required. This time it was due to uncontrolled ulcerations unresponsive to accommodative footwear (8/15). A total of 15

feet required the following surgical procedures: 13 exostectomies (10 feet), 11 wound revisions (10 feet), three mid-foot realignment arthrodeses (three feet) and two below-knee-amputations (two feet, 7%). The success rate of simple exostectomy was 62% (8/13). Only 18% (2/11) of superficial wound revisions were successful (as an independent intervention) and all three mid-foot realignment arthrodeses were successful.

The mean AOFAS score for all patients was 80.7 (range 60-100). The functional outcome (AOFAS) was significantly better in patients with less than 3 months initial diagnostic delay (AOFAS 89.3 ± 11.5) than in those who had diagnostic delay of more than 3 months (AOFAS 73.7 ± 7.5) (p=0.006). No significant differences in functional outcome were noted between Eichenholtz stages at the time of diagnosis and anatomical area of CF. Table 13 summarizes the clinical and functional outcome of the study population.

Table 13. Clinical and functional outcome of patients with Charcot foot by involvement site at the time of initial diagnosis and all performed operative procedures.

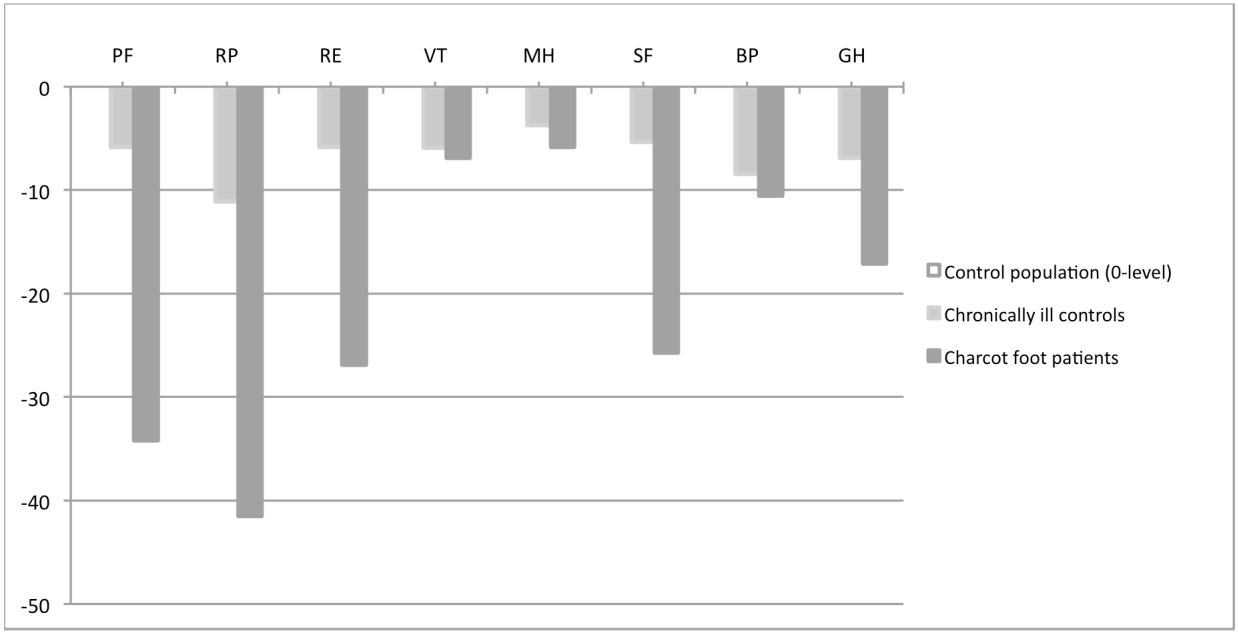
		Charcot foot affected area			
	Total	**Forefoot**	**Midfoot**	**Ankle**	**Calcaneus**
Number of cases	**30(100%)**	2 (7%)	25 (83%)	2 (7%)	1 (3%)
Ulceration(s)					
No	**10 (33%)**	0 (0%)	10 (40%)	0 (0%)	0 (0%)
Yes	**20 (67%)**	2 (100%)	15 (60%)	2 (100%)	1 (100%)
Multiple ulcers	12 (40%)	1 (50%)	9 (36%)	1 (50%)	1 (100%)
Surgical management					
No	**15 (50%)**	1 (50%)	13 (52%)	1 (50%)	0 (0%)
Yes	**15 (50%)**	1 (50%)	12 (48%)	1 (50%)	1 (100%)
Walking distance					
< 1km	**6 (20%)**	1 (50%)	5 (20%)	0 (0%)	0 (0%)
1-5 km	**16 (53%)**	0 (0%)	13 (52%)	2 (100%)	1 (100%)
>5km	**8 (27%)**	1 (50%)	7 (28%)	0 (0%)	0 (0%)
AOFAS* (±SD)	**80.7 (±9.0)**	**73,0** (±8,5)	**81,4** (±12,3)	**63,0** (±0,0)	**80,0** (±0,0)
Operative procedures					
n	**29 (100%)**	2	26	1	0
Amputation	**2 (7%)**	0	1	1	0
Arthrodesis	**3 (10%)**	0	3	0	0
Exostectomy	**13 (45%)**	1	12	0	0
Successful	8	1	7	0	0
Failed	5	0	5	0	0
Wound revision	**11 (38%)**	1	10	0	0
Successful	2	0	2	0	0
Failed	9	1	8	0	0

* AOFAS = American Orthopaedic Foot and Ankle Society score

At the follow-up visit 18 patients (62%) used prescribed custom made depth inlay shoes or insoles, nine patients (31%) used normal shoes and two patients (7%) had prosthesis due to below knee amputation. Non-adherence to prescribed custom-made footwear had no effect on ulceration frequency or need for surgical interventions during the follow-up period (normal shoes: ulcers 6/9 (67%), operation 4/9 (44%), custom made shoes: ulcers 12/19 (63%), operation 9/19 (47%), p=0.86, and p=0.89 respectively). All those patients who were diagnosed within three months of the onset of symptoms wore commercially manufactured shoes and could walk over 1 km. However only 23% of those with diagnostic delay over three months wore normal shoes and only 54% could walk more than 1km ($p<0.001$ and $p=0.008$ respectively).

The SF-36 component scores were compared to Finnish general population and chronically ill population standards (Figure 10).

Figure 10. Mean difference in SF-36 component scores (points) in Charcot foot patients (n=29) when compared to values for Finnish control population (Aalto et al. 1999). (0-level is the mean of the healthy control population).



Domain legends: PF=Physical Functioning; RP=Role Physical (role limitations due to physical health problems); RE=Role Emotional (role limitations due to emotional health problems); VT=Vitality; MH=Mental Health; SF=Social Functioning; BP=Bodily Pain; GH=General Health.

The mean physical functioning (PF) component for all the Charcot foot patients was 50.7 compared to the general population score of 84.9. The role-physical (RP) component (perceived disruption to individuals' lifestyle) score was 33.3 for the study patients compared to 74.8 of general population. Additionally, role-emotional (RE) and social functioning (SF) component scores were lower than the population standards. The scores for PF and RP components were better in the patients with type 1 diabetes than in the patients with type 2 diabetes ($p<0.001$ and $p=0.002$, respectively). Female patients had lower scores in vitality (VT) and general health (GH) components than male patients ($p=0.02$ and $p=0.01$ respectively). The component scores of PF ($p<0.001$), RP ($p>0.001$), RE ($p<0.001$) and VT ($p=0.03$) were reduced when patients' walking capacity was less than 500m. The number of patients retired due to medical problems (excluding old-age pensioners) increased from 15% at the diagnosis to 52% at study follow-up visit in autumn 2007. No significant differences in SF-36 component scores were noted between Eichenholtz stages at the time of the diagnosis and CF involvement sites.

6. DISCUSSION

6.1 Diagnosis of the Charcot foot

CF is a devastating and disabling complication of diabetes and is associated with significantly increased morbidity and mortality (Gazis et al. 2004, Sohn et al. 2009, van Baal et al. 2010). CF is frequently considered a rare disease but with a reported incidence of 0.1-0.9% / year we should annually diagnose 300-2700 new cases of CF in Finland (population approximately 5 million) (Bailey and Root 1947, Sinha et al. 1972, Fabrin et al. 2000, Lavery et al. 2003). The number of diagnosed CF cases has increased considerably in our institution in recent decades, mainly due to the increased awareness of patients and health care professionals of the clinical signs and symptoms of acute CF. In previous decades a few CF cases were possibly misdiagnosed as severe infections or neglected fractures and below-knee amputations may have been performed without making the correct diagnosis. Before 1998, only sporadic CF diagnoses were made at our institution, but since then approximately 10-15 new acute CF cases are diagnosed each year and the number of new cases is constantly increasing.

It seems to be difficult to make the correct diagnosis early enough. The initial diagnosis of acute CF is usually clinical, based on the presence of unilateral swelling, elevated local temperature, erythema and bone resorption in a patient with peripheral neuropathy (Cofield et al. 1983, Armstrong et al. 1997). The long delay from the first symptoms to the right diagnosis is partly a consequence of patients underrating their swollen and red but often fairly painless foot. However, physicians often incorrectly presumed infection or venous thrombosis (39% of cases in our series) as a cause for swollen, warm and erythematous foot in patients with complicated diabetes. Therefore, in our series 50% of patients were not prescribed for appropriate immobilization and non-weightbearing at the initial visit to our institution. The literature reports that the diagnosis of CF is missed from 25 to 79% of the time and our findings are consistent with these studies (Myerson et al. 1994, Chantelau 2005). The average delay was 29 weeks in our series (Study I) and the most frequent incorrect diagnoses were erysipelas, deep venous thrombosis, gout, arthritis,

fracture or osteomyelitis. In the absence of elevated temperature, elevated CRP or ESR, infection is highly unlikely, and a CF should be considered (Petrova et al. 2007, Judge 2008). According to Schon et al. (1998) and Armstrong et al. (1997) in as many as 46-73% of CF patients an instigating event had triggered the destructive process. In our retrospective analysis a preceding trauma could be identified in only 22% of cases. The retrospective design of our study may be partly responsible for this difference and due to the presence of insensitivity of the foot, anamnestic data on trauma is often unreliable.

An interesting finding in Study I was that 8/18 (44%) patients who were initially not appropriately immobilized and off-loaded underwent surgical treatment, compared with 2/18 (11%) patients who were appropriately immobilized and advised to not put weight on the affected extremity. The importance of early diagnosis and appropriate initial treatment was also recently stressed by (Chantelau 2005, Wukich et al. 2011b).

6.2 Medical management of the Charcot foot

Fifteen years ago the first medical trials were conducted to investigate if osteoclast-inhibitors (bisphosphonates) had an effect on acute CF (Selby et al. 1994). Promising results were reported with alendronate and pamidronate, and most recently with calcitonin (non-bisphosphonate osteoclast inhibitor) (Jude et al. 2001, Anderson et al. 2004, Pitocco et al. 2005, Bem et al. 2006). A clear reduction in bone turnover markers was reported in these trials, but no differences in clinical or radiographic outcomes were reported. The reduction in bone turnover markers was an expected pharmacological effect of these drugs and the clinical significance of this remained unclear. The rarity of CF and difficulty in enrolling patients in a similar stage of CF has made it difficult to mount a study with sufficient power and clinical relevant outcome measures.

Our prospective randomized study (II) was planned according to data from our retrospective study (Study I). A power calculation for the total sample size was calculated and the number of patients needed to detect a 25% difference in total immobilization time was 22 in both treatment groups. However, although slightly underpowered, our prospective randomized trial did not show any beneficial effect of zoledronic acid on the clinical resolution of the acute CF. On the contrary, patients treated with zoledronic acid required longer immobilization time compared with placebo

group (p=0.04). The reason for this may be the relatively small sample size of our series and the wide variation of total immobilization times. Furthermore, we were unable to monitor patients' compliance with the non-weightbearing protocol during treatment, but recently the absolute necessity of total non-weightbearing has been questioned by de Souza (2008). The activation of osteoclasts and bone resorption may also represent a rather late stage of the CF disease process and a series of immuno-inflammatory reactions is suspected to occur before fragmentation is noticed on radiographs (Jeffcoate et al. 2005, Baumhauer et al. 2006). This is one possible explanation why bisphosphonate treatment, in our series, did not prove to be as effective as expected in halting the acute CF process. Recently the understanding of the basic pathophysiological cascade responsible for the initiation of CF has advanced (Jeffcoate et al. 2005) and further investigation is needed to show if medications addressing the imbalance of RANKL and OPG (i.e. TNF-α inhibitors or denosumab) could lead to a faster clinical resolution of acute CF.

In conclusion, the use of zoledronic acid as an adjunct in the management of acute CF did not provide a faster resolution of the disease process and the mainstay of the initial management of acute CF is immobilization and non-weightbearing in a plaster cast with continuous monitoring of clinical signs of the activity of the CF process (Armstrong and Lavery 1997, Chantelau 2005, Tan et al. 2005).

6.3 Bone mineral density and the Charcot foot

Type 1 diabetes is associated with a fall in BMD and elevated fracture risk (Hofbauer et al. 2007, Vestergaard 2007). The decrease in BMD is infrequent in type 2 diabetes, but increased risk for fracture still exists, mainly due to the increased risk of falling (Rakel et al. 2008). In our series patients with type 1 diabetes and acute CF had BMD levels in lumbar spine and proximal femurs similar to those of patients with type 2 diabetes. The difference may become apparent after some years, because patients with acute CF are usually 50-60 years old and most of these population-based studies investigating the relationship between diabetes and BMD have been conducted in older age groups and with postmenopausal women (Hofbauer et al. 2007). The high percentage of men (83%) in our series may also contribute to this difference. The baseline BMD of the lumbar spine was equal (T-score 0.0) to that in general population and only moderately reduced in the hip (T-score -0.8); in the sub-group of patients with type 1 diabetes not even reaching the level of

osteopenia (T-score <-1.0). This finding concurs with a recent report by (Christensen et al. 2010), who did not find any difference in proximal femur BMD between the CF-affected and CF-free hips. Immobilization and protected weightbearing in the management of acute CF are frequently continued up to 6-12 months before the resolution stage is reached (Armstrong et al. 1997, Jude et al. 2001, Petrova and Edmonds 2010). Disuse osteoporosis is a known phenomenon described previously after ankle and tibia fractures that usually require only 2-3 months of protective weight-bearing (Finsen et al. 1989, Emami et al. 1999, van der Poest Clement et al. 1999, Emami et al. 2001, van der Poest Clement et al. 2002). The decrease in trochanteric BMD after these fractures is reported to average 3-12.5% and the recovery of bone mineral content after returning to normal weightbearing is often slow and incomplete (Weinreb et al. 1989, Ingle et al. 1999, van der Poest Clement et al. 1999, Emami et al. 2001, van der Poest Clement et al. 2002, Veitch et al. 2006). It is also estimated that 4-5% persistent reduction in hip BMD may be clinically relevant, resulting in increased risk for osteoporotic fractures (van der Poest Clement et al. 1999, Chapurlat et al. 2005). In our series, the BMD of the hip in the placebo group decreased only 1.5% on the CF-affected side and 1.2% on the CF-free side, indicating a very minor effect of off-loading to hip BMD in patients with acute CF. The only significant difference (in pairwise comparison of the BMD measurements in the placebo group) was observed in the femoral neck of the CF-affected side (-3.2%) indicating that the development of disuse osteoporosis was not clinically significant in patients with acute CF. One possible explanation for this could be the fact that all CF patients have some form of peripheral neuropathy and loss of pain sensation, which often leads to weight-bearing with the cast and so the effect of off-loading may be less than in patients with normal sensation. The T-score of -0.8 in the CF-affected hip at baseline (in both groups) may also indicate a rather low basic loading of the hips that may be a result of physical inactivity due to numerous co-morbidities, or any other lower extremity problems. These problems are frequently seen in patients with complicated diabetes and in these patients further immobilization and off-loading may have less impact on BMD than on patients with normal BMD at baseline.

Management with zoledronic acid in our study showed a trend for increased BMD in all areas of the proximal femur if mean BMD at baseline was compared with mean BMD at 6 months. The only statistically significant increase in BMD (in pairwise comparison) was observed in the CF-free hip, which may be a result of increased loading of the CF-free extremity during the immobilization of acute CF. A significant difference in the change of the hip BMD was also observed between the zoledronic acid group and the placebo group in favour of zoledronic acid. The difference in BMD change (CF-free +2.5% and CF-affected +2.2%) was statistically significant, but the clinical

significance of this difference is not clear in terms of fracture risk reduction. The maximum level of disuse osteoporosis is often reached six months after the initiation of immobilization and off-loading (Sievanen 2010), so the six months of follow-up in our series was considered adequate, although the positive effect of bisphosphonate on BMD may be more apparent after 12 or 18 months after treatment.

Immobilization and off-loading did not lead to obvious disuse osteoporosis in patients with acute CF after six months of treatment. Management with zoledronic acid led to a statistically significant increase (CF-free +2.5% and CF-affected +2.2%) in hip BMD on both sides compared to the placebo, but the clinical significance of this is uncertain. According to recent reports, bisphosphonates seem to have potentially serious side effects (i.e. increased risk for atrial fibrillation, osteonecrosis of the jaw, aesophageal cancer, atypical subtrochanteric femur fractures and deranged bone remodelling (Lewiecki 2011) and caution in their use in acute CF should be exercised if the benefits of these drugs are uncertain.

6.4 Surgery of Charcot foot

Reconstructive surgery of an acute CF may be considered if the deformity or instability cannot be effectively controlled or accommodated by immobilization and off-loading (Pinzur 2004, Trepman et al. 2005, Pinzur 2007b, Mittlmeier et al. 2010). This is often seen in cases of severe ankle CF and surgery could be considered as a primary treatment for this subset of patients (Rogers et al. 2011). We had two severe ankle CFs in our retrospective series (Study I). One was successfully managed with tibio-talo-calcaneal arthrodesis and the other patient was managed with below-knee amputation.

Indications for reconstructive surgery in chronic CF are the correction of fixed deformities causing recurrent ulcerations and fixation of marked instability not amenable to custom made shoes, orthosis or walkers (Schon et al. 1998). In our long-term follow-up study (Study IV), 29 operations were performed on 15 feet (50%) which concurs with earlier reports (Schon et al. 1998, Pinzur 1999, Pinzur 2004). We observed bimodal distribution of the surgical procedures performed. The first group of operations during the first year after diagnosis were performed mainly due to diagnostic delay and development of severe deformities and ulcerations prior to referral to our unit.

The second group of operations was performed four years after the initial diagnosis and represents better the current natural history of primarily nonsurgical management of CF. This bimodal distribution of surgery has not been previously reported and emphasizes the importance of continuous foot care and the need for routine renewal of accommodative footwear. In this series patients with severe or repetitive ulcers required most surgery; exostectomy, wound revision, realignment arthrodesis or amputation. Simple exostectomy was successful in 62% of our cases and seems to be an effective and safe procedure for these high-risk patients (Brodsky and Rouse 1993, Pinzur 2004, Laurinaviciene et al. 2008).

Recently some authors have proposed that in the presence of severe deformity or unstable deformities early realignment surgery could decrease the risk for ulcers and avoid subsequent amputations (Simon et al. 2000, Farber et al. 2002, Mittlmeier et al. 2010) and potentially even improve patients' quality of life (Pinzur and Sostak 2007). It must be emphasized that the reconstructive surgery of the CF is a major challenge for both surgeon and patient. The patient must be able to tolerate an extremely long and demanding postoperative immobilization and accept the risks, benefits and limitations of the operation. At the moment there are no studies available on the effect of realignment surgery on the future risk for ulcers or any other outcome measure.

6.5 Long-term outcome of patients with Charcot foot

Long-term outcome of CF patients was assessed in our long-term follow-up study (Study IV) with a mean follow-up time of eight years. This was the first consecutive series of CF patients in which long-term clinical outcome and quality of life of CF were evaluated and described. All registered and living patients were followed up, however 29% of the patients died during the follow-up period. This mortality rate is similar to that reported by Saltzman et al. (2005) and Sohn et al. (2009) described in patients with CF, but lower than that reported by (Gazis et al. 2004). It seems that it is neuropathy, rather than CF, which is independently associated with increased mortality among patients with diabetes but the exact mechanisms behind it are not known (Gazis et al. 2004).

The functional outcome of patients was surprisingly good (AOFAS average 81 points). It was significantly better in patients correctly diagnosed within 3 months after the onset of symptoms than in the group whose diagnosis was made after 3 months. There is a potential pitfall in using AOFAS

scoring (Kitaoka et al. 1994) for CF patients because 40% of the AOFAS score consists of the component measuring pain. Due to high levels of peripheral neuropathy (100% of the study group) pain perception is impaired. Consequently, caution is required when comparing AOFAS results in patients with insensate feet with patients that have normal sensation. Another confounding factor is neuropathic pain in some patients with diabetes.

Previous data suggest that CF has a similar effect on individuals' health status to lower extremity amputation (Pinzur and Evans 2003, Dhawan et al. 2005, Saltzman et al. 2005). This study suggests that the impairment in overall physical functioning is a long lasting finding if nonsurgical management is used. Pinzur and Evans (2003) in their small preliminary trial showed that all component scores of SF-36 were lower in CF patients than the control population. In our series we did not find as extensive reduction in component scores. The decrease was most evident in the area of physical and social functioning. The physical components of SF-36 were lower when compared to general controls or chronically ill controls. The social functioning score was also lower than control population, which reflects restrictions in individuals' routine activities of daily living and the diminished social network commonly found.

The rocker bottom deformity (collapse of the midfoot area) in consolidated CF is a major risk factor for plantar ulceration (Boyko et al. 1999, Pinzur 1999, Fabrin et al. 2000, Saltzman et al. 2005) and foot ulceration is considered as the single most common precursor to lower extremity amputations in diabetic patients (Pecoraro et al. 1990, Larsson et al. 1998). Fabrin et al. (2000) reported an ulceration incidence of 37% after a median of 36 months of follow-up of CF patients and Saltzman et al. (2005) reported an incidence of 47% after a median of 3.8 years of follow-up. In this study 67% of the patients suffered at least one ulcer episode. The slightly higher percentage of plantar ulcerations in the present series may have several explanations. First, the minimum follow-up time in our series was five years (average 8 years), which is notably longer than in earlier studies (Fabrin et al. 2000, Saltzman et al. 2005), thus presenting the natural behaviour of diabetic CF. On the other hand, 31% of our patients were non-compliant regarding the prescribed custom made footwear. Although it did not have significant effect on ulceration frequency, it certainly predisposes these high-risk feet to foot ulcerations. There were two (7%) transtibial amputations: one due to gross hind-foot instability and the other due to a septic life-threatening infection. Most cases with severe deformity or instability were managed with custom made depth inlay shoes or custom made orthoses. Only three patients (10%) had a realignment arthrodesis performed due to mid-foot

deformity. Previously reported amputation rates in CF patients have varied between 2% and 9.7% (Fabrin et al. 2000, Saltzman et al. 2005).

Prevention of subsequent ulceration in deformed CF is challenging and requires continuous monitoring of multiple risk factors (Boyko et al. 1999). Effective prevention of ulcerations requires identification of CF and initiation of treatment at Eichenholtz stage 0, prior to the degeneration of normal foot architecture (Yu and Hudson 2002, Chantelau 2005, Wukich et al. 2011b). It is possible that if the correct diagnosis is made in the early phase and conservative treatment is successful, surgery may be avoided and the risk of subsequent ulcerations or the need for further surgical intervention may be decreased. In our series 62% of patients initially diagnosed within 3 months did not need surgical intervention during follow-up compared to 46% of those who had diagnostic delay of over 3 months demonstrate the importance of early diagnosis of acute CF.

7. CONCLUSIONS

Diagnosis of acute CF is demanding and significant delays in diagnosis are common. Bisphosphonates are widely used in the management of acute CF. We observed that patients who received zoledronic acid as an adjuvant for the treatment of the acute CF were immobilized notably longer than those with placebo. Management of acute CF requires immobilization and off-loading that frequently take more than six months. However, this prolonged immobilization does not lead to obvious disuse osteoporosis in patients with acute CF after 6 months of treatment. Management with zoledronic acid led to a significant increase in hip BMD on both sides compared to placebo, but the clinical significance of this is uncertain. Thus, we cannot recommend the use of zoledronic acid in the management of acute CF. Chronic CF impairs patient's physical functioning and general health but does not usually affect mental health. Surgical management is often required with an increase in surgery 4 years post diagnosis. A delay of diagnosis of more than three months was found to adversely affect quality of life and functional outcome. The long-term functional outcome of patients with CF is usually relatively good, mainly due to the absence of pain and if the diagnosis is reached early.

8. FUTURE PERSPECTIVES

Early detection. The prevention of deformities in the early stages of acute CF is crucial to prevent long-term problems encountered with distorted anatomy. More attention to the risks of developing CF and early detection with advanced imaging modalities must be instituted to minimize the risk for development of severe deformities. The early management of CF stage 0 may reduce the rate of future complications. Patient education, podiatric nurses and primary care physicians play a crucial role in the early detection and appropriate initial management of acute CF.

New pharmacological treatments. Now that the understanding of the basic pathophysiological mechanisms (inflammation and RANKL/OPG pathway) responsible for the development of acute CF has evolved, it opens up the possibility of new, more specific therapies. There is a theoretical basis for investigating the effects of specific TNF-α antagonists (e.g. infliximab and etanercept) and RANKL antagonist (e.g. denosumab) in the management of acute Charcot foot. However, the effect and safety of these drugs must be determined with clinically relevant outcome measures and long-term follow-up.

Early realignment surgery. Once the deformity has developed management has traditionally centred on accommodating the affected foot in custom made footwear or orthoses. The long-term outcome for these patients in terms of functional or clinical outcome is not so bleak, although ulcers are frequently seen and surgery is often needed. Whether ulcers or subsequent surgery can be avoided with early realignment surgery is still not clear and studies should also use primary outcomes that are long term, clinically relevant, and patient-centred.

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