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EDITORIAL

Charcot osteoarthropathy in diabetes: A brief review with an emphasis on clinical practice

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Abstract

Charcot osteoarthropathy (COA) is a potentially limbthreatening condition that mainly affects diabetic patients with neuropathy. In everyday practice, it presents as a red, hot, swollen foot, usually painless, and is frequently triggered by trivial injury. Its etiology is traditionally attributed to impairment of either the autonomic nervous system, leading to increased blood flow and bone resorption, or of the peripheral nervous system, whereby loss of pain and protective sensation render the foot susceptible to repeated injury. More recently, excessive local inflammation is thought to play a decisive role. Diagnosis is based on clinical manifestation and imaging studies (plain X-rays, bone scan, Magnetic Resonance Imaging). The mainstay of management is immediate off-loading, while surgery is usually reserved for chronic cases with irreversible deformities and/or joint instability. The aim of this review is to provide an overview of COA in terms of pathogenesis, classification and clinical presentation, diagnosis and treatment, with an emphasis on the high suspicion required by clinicians for timely recognition to avoid further complications.

INTRODUCTION

In diabetes, Charcot osteoarthropathy (COA) is a specific manifestation of neuropathy. It is named after Jean-Martin Charcot, who first described it in 1868. Although the arthropathy described by Charcot was associated with tabes dorsalis, the most common cause of COA today is diabetic neuropathy[1]. Less common causes include leprosy, poliomyelitis, syringomyelia, alcohol abuse, traumatic injury, heavy metal poisoning, multiple sclerosis, congenital neuropathy and rheumatoid arthritis[2-4].

COA is a potentially limb-threatening condition which, beyond the emotional and social burden of physical dysfunction[5], has been associated with increased mortality[6,7]. Given the rising prevalence of diabetes, a high index of suspicion is required from both diabetic patients (especially those with neuropathy) and their physicians for the early diagnosis and treatment to prevent major complications[3,8]. The aim of this review is to provide an overview of COA in terms of pathogenesis, classification and clinical presentation, diagnosis and treatment.

EPIDEMIOLOGY

Although COA is a well established complication of dia-

betes mellitus recognized by specialists, it is not easily diagnosed by non-specialists[9], particularly in its early stages. Therefore, its true prevalence and incidence are unknown but it is estimated to affect 0.8%-8% of diabetic populations[10,11]. This frequency increases up to 10% of diabetic patients with neuropathy when radiographic findings are used[12,13]. Although prospective studies are limited, incidence rates ranging from 3 to 11.7/1000 patients per year have been reported[3,14].

Importantly, the incidence of COA is reported to be increasing[10]. This increase is attributable to both improved diagnosis with the use of the new imaging modalities and decreased rates of hospital admission, fewer amputations and increasing number of diabetic patients with foot ulcers being treated as outpatients with early mobilization[10,15].

Patients with COA are usually in their fifth and sixth decades of life, 80% of them having had diabetes for at least 10 years[16]. Bilateral COA has been reported as present in 9% of patients with acute COA[17]. However, in another study, when feet were prospectively examined by computerized tomography, bilateral changes of neuroarthropathy were found in 75% of patients[18].

The prevalence of COA does not differ between men and women, but differences have been reported between patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). In the former, COA presents during their fifth decade of life, while the latter develop this condition during their sixth decade (42 ± 10.2 *vs* 59 ± 7.8 years, $P < 0.001$)[19]. Moreover, longer diabetes duration has been reported among T1DM patients as compared to T2DM patients (24 ± 8.4 *vs* 13 ± 8.1 years, $P < 0.001$)[19]. Interestingly, peripheral arterial disease seems to protect patients from developing COA[10]. This is probably due to limited inflammatory response as a result of ischemia[3].

PATHOGENESIS

The neurovascular and neurotraumatic theories have classically been proposed to explain the pathogenesis of COA. However, recent evidence suggests that a combination of the two theories is likely to provide the most accurate explanation for disease pathogenesis[1,4,14].

Neurovascular theory (French theory)

Mitchell and Charcot proposed increased blood supply to bone as the principal etiological factor. Increased blood flow mainly occurs through arteriovenous shunting, which is a manifestation of autonomic neuropathy (hence the term *neurovascular*). Increased blood flow could lead to bone resorption and mechanical weakening, ultimately resulting in fractures and deformity[1,20]. At the same time, increased blood flow becomes clinically manifest as a warm foot with dilated veins[1,20].

Neurotraumatic theory (German theory)

Volkman and Virchow suggested that peripheral neuropathy leading to loss of protective sensation may render the foot susceptible to injury from either repeated or acute trauma[1,10]. Pathology worsens with continued weight-bearing (hence the term *neurotraumatic*)[1,20]. Thus, fractures might ensue and, in the case of continued activity, patients could end up with severe deformities[1,10].

Additional potentially contributory factors:

Bone pathology: Reduced bone density in the lower limbs has been observed in patients with COA. Such patients appear to exhibit increased osteoclastic activity[21], predisposing to fracture even after minimal trauma[22].

Atypical neuropathy: It could, possibly, explain why not every neuropathic patient invariably develops COA[23]. A specific form of neuropathy with preservation of light touch and hot sensation but loss of cold sensation has been reported. However, these findings have never been replicated.

Non-enzymatic collagen glycation: It could contribute to Achilles tendon shortening and also render joints prone to abnormal pressure distribution, resulting in deformity and Charcot foot[24].

Increased plantar pressures: In comparison to diabetic patients without COA, increased plantar pressures were found in those developing COA, leading to excessive mechanical stress on the forefoot, which is, in turn, transmitted to the Lisfranc region[10].

Excessive local inflammation: The most recent view focuses on the presence of excessive and uncontrollable local inflammatory response to trauma[25-28]. Patients with COA are believed to harbor a grossly increased inflammatory response with excess production of pro-inflammatory cytokines (Tumor necrosis factor alpha, TNF-α; Interleukin 1 beta, IL-1β)[25-28]. These, in turn, lead to elevation of RANKL (receptor activator of nuclear factor kappa B ligand), thereby activating NF-κB (Nuclear factor κB). The latter is a potent promoter of osteoclastic activity[25-28]. Hence, the predilection of COA for joints held together with ligaments, notably the Lisfranc and Chopart joints, may be accounted for by the inflammatory infiltration of these ligaments. In the same context, temperature elevation in acute COA provides further evidence of excess inflammation[25-28].

In a combined interpretation of the pathogenesis of COA, this condition is rare because there are several prerequisite factors. Autonomic neuropathy with increased blood flow to bones and peripheral neuropathy with loss of protective sensation may be, to a variable degree, combined. The condition may be triggered by trauma and, importantly, there may be an excessive inflammatory response to the latter[2,14,29].

Predisposing factors for the development of COA include pronounced peripheral and autonomic neuropathy, normal circulation, osteopenia in T1DM but not in T2D-

Table 1 Anatomical classification of charcot osteoarthropathy

Anatomical classification of charcot osteoarthropathy	
Pattern	**Foot joints involved**
Ⅰ	Metatarsophalangeal and interphalangeal joints
Ⅱ	Tarso-metatarsal (Lisfranc's) joints
Ⅲ	Naviculocuneiform, talonavicular and calcaneocuboid joints
Ⅳ	Ankle and subtalar joints
Ⅴ	Calcaneum

M[30], trauma (often minor, including foot deformities, joint infections or surgery)[14] and renal impairment, with a medical history of renal transplantation being associated with a high risk for Charcot osteoarthropathy[31]. Trauma has been reported in 22-53% of cases and may require a very detailed medical history to be disclosed[13].

ANATOMICAL CLASSIFICATION

COA can be classified into five different patterns according to the involvement of several foot joints (Table 1)[32]. It almost exclusively affects the foot and ankle, other locations being extremely rare[33,34]. (1) Pattern Ⅰ (15%) involves the forefoot, i.e. the metatarsophalangeal (MTP) and interphalangeal (IP) joints; (2) Pattern Ⅱ (40%) involves the tarso-metatarsal (TMT) (Lisfranc's) joints; (3) Pattern Ⅲ (30%) involves the naviculocuneiform, talonavicular and calcaneocuboid joints; (4) Pattern Ⅳ (10%) involves ankle and subtalar joints; and (5) Pattern Ⅴ (5%) involves the calcaneum[10].

According to another classification system[35], COA can be divided into: (1) forefoot COA involving the IP and MTP joints; (2) midfoot COA involving the TMT and tarsal joints; and (3) hindfoot COA, including lesions of the ankle joint and calcaneum. The midfoot (particularly pattern Ⅱ) is the most commonly affected area (60%)[10].

Anatomical classifications could be clinically important as they have been reported to predict outcomes. For example, forefoot COA seems to have a better prognosis than hindfoot arthropathy, since lesions of the calcaneum may have detrimental effects on weight distribution during walking[10].

CLINICAL PRESENTATION

COA arthropathy can present either as an acute or a chronic condition but sometimes these two phases seem to overlap[9,10].

Acute COA

The acute phase is usually characterized by the presence of a warm, red, edematous foot and ankle, usually the midfoot[10]. The affected foot is usually painless. Even when pain is reported, it is less than might be anticipated based on the physical findings[1,14]. Skin temperature is elevated by 2-6℃ in comparison to the contralateral foot[1,36]. Hyperemia may persist for months or years[9], but in some cases the acute phase rapidly progresses to the chronic one, sometimes in less than 6 months, resulting in irreversible deformity[10].

Table 2 The course of charcot osteoarthropathy according to the clinical presentation of the foot: modified Eichenholtz classification

The course of Charcot osteoarthropathy: Eichenholtz stages	
Stage	**Clinical presentation**
0: Patients at risk for COA	Diabetic neuropathy and an acute sprain or fracture
Ⅰ: Development-Fragmentation	Erythema, edema and increased warmth, usually absence of pain
Ⅱ: Coalescence	Diminution of erythema, edema and warmth; Decreased joint mobility
Ⅲ: Reconstruction-Consolidation	Erythema, edema and warmth are no longer present; Ulcers at sites of residual deformity

COA: charcot osteoarthropathy.

Chronic COA

Temperature elevation and redness gradually subside, while permanent deformities may develop[9,10]. Typically, the latter include arch collapse with rocker bottom deformity and medial convexity[9,10]. As a result, pressures during standing and walking are redistributed so that areas of deformity develop high pressure and become prone to ulceration. Finally, ulcerated areas may become infected and infection may spread to the bone, leading to osteomyelitis[9,10].

Natural course

COA is usually of a self-limiting nature. Nonetheless, it may induce localized osteoporosis in the affected foot[37]. Long-term complications such as deformity, ulceration and osteomyelitis[1] may now be preventable thanks to an improved early diagnosis. COA practically never re-activates but may later affect the contralateral foot[1,9]. Of note, current evidence confirms that long-term survival of patients with acute COA is diminished even after successful treatment. The reduced survival is generally attributable to morbidity associated with distal symmetrical neuropathy[6,7].

THE COURSE OF COA: EICHENHOLTZ STAGES

Progression of COA from onset to consolidation runs through three stages, as described by Eichenholtz (Table 2)[38]. Progression from one stage to the other may last from weeks or months to several years, although sometimes the process is arrested in the early stages[1,38].

Stage Ⅰ: Development-fragmentation

The foot is red, hot and swollen. Initial radiographs may be normal. However, if the foot is not immobilized, radiogra-

phic findings such as bony debris at joints, fragmentation of subchondral bone, subluxation and dislocation can subsequently develop[39].

Stage Ⅱ: Coalescence

Erythema, warmth and swelling are decreased in this stage and radiography findings include absorption of fine debris, formation of new bone, coalescence of larger fragments and sclerosis of bone ends. This results in decreased joint mobility and increased stabilization[38,39].

Stage Ⅲ: Reconstruction-consolidation

Clinically, edema, erythema and warmth are not present, unless fractures have not healed. Ulcers may develop at sites of residual deformity, while X-rays reveal bony remodeling, rounding of bone ends and decreased sclerosis[38,39].

Furthermore, a "prodromal" stage 0 or "pre-stage Ⅰ" has been described. This stage includes diabetic patients with neuropathy who have an acute sprain or fracture and are, therefore, at high risk of acute COA[1,40].

DIAGNOSIS

Diagnosis of COA is based on medical history and clinical examination, radiographic features, bone scintigraphy and magnetic resonance imaging (MRI).

Clinical presentation

Diagnosis of COA is primarily based on clinical presentation, as described above[1,3]. A red, hot, swollen, usually painless foot in patients with diabetic neuropathy should prompt the diagnosis of COA until proven otherwise[3]. Temperature elevation usually over 2℃ in comparison to the contralateral foot is clinically demonstrable[1,3]. Mild antecedent trauma makes the diagnosis more likely, but it may not be recalled by the patient[41].

Radiographic features

Plain radiographs may initially be negative, for a few days up to three weeks, and the only finding in acute COA may be soft tissue swelling[1,3,42]. However, as the disease progresses, radiographic features appear. These can be divided into atrophic (bony resorption and little fragmentation) or hypertrophic (bony proliferation and destruction of joints, fragmentation and new bone formation)[1]. Osteophytes, subchondral sclerosis and narrowing of joint spaces are often seen in radiographs[42]. Specifically, radiographic features of the forefoot include demineralization, bone destruction and periosteal reaction, making the differential diagnosis from uncomplicated osteomyelitis difficult[42,43]. Furthermore, "pencil and cup" deformity at the MTP joints or fragmentation of the metatarsal heads can also occur[10,43]. In the midfoot, Lisfranc fracture or dislocation develops with bony fragmentation of the TMT joints and collapse of the longitudinal arch[10,43]. These changes in X-rays may occur very rapidly (within a few weeks)[10,43]. Finally, in the hindfoot, talocalcaneal dislocation with talar collapse and atypical calcaneal fractures may occur[10].

Bone scintigraphy

Bone scintigraphy is very sensitive but not specific enough for the diagnosis of COA. The three-phase technetium-99m methylene diphosphonate bone scan is positive in all phases[10]. Thus, differential diagnosis from osteomyelitis is difficult as increased bone turnover characterizes both entities[1,44]. Neither are indium-111-labeled leukocyte scans specific, given that labeled leukocytes may be found in both infected and non-infected joints[44]. It has been suggested that the combination of technetium-99m methylene diphosphonate scintigraphy with indium-111-labeled leukocyte scintigraphy may improve sensitivity (93-100%) and specificity (almost 80%) in the differential diagnosis from osteomyelitis[1,10,44-46].

Magnetic resonance imaging

MRI is being increasingly used for the diagnosis of COA due to its diagnostic accuracy[47], especially in the early stages when radiographic findings are absent[1,48]. Acute COA is characterized by reduced signal intensity on T1 sequence and increased signal intensity on T2 sequence[42,47,48]. Chronic COA is characterized by diffusely diminished marrow signal intensity and cyst formation. MRI is valuable both for the differential diagnosis from osteomyelitis and for the detection of superimposed osteomyelitis on pre-existing COA[10,42].

DIFFERENTIAL DIAGNOSIS

Acute COA needs to be differentiated from other conditions that cause pain and swelling, notably cellulitis, trauma or sprain, acute gout, deep vein thrombosis and osteomyelitis[49]. Accurate diagnosis is not always easy and can be a considerable clinical challenge. It is important to exclude infection, i.e. cellulitis or osteomyelitis. This is usually ruled out when there is no presence or history of foot ulceration[10,39]. Furthermore, in order to distinguish whether the redness appearing in acute COA is due to infection or to COA, a simple method could be used: keeping the affected leg elevated, a decrease in erythema suggests COA[42]. Positive systemic signs of infection like fever, leukocytosis, elevated C-reactive protein or erythrocyte sedimentation rate levels are more likely to be found in infection than COA, but some overlap exists[42,50]. As a rule of thumb though, patients with acute COA only exhibit local signs of inflammation (increased skin temperature) without systemic signs and symptoms[50].

Imaging techniques are helpful in the differential diagnosis of COA. Plain X-rays are normal in acute COA[3] as opposed to typical changes seen in gouty and rheumatoid arthritis[1]. Nevertheless, plain X-rays are not reliable in order to differentiate COA from osteomyelitis[10]. Instead, nuclear modalities (phase technetium-99m methylene diphosphonate and indium-111-labeled leukocyte scintigraphy) may be required[6].

MRI may be also used in differentiating acute COA from osteomyelitis. The former is characterized by periarticular and subchondral marrow edema[47], whereas the lat-

ter exhibits bone marrow typically affecting a single bone with diffuse marrow involvement. Furthermore, COA affects several joints while osteomyelitis mostly occurs in weight-bearing surfaces of the toes, metatarsal heads or calcaneum[51].

TREATMENT

Treatment of COA depends on many factors including clinical stage, location of involvement, degree of deformity and patient comorbidities. The mainstay of treatment is off-loading, while surgery is usually reserved for chronic cases with joint instability or severe deformity[3,39,42].

Non-surgical treatment

Off-loading is essential when acute COA is suspected, even if not proven, in order to prevent disease progression and foot deformity[3,39,42]. In stage Ⅰ, non weight-bearing of the affected limb allows healing of joint fractures. The gold standard of off-loading is the total contact cast (TCC)[3,39,42]. It is made of stockinette, low-density foam, elastic plaster and fiberglass, with a rocker bottom sole created by layering standard plaster on the bottom of the cast from the heel to an area just proximal to the metatarsal heads, facilitating movement[52]. The TCC is usually necessary for 2 to 4 mo[1,42] until resolution of fragmentation on radiographs is seen and normal skin temperature is observed. The TCC should be checked regularly as edema might decrease and the cast might become loose[52]. A disadvantage of the TCC is that it requires specialized personnel to construct and fit it[52]. A more practical alternative is the Aircast walker, a bivalved cast, lined with four air cells and inflated by a hand pump to ensure a close fit[52]. For maximal reduction of weight-bearing, patients may, additionally, use crutches, wheelchairs and Zimmer frames[1,13]. Immobilization may last from 3 mo to over a year when the hindfoot and ankle are affected[42]. Afterwards, the cast might be removed and replaced by a protective bracing combined with the use of appropriate footwear. The latter must be designed to relieve high-pressure areas, ensure joint stability and accommodate any pre-existing deformity, so that gradual weight bearing on the affected foot will not pose any risk of ulceration or COA re-activation[13].

In stage Ⅱ, when swelling has been controlled, the Charcot Restraint Orthotic Walker (CROW) is preferred. CROW is a total contact ankle-foot orthosis which resembles to TCC but is removable. However, in stage Ⅲ, use of suitable therapeutic shoes with rigid shank and rocker bottom sole to minimize instability is recommended[1,13,42].

Protection of the contralateral extremity, although practically difficult, should not be neglected because contralateral fracture may occur in almost 80% of cases[1,42].

Additional pharmacological treatment: As osteopenia is observed in COA, bisphosphonates have been used to inhibit osteoclast activity[13,53]. Short-term results are promising but these agents are not yet recommended for routine use[13,53]. Similarly, use of calcitonin and non-steroidal anti-inflammatory drugs has been reported as adjunct treatment to conventional therapy[10,42,53,54]. Recently, new anti-inflammatory therapeutic agents such as corticosteroids, TNF-α antagonists (infliximab, etanercept) and RANK-L antagonists (denosumab) have been proposed, but further research is needed[28].

Surgical treatment

Surgical treatment should be considered in chronic cases with joint instability or severe deformity failing a conservative approach[1,13,39]. Surgical interventions include:

Exostectomy: When a patient with stable COA develops a bony prominence leading to recurrent skin ulceration and infection. It is a common off-loading surgical procedure performed to simply remove the bony prominence which is held responsible for the ulcer[39]. After exostectomy, a protective bracing and antibiotics are used[39,55].

Achilles tendon lengthening: When there is contracture of the Achilles tendon leading to abnormal plantar pressure distribution[39,55].

Arthrodesis: When the deformity cannot be appropriately treated with bracing[39,55].

Internal fixation techniques (single or staged procedure) are used and should be followed by non-weight-bearing, which continues until radiographic evidence of bony consolidation (from 6 wk up to 3 mo)[39] and bracing for a long time[42,56]. Complications include deep wound infection, recurrent ulceration, unstable non-union or malunion, fracture and hardware failure[1,39]. External fixation (single-stage procedure) can also be used, especially when underlying osteomyelitis is present. Recurrence of ulceration has been rarely reported[57,58].

Amputation: Regrettably, this may be inevitable when surgery has failed due to recurrent ulceration/infection or unstable arthrodesis. It has been reported that 2.7% of Charcot deformities annually lead to amputation[59].

SIX PRACTICAL POINTS FOR CLINICIANS

Increased clinician alertness is required for the early detection and management of COA and the following points are of practical importance[3,60]: (1) COA should always be suspected in every diabetic patient with peripheral neuropathy who presents with a red, hot, swollen foot. The virtual absence of pain and the diffuse redness may help differentiate this condition from cellulitis or deep venous thrombosis; (2) Even when the diagnosis is only suspected, immediate immobilization and off-loading is the wisest practice; (3) Initially, plain X-rays may be normal but this should not deter off-loading; (4) Education of both patients and physicians to increased early detection and diagnosis of COA will be helpful; (5) Ulceration or infection in the plantar aspect of the foot should be avoided; and (6) Surgical intervention may be required, mainly in

chronic cases with joint instability or severe deformity.

CONCLUSION

In everyday practice, clinicians need to consider COA in every patient with diabetic neuropathy who presents with a red, hot, swollen, usually painless, foot[1,3,9,13]. Currently, diagnosis remains clinical but may be confirmed by appropriate imaging studies[1,3,9,13]. Prompt immobilization and off-loading are indispensible when COA is suspected and should be pursued until confirmation of diagnosis[1,3,9,10,13,29]. In cases of uncertainty or suspected osteomyelitis, antibiotics may be administered as well[1,3,9,13,29]. Surgery is usually reserved for chronic cases with severe deformity or joint instability. Finally, the importance of patient and physician awareness to enable prompt diagnosis cannot be emphasized enough in an endeavor to reduce the burden of foot complications[1,3,9,10,13,29].

REFERENCES

1 **Trepman E**, Nihal A, Pinzur MS. Current topics review: Charcot neuroarthropathy of the foot and ankle. *Foot Ankle Int* 2005; **26**: 46-63
2 **Gupta R**. A short history of neuropathic arthropathy. *Clin Orthop Relat Res* 1993; **296**: 43-49
3 **Wukich DK**, Sung W. Charcot arthropathy of the foot and ankle: modern concepts and management review. *J Diabetes Complications* 2009; **23**: 409-426
4 **Mabilleau G**, Edmonds ME. Role of neuropathy on fracture healing in Charcot neuro-osteoarthropathy. *J Musculoskelet Neuronal Interact* 2010; **10**: 84-91
5 **Pinzur MS**, Evans A. Health-related quality of life in patients with Charcot foot. *Am J Orthop (Belle Mead NJ)* 2003; **32**: 492-496
6 **Sohn MW**, Lee TA, Stuck RM, Frykberg RG, Budiman-Mak E. Mortality risk of Charcot arthropathy compared with that of diabetic foot ulcer and diabetes alone. *Diabetes Care* 2009; **32**: 816-821
7 **van Baal J**, Hubbard R, Game F, Jeffcoate W. Mortality associated with acute Charcot foot and neuropathic foot ulceration. *Diabetes Care* 2010; **33**: 1086-1089
8 **Mayfield JA**, Reiber GE, Sanders LJ, Janisse D, Pogach LM; American Diabetes Associaion. Preventive foot care in diabetes. *Diabetes Care* 2004; **27** Suppl 1: S63-S64
9 **Jeffcoate W**, Lima J, Nobrega L. The Charcot foot. *Diabet Med* 2000; **17**: 253-258
10 **Rajbhandari SM**, Jenkins RC, Davies C, Tesfaye S. Charcot neuroarthropathy in diabetes mellitus. *Diabetologia* 2002; **45**: 1085-1096
11 **Fabrin J**, Larsen K, Holstein PE. Long-term follow-up in diabetic Charcot feet with spontaneous onset. *Diabetes Care* 2000; **23**: 796-800
12 **Cavanagh PR**, Young MJ, Adams JE, Vickers KL, Boulton AJ. Radiographic abnormalities in the feet of patients with diabetic neuropathy. *Diabetes Care* 1994; **17**: 201-209
13 **Petrova NL**, Edmonds ME. Charcot neuro-osteoarthropathy-current standards. *Diabetes Metab Res Rev* 2008; **24** Suppl 1: S58-S61
14 **Frykberg RG**, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, Landsman AS, Lavery LA, Moore JC, Schuberth JM, Wukich DK, Andersen C, Vanore JV. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg* 2006; **45**: S1-S66
15 **Foster AV**, Snowden S, Grenfell A, Watkins PJ, Edmonds ME. Reduction of gangrene and amputations in diabetic renal transplant patients: the role of a special foot clinic. *Diabet Med* 1995; **12**: 632-635
16 **Cofield RH**, Morrison MJ, Beabout JW. Diabetic neuroarthropathy in the foot: patient characteristics and patterns of radiographic change. *Foot Ankle* 1983; **4**: 15-22
17 **Armstrong DG**, Todd WF, Lavely LA, Harkless LB, Bushman TR. The natural history of acute Charcot's arthropathy in a diabetic foot specialty clinic. *Diabet Med* 1997; **14**: 357-363
18 **Griffith J**, Davies AM, Close CF, Nattrass M. Organized chaos? Computed tomographic evaluation of the neuropathic diabetic foot. *Br J Radiol* 1995; **68**: 27-33
19 **Petrova NL**, Foster AV, Edmonds ME. Difference in presentation of charcot osteoarthropathy in type 1 compared with type 2 diabetes. *Diabetes Care* 2004; **27**: 1235-1236
20 **Edmonds ME**, Roberts VC, Watkins PJ. Blood flow in the diabetic neuropathic foot. *Diabetologia* 1982; **22**: 9-15
21 **Gough A**, Abraha H, Li F, Purewal TS, Foster AV, Watkins PJ, Moniz C, Edmonds ME. Measurement of markers of osteoclast and osteoblast activity n patients with acute and chronic diabetic Charcot neuroarthropathy. *Diabet Med* 1997; **14**: 527-531
22 **Cundy TF**, Edmonds ME, Watkins PJ. Osteopenia and metatarsal fractures in diabetic neuropathy. *Diabet Med* 1985; **2**: 461-464
23 **Stevens MJ**, Edmonds ME, Foster AV, Watkins PJ. Selective neuropathy and preserved vascular responses in the diabetic Charcot foot. *Diabetologia* 1992; **35**: 148-154
24 **Grant WP**, Sullivan R, Sonenshine DE, Adam M, Slusser JH, Carson KA, Vinik AI. Electron microscopic investigation of the effects of diabetes mellitus on the Achilles tendon. *J Foot Ankle Surg* 1997; **36**: 272-278; discussion 330
25 **Jeffcoate W**. Vascular calcification and osteolysis in diabetic neuropathy-is RANK-L the missing link? *Diabetologia* 2004; **47**: 1488-1492
26 **Jeffcoate WJ**. Theories concerning the pathogenesis of the acute charcot foot suggest future therapy. *Curr Diab Rep* 2005; **5**: 430-435
27 **Jeffcoate WJ**, Game F, Cavangh PR. The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charct foot) in diabetes. *Lancet* 2005; **366**; 2058-2061
28 **Boulton AJ**, Jeffcoate WJ, Jones TL, Ulbrecht JS. International collaborative research on Charcot's disease. *Lancet* 2009; **373**: 105-106
29 **Jeffcoate WJ**. Charcot neuro-osteoarthropathy. *Diabetes Metab Res Rev* 2008; **24** Suppl 1: S62-S65
30 **Petrova NL**, Foster AV, Edmonds ME. Calcaneal bone mineral density in patients with Charcot neuropathic osteoarthropathy: differences between Type 1 and Type 2 diabetes. *Diabet Med* 2005; **22**: 756-761
31 **Thompson RC Jr**, Havel P, Goetz F. Presumed neurotrophic skeletal disease in diabetic kidney transplant recipients. *JAMA* 1983; **249**: 1317-1319
32 **Sanders LJ,** Frykberg RG. Diabetic neuropathic osteoarthropathy: the Charcot foot. In: Frykberg RG. The high risk foot in diabetes mellitus. New York: Churchill Livingstone, 1991; pp 297-338
33 **Bayne O**, Lu EJ. Diabetic Charcot's arthropathy of the wrist. Case report and literature review. *Clin Orthop Relat Res* 1998; **357**: 122-126
34 **Lambert AP**, Close CF. Charcot neuroarthropathy of the knee in Type 1 diabetes: treatment with total knee arthroplasty. *Diabet Med* 2002; **19**: 338-341
35 **Giurini JM**, Chrzan JS, Gibbons GW, Habershaw GM. Charcot's disease in diabetic patients. Correct diagnosis can prevent progressive deformity. *Postgrad Med* 1991; **89**: 163-169
36 **McGill M**, Molyneaux L, Bolton T, Ioannou K, Uren R, Yue DK. Response of Charcot's arthropathy to contact casting: assessment by quantitative techniques. *Diabetologia* 2000; **43**: 481-484

37 **Young MJ**, Marshall A, Adams JE, Selby PL, Boulton AJ. Osteopenia, neurological dysfunction, and the development of Charcot neuroarthropathy. *Diabetes Care* 1995; **18**: 34-38
38 **Eichenholtz SN**. Charcot Joints. Springfield, Illinois: Charles C Thomas, 1966: 7-8
39 **Stefansky SA**, Rosenblum BI. The Charcot foot: a clinical challenge. *Int J Low Extrem Wounds* 2005; **4**: 183-187
40 **Schon LC**, Marks RM. The management of neuroarthropathic fracture-dislocations in the diabetic patient. *Orthop Clin North Am* 1995; **26**: 375-392
41 **Chantelau E**, Richter A, Schmidt-Grigoriadis P, Scherbaum WA. The diabetic Charcot foot: MRI discloses bone stress injury as trigger mechanism of neuroarthropathy. *Exp Clin Endocrinol Diabetes* 2006; **114**:118-123
42 **van der Ven A**, Chapman CB, Bowker JH. Charcot neuroarthropathy of the foot and ankle. *J Am Acad Orthop Surg* 2009; **17**: 562-571
43 **Gold RH**, Tong DJ, Crim JR, Seeger LL. Imaging the diabetic foot. *Skeletal Radiol* 1995; **24**: 563-571
44 **Palestro CJ**, Mehta HH, Patel M, Freeman SJ, Harrington WN, Tomas MB, Marwin SE. Marrow versus infection in the Charcot joint: indium-111 leukocyte and technetium-99m sulfur colloid scintigraphy. *J Nucl Med* 1998; **39**: 346-350
45 **Crerand S**, Dolan M, Laing P, Bird M, Smith ML, Klenerman L. Diagnosis of osteomyelitis in neuropathic foot ulcers. *J Bone Joint Surg Br* 1996; **78**: 51-55
46 **Pinzur MS**, Lio T, Posner M. Treatment of Eichenholtz stage Ⅰ Charcot foot arthropathy with a weightbearing total contact cast. *Foot Ankle Int* 2006; **27**: 324-329
47 **Tan PL**, Teh J. MRI of the diabetic foot: differentiation of infection from neuropathic change. *Br J Radiol* 2007; **80**: 939-948
48 **Chantelau E**, Poll LW. Evaluation of the diabetic Charcot foot by MR imaging or plain radiography—an observational study. *Exp Clin Endocrinol Diabetes* 2006; **38**: 361-367
49 **Chantelau E**. The perils of procrastination: effects of early vs. delayed detection and treatment of incipient Charcot fracture. *Diabet Med* 2005; **22**: 1707-1712
50 **Petrova NL**, Moniz C, Elias DA, Buxton-Thomas M, Bates M, Edmonds ME. Is there a systemic inflammatory response in the acute charcot foot? *Diabetes Care* 2007; **30**: 997-998
51 **Ledermann HP**, Morrison WB, Schweitzer ME. MR image analysis of pedal osteomyelitis: distribution, patterns of spread, and frequency of associated ulceration and septic arthritis. *Radiology* 2002; **223**: 747-755
52 **Papanas N**, Maltezos E. The diabetic foot: established and emerging treatments. *Acta Clin Belg* 2007; **62**: 230-238
53 **Jude EB**, Selby PL, Burgess J, Lilleystone P, Mawer EB, Page SR, Donohoe M, Foster AV, Edmonds ME, Boulton AJ. Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomised controlled trial. *Diabetologia* 2001; **44**: 2032-2037
54 **Bem R**, Jirkovská A, Fejvarová v, Skibová J, Jude EB. Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. *Diabetes Care* 2006; **29**: 1392-1394
55 **Armstrong DG**, Stacpoole-Shea S, Nguyen H, Harkless LB. Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. *J Bone Joint Surg Am* 1999; **81**: 535-538
56 **Simon SR**, Tejwani SG, Wilson DL, Santner TJ, Denniston NL. Arthrodesis as an early alternative to nonoperative management of charcot arthropathy of the diabetic foot. *J Bone Joint Surg Am* 2000; **82**-A: 939-950
57 **Pinzur MS**. Neutral ring fixation for high-risk nonplantigrade Charcot midfoot deformity. *Foot Ankle Int* 2007; **28**: 961-966
58 **Conway JD**. Charcot salvage of the foot and ankle using external fixation. *Foot Ankle Clin* 2008; **13**: 157-173, vii
59 **Saltzman CL**, Hagy ML, Zimmerman B, Estin M, Cooper R. How effective is intensive nonoperative initial treatment of patients with diabetes and Charcot arthropathy of the feet? *Clin Orthop Relat Res* 2005; **435**: 185-190
60 **Caputo GM**, Ulbrecht J, Cavanagh PR, Juliano P. The Charcot foot in diabetes: six key points. *Am Fam Physician* 1998; **57**: 2705-2710

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