REVIEW ARTICLE

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Etiology, pathophysiology and classifications of the diabetic Charcot foot

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In people with diabetes mellitus, the Charcot foot is a specific manifestation of peripheral neuropathy that may involve autonomic neuropathy with high blood flow to the foot, leading to increased bone resorption. It may also involve peripheral somatic polyneuropathy with loss of protective sensation and high risk of unrecognized acute or chronic minor trauma. In both cases, there is excess local inflammatory response to foot injury, resulting in local osteoporosis. In the Charcot foot, the acute and chronic phases have been described. The former is characterized by local erythema, edema, and marked temperature elevation, while pain is not a prominent symptom. In the latter, signs of inflammation gradually recede and deformities may develop, increasing the risk of foot ulceration. The most common anatomical classification describes five patterns, according to the localization of bone and joint pathology. This review article aims to provide a brief overview of the diabetic Charcot foot in terms of etiology, pathophysiology, and classification.

Keywords: *Charcot foot*; *classification*; *diabetes mellitus*; *diabetic foot*; *neuropathy*; *osteoarthropathy*

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In diabetes mellitus, the Charcot foot is a specific manifestation of neuropathy (1–4). It is named after Jean-Martin Charcot, who recognized that peripheral neuropathy (in his case, *tabes dorsalis*) could lead to neuropathic joints (1). This condition has many names, including Charcot osteoarthropathy, neuropathic osteoarthropathy, and many others (5). Other than diabetes mellitus, Charcot foot may occur as a complication of neurosyphilis, syringomyelia, leprosy, poliomyelitis, and/or congenital neuropathy (1).

The prevalence of Charcot foot in diabetes is not clearly known, but it is now appreciated that the condition is not as infrequent as might be generally thought (1). Indeed, it may be easily overlooked by the non-specialists, especially in early stages and/or minor forms, leading to some underestimation of its frequency (1, 3). The authors have occasionally seen in their foot clinic patients in whom the initial clinical manifestation of a hot swollen foot with minute tenderness was misinterpreted, so that antibiotics, bone biopsies, and even arthrodesis had been recommended. Such patients presented very late with severe deformities. In an observational study on acute Charcot foot in the United Kingdom and Ireland between June 2005 and February 2007, overall 288 patients were registered from 76 centers (6).

Etiology of the Charcot foot in diabetes mellitus

The main underlying cause of the Charcot foot in diabetes involves neuropathy, associated with a trivial trauma in many cases (1–3, 6, 7). The cardinal pathogenic mechanisms underlying diabetic neuropathy are chronic hyperglycemia and microvascular disease, leading to nerve injury via osmotic changes and ischemia, respectively (8). Foot trauma can be ascertained on detailed medical history, although many patients do not recall such injury (1–3). Trauma may be sustained during daily activities (such as prolonged walking), and, importantly, it may also include surgery of the affected foot. In the recent audit on acute Charcot foot in United Kingdom and Ireland (6), 36% of patients reported some trauma, and 12% reported foot surgery during the preceding 6 months.

While neuropathy is certainly the common denominator, the type of neuropathy is a matter of discussion (1–3). Neuropathy may affect the peripheral nervous system leading to sensory loss or the autonomic system, impairing arterial perfusion and cellular turnover of foot and ankle bones (1–3). The consequences of these neuropathic changes will be discussed in the next section. Traditionally, one school of thought supported the

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former and another supported the latter neuropathy type (1–3, 9, 10). However, it appears more likely that both the peripheral and the autonomic nervous system may be affected (11), although one or the other manifestation may predominate in the individual patient (11, 12). Moreover, a specific type of neuropathy predominantly affecting cold sensation with relative sparing of other sensory modalities has been reported (13), but this theory has not gained widespread acceptance (7).

Pathophysiology of the Charcot foot in diabetes mellitus

Autonomic neuropathy may result in impaired vascular reflexes with arteriovenous shunting and increased arterial perfusion (14, 15). Arteriovenous shunting has been demonstrated in the neuropathic foot (16–18). This becomes clinically manifested as localized increased temperature with redness and dilated dorsal veins (18–20). Increased blood flow has also been noted in the foot bones and held responsible for increased bone resorption with reduced bone mineral density and, hence, predilection for fractures (21). More recently, increased blood flow has been shown in patients with acute Charcot foot (22). Importantly, reduced bone mineral density has been confirmed in patients with Charcot foot (23–25), and increased osteoclastic activity in such patients has been documented as well (26). Additionally, the literature suggests that autonomic neuropathy predisposes to Charcot foot via increased blood flow and increased bone resorption (1, 3). This theory was initially proposed under the name 'neurovascular theory' (1, 3). It also attempts to explain why subjects with peripheral arterial disease, in whom increased blood flow is restricted by arterial lesions, are relatively protected from the development of Charcot foot (1, 3).

In contrary, the 'neurotraumatic theory' (1, 3, 10, 27) states that peripheral neuropathy, also called distal sensorimotor polyneuropathy, is responsible for sensory loss in the feet (8). Sensory deficits may involve light touch, temperature, and pain perception (8). Consequently, the feet lose protective sensation and become vulnerable with increased risk of unrecognized trauma (1, 3, 10). The latter can be a minor acute injury during normal daily activities such as walking, running or dancing, or it may be a chronic injury resulting from inappropriate footwear (1, 3, 10). In both cases, continued weight-bearing due to the absence of pain may induce local aseptic inflammation and aggravate bone destruction (1, 3, 10). Naturally, the harmful effect of continued weight-bearing is more important in obese subjects (12). Of note, Chantelau et al. (28) have used magnetic resonance imaging (MRI) to document bone trauma in the earliest stages of Charcot foot, providing further evidence on the pathophysiologic role of unperceived trauma. Such unnoticed bone trauma is not uncommon in patients with polyneuropathy (29), including the contralateral foot of Charcot patients (30), again highlighting unnoticed trauma as a dangerous triggering factor. In neuropathic patients, the intensity of weight-bearing has been correlated with development of Charcot foot (31), further strengthening the argument for the 'neurotraumatic' theory.

Nonetheless, neuropathy in the traditional sense cannot fully explain the development of Charcot foot and why it is not encountered in the majority of neuropathic patients (1). Indeed, Christensen et al. (22) have provided evidence that local hyperemia in the affected Charcot foot is not accompanied by more severe neuropathic deficits in such patients. The authors suggested that increased blood flow was attributable to excess local inflammation rather than neuropathy *per se* (22). Nowadays, a markedly excessive local inflammatory response to trauma is known to be elicited in patients with acute Charcot foot (1, 2, 7, 32–34). In contrast to the local inflammation, there is no systemic inflammatory response (35). As a result of local inflammation, pro-inflammatory cytokines [mainly tumor necrosis factor alpha (TNF-α) and Interleukin 1 beta (IL-1β)] are produced excessively and beyond control (1, 2, 7, 32–34). The next pathophysiologic event is cytokine-driven elevation of the receptor activator of nuclear factor kappa B ligand (RANKL), which, in turn, enhances the synthesis of nuclear factor κB (NF-κB). The latter promotes osteoclast maturation and osteoclastic activity, leading to osteoporosis in the affected bones (2, 7, 32–34). In parallel, NF-κB enhances the production of osteoprotegerin from osteoblasts, in order to provide an antagonist of RANKL and mitigate its effects (2, 7, 32–34). Increased osteoclastic activity is manifested by an increase in their resorptive capacity *in vitro*, which is predominantly, but not exclusively, driven by RANKL (26). Intriguingly, healthy neurons secrete the beneficial calcitonin gene-related peptide (CGRP), which reduces the synthesis of RANKL and contributes to the maintenance of joint integrity (2, 7). It follows that any reduction of CGRP will be detrimental, because it will, indirectly, increase the action of RANKL, aggravating the disease process (2, 7). The role of CGRP is particularly relevant in cases of neuropathy, whereby its secretion has been documented to be reduced (2, 7). Hence, it is now deemed most likely that neuropathy exerts a contributory role to the inflammation-induced osteolysis through reduced secretion of CGRP from affected neurons (2, 7).

Alternatively, one may argue that a specific form of neuropathy is required to induce the Charcot foot, but supporting literature is still sparse. In a small series, Stevens et al. (13) have reported that Charcot patients exhibited a relative preservation of warm and light touch perception with complete loss of cold perception. This contrasted with patients who had recurrent neuropathic foot ulcerations, in whom there was severe perturbation

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of both warm and cold sensation, as well as light touch perception (13). Young et al. (23) have reported more severe neuropathy in Charcot patients as compared to their neuropathic peers without Charcot foot. Among the former, autonomic neuropathy was significantly ($p = 0.03$) more frequent than among the latter (23). However, the recent consensus report on Charcot osteoarthropathy (7) has not provided further support to the notion that a specific type of neuropathy may be accountable.

Some other factors have been also implicated in the pathophysiology of the Charcot foot (1, 3). Among these, the most important include increased non-enzymatic collagen glycation and elevated plantar pressures. In particular, non-enzymatic collagen glycation may lead to Achilles tendon shortening, which, in turn, will increase forefoot pressures, predisposing to trauma and bone destruction (36). Elevated plantar pressures have been found in patients with acute Charcot foot as compared to their peers without Charcot (37). Such pressure elevation would lead to forefoot strain, which, in turn, would be transmitted as increased mechanical stress in the midfoot (primarily, the region of the Lisfranc ligament) (37). More recently, genetic factors, notably polymorphisms of the gene encoding the beneficial glycopeptide osteoprotegerin, are beginning to be discussed as potential contributors to pathophysiology (38). Korzon-Burakowska et al. (38) examined 54 patients with Charcot foot, 35 patients with diabetic neuropathy but no Charcot foot and 95 healthy controls (all from Poland). Significant differences were seen in 1217C > T and 245T > G polymorphisms between Charcot patients and patients with neuropathy but no Charcot foot, while differences were noted in every two-group comparison (38). These findings open new perspectives for improved understanding and further research in the field of pathophysiology, but confirmation in other populations is eagerly awaited.

Interestingly, there may be some differences in the pathophysiology between type 1 (T1DM) and type 2 diabetes (T2DM), but little is known on the subject. Petrova et al. (12) have found significantly ($p < 0.001$) younger age but significantly ($p < 0.001$) longer diabetes duration in Charcot patients with T1DM than in those with T2DM. More impressively, the same group has found generalized reduction of bone mineral density in Charcot patients with T1DM but not T2DM (24). At the same time, Charcot patients with T2DM exhibited more severe peripheral neuropathy (impaired temperature and vibration perception) than their T1DM peers (impaired temperature perception but normal vibration sensation) (24). Thus, it would appear that the neurotraumatic theory with severe loss of protective sensation and mechanical stress from weight-bearing in the setting of obesity might apply more to T2DM than T1DM (24). Conversely, the neurovascular theory with pronounced bone resorption might apply more to T1DM than T2DM, but clearly further information is needed in this area (24).

In the light of available knowledge, the complex pathophysiology of the Charcot foot may be currently outlined as follows. Autonomic neuropathy with increased blood flow and osteolysis, as well as peripheral neuropathy impairing protective sensation predispose to the Charcot foot (1, 7, 11). In the individual patient, the former or latter component of neuropathy may predominate (1, 11). The condition is triggered by a minor trauma, which initiates an inappropriately excessive local inflammatory response, culminating in bone resorption (1, 2, 7, 10, 11). In this conundrum, neuropathy has yet another contributory role to exert via reduced secretion of CGRP from injured neurons (2, 7). Other factors, including the emerging role of genes (38), may be of importance (1, 3), while additional inquiry is welcome to ascertain the potential differences between T1DM and T2DM.

Ultimately, the cascade of all pathophysiologic changes leads to the development of the Charcot foot and this point is critical for its natural history (1, 3, 7, 39). If the condition is correctly diagnosed and the patient is appropriately immobilized, the local inflammation will subside and further bony destruction including progressive loss of mineral density can be minimized or avoided (7, 39). In contrary, sustained mechanical stress perpetuates the disease process and may lead to ligament strain, fracture-dislocations of forefoot bones, midfoot collapse and severe foot deformity and/or joint instability (1, 3, 7, 39, 40). Charcot foot deformities may be further complicated by an ulceration that is frequently difficult to heal and frequently encountered by high recurrence rates (1, 3, 7, 39). Moreover, they carry a high risk of infection and even osteomyelitis.

Classifications of the diabetic Charcot foot

The Charcot foot can be classified in terms of clinical stage, anatomical localization, and stage of natural history.

Clinical classification

In clinical practice, the Charcot foot can be classified into the acute and chronic stage (1, 3, 7, 10, 27). In the acute (also called *active*) stage, the foot is remarkably red, warm and swollen. This pathology usually affects the midfoot. Pain is not a prominent feature and patients may report no pain or only some discomfort, which is usually much less in comparison to patients without neuropathy and similar degree of local inflammation (1, 3, 7). Using a portable infrared thermometer (41), the physician may document a 2–6°C temperature elevation in the affected vs. the contralateral foot (1, 3, 7, 10). At this stage, there is no deformity and the plain foot radiographs are most typically normal. The importance of early diagnosis to

arrest the disease progress and avoid further bony destruction cannot be emphasized enough (1, 3, 7, 10).

In the chronic (also called *inactive*) stage, signs of local inflammation progressively recede (1, 3, 7, 10). The associated lower-extremity redness subsides, and the difference in skin temperature between the two feet diminishes. Instead, stable deformities may develop (1, 3, 7, 10) including the most frequent as: a) collapse of the plantar arch in the midfoot with rocker bottom deformity; and b) prominent medial aspect of the foot in the midfoot (medial convexity). Both of these deformities result in abnormal high-pressure areas that are particularly prone to ulceration (1, 3, 7, 10).

Anatomical classifications

The most frequently used anatomical classification was proposed by Sanders and Frykberg (42). This describes five different patterns, depending on foot areas involved. In Pattern I (15%), the forefoot [metatarsophalangeal (MTP) and interphalangeal (IP) joints] is affected; in Pattern II (40%), tarso-metatarsal (TMT) joints are affected; in Pattern III (30%), the naviculocuneiform, talonavicular, and calcaneocuboid joints are involved; in Pattern IV (10%), the ankle and subtalar joints are affected; in Pattern V (5%), the calcaneum is affected (42).

A simpler anatomical classification distinguishes between three types (43). These are: the forefoot type involving the IP and MTP joints, the midfoot type involving the TMT and tarsal joints, and the hindfoot variation, in which the ankle joint and calcaneum are involved (43).

Another classification in three types has been proposed by Dounis (44). In type I, the forefoot is affected. In type II, the midfoot (TMT, naviculocuneiform, talonavicular, and calcaneocuboid joints) is affected (44). Type III involves the hindfoot causing severe instability and is classified into IIIa (involving the ankle joint), IIIb (involving the subtalar joint) and IIIc (resorption of talus and/or calcaneus with impaired weight-bearing) (44).

Classification based on natural history

This classification into three stages is based on Eichenholtz's work (45). It is a radiological classification describing the natural history of the Charcot foot from initiation through coalescence to consolidation and has been recently reviewed in more detail by the authors elsewhere (1). In stage I (development), there is erythema, foot edema and elevated temperature. Plain foot radiographs are commonly normal, but bony debris at joints, fragmentation of subchondral bone, joint subluxation and fracture dislocation of joints may soon ensue (45). In stage II (coalescence), signs of local inflammation gradually diminish, but radiological pathology becomes more evident. This includes absorption of debris with new bone formation, coalescence of larger fragments and sclerosis of bone ends (45). At this stage, affected joints may become more stable (45). In stage III (consolidation), signs of local inflammation are no longer discernible, and radiographs reveal remodelling of affected bones and joints (45). It is during this advanced stage that severe deformities may change foot architecture, predisposing to ulceration (45).

Conclusions

The Charcot foot is a specific complication of diabetes mellitus (1, 3, 7). Its main pathophysiological mechanisms are peripheral and autonomic neuropathy, as well as excessive local inflammatory response to minor trauma (1, 3, 7). Clinically, it may be classified into an acute and chronic stage (1–3). Other classifications are based on anatomical localization and staging of natural history (1–3). In clinical practice, a high level of suspicion, including urgent specialist referral when appropriate, is required for timely diagnosis and treatment (1, 3), as is generally true for diabetic foot pathology (46). This increased awareness may be anticipated to help towards avoiding more severe complications and improving diabetic foot outcomes (47–49).

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