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An overview of Charcot's neuroarthropathy

Dured Dardari [a,b,*]

[a] Diabetology Department, Centre Hopitalier Sud Francilien, Corbeil Essonnes, France
[b] LBEPS, Univ Evry, IRBA, Université Paris Saclay, 91025 Evry, France

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ABSTRACT

Charcot's neuroarthropathy is a destructive complication of the joints, which is often found in people with diabetes with peripheral neuropathy. Despite the fact that its description was published almost 130 years ago, its pathophysiology, diagnosis, and treatment remain areas that need to be described. Thanks to the use of bone remodelling, new therapeutic classes have emerged, we hope that this review will shed light on the pathology from its discovery through to the current state of knowledge on its classification, diagnosis and treatment methods.

Definition

Charcot neuroarthropathy (CN) is a chronic, devastating, and destructive disease of the bone structure and joints in patients with neuropathy; it is characterized by painful or painless bone and joint destruction in limbs that have lost sensory innervation [1].

A bit of history

Although K. Mitchell of Philadelphia described twelve cases of "arthritis" in 1831 linked to spinal cord injuries [2], and two years later reported 35 other patients with similar pathologies [3], the discovery of CN was attributed to Jean-Martin Charcot, opening the way for a long debate [4]. This French pathologist and neurologist, who practiced at the Pitié Salpetrière hospital [5], described the presence of specific arthritis in patients with myelopathy due to syphilis in 1868 [6]. In 1882, the "Congress Report" published in London named these pathological changes "Charcot joint". Since then, cases of CN have been reported in association with neurological disorders. In 1936, Jordan published the first report of CN in diabetes [7]. Several neurological conditions such as spina bifida, meningomyelocele, cerebral palsy, and syringomyelia have been associated with the development of CN [8,9] and also in patients with leprosy [10] and in those with excessive alcohol intoxication [11].

Epidemiology

The incidence and prevalence of CN varies from 0.1 to 0.4% in people with diabetes [12-15]; this prevalence increases to 35% in patients with peripheral neuropathy [16]. The risk of developing CN is not generally linked to the type of diabetes (I or II), but a study by Petrova did show a greater risk of the development of CN in people with type I diabetes [17]. People with Charcot neuroarthropathy are usually in their 50 s or 60 s, and most have had diabetes for at least 10 years [12,13,18-20]. Unilateral involvement of CN is much more common than bilateral [21]. Armstrong described a relative risk of developing multifocal CN in 9% of people with CN [22]. Lomax observed that this prevalence of CN increases significantly in a population in which diabetes has been followed for 10 years (10.8 vs. 27.4 per 10,000), but the incidence remained constant over the period 11 years of age (average 3.1 per 10,000 cases) [23]. However, during the last decade, and due to the early management of diabetic foot injuries as well as the increase in the number of centres specializing in the management of diabetic foot [24,25], the prevalence of CN seems to be increasing; however, this may be linked to better screening.

The anatomy of CN

The joint that is most commonly affected by CN in people with diabetes is the foot, although other sites including the knee [26-29], wrist [30-32], hip [33], and spine [34] have been reported. In the knee,

Abbreviations: CN, Charcot neuroarthropathy; OAD, oral antidiabetic; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIND, treatment-induced neuropathy of diabetes; RANKL, receptor activator of nuclear factor-B; OPG, osteoprotegerin.

* Address at: Diabetology Department, Centre Hopitalier Sud Francilien, Corbeil Essonnes France, Université Paris Saclay, 91025 Evry, France.
E-mail address: dured.dardari@gmail.com.

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with respect to the patients reported, this localization seems to be more specific for people with type 1 diabetes. Since the location of the CN is at the level of the articulation of the foot, the anatomical classification of CN is based on a graduation according to the articular level [35].

In the manuscript of Frykberg [36], there is a narrative on the incidence of each area of CN at the level of the foot: 36–67% for type I, 15–48% for type II, 32% for type III, 3–10% for type IV and 2% for type V; another evaluation describes type II as the most frequent with regard to CN in the foot [37]. Overall, and in the literature, types I and II CN seem to be the most frequent according to this anatomical classification. There is another anatomical classification of CN according to the articulation, where the present CN described by Trepman [38] is different to that of Frykberg [36] but has the merit of speaking to the multi-site appearance of CN (Table 1).Table 2.

The physiopathology of CN

The pathogenic mechanisms of CN have been the subject of long debate, and there are a certain number of competing theories, which are not necessarily exclusive; however, one can quote certain theories according to chronology.

A. Neurovascular theory

Mitchell and Charcot favour the so-called "neurovascular" theory, which suggests that increased blood flow to the bones due to damage to the "trophic nerves" results in bone resorption and weakening, ultimately leading to fractures and deformities. It is now clear that these "trophic nerves" are a consequence of vegetative neuropathy [39]. Few studies have compared the blood flow in CN feet with that of the diabetic peripheral neuropathy without CN, but Charcot described it well in participants with active CN [40]. The regulation of blood flow and vasomotricity to the skin of the lower limb is preserved in CN [39]. Elevated venous pressure in the foot was observed in both groups (17 participants with CN neuropathy) compared to control subjects [41]. Clinical findings of a warm foot with dilated veins suggest that there is an arteriovenous shunt in CN [42]. However, others have shown that no index entry was found. Differences in microcirculation between a group with CN and a group of participants with neuropathy were shown by laser Doppler measurements [43].

B. Neuro-traumatic theory

Volkman and Virchow proposed the "neuro-traumatic theory" which suggests that the joints affected by CN undergo traumatic repetitions, leading to complicated fractures and inducing deformation during healing. In 1917, Eloesser [44] conducted his famous experiments on cats. The dorsal roots of the spinal cord of 42 cats were ligated to one side and the animals were observed for 3 years; during this time, the majority developed CN. He also subjected 3 cats to iatrogenic joint damage, and these animals developed typical CN changes within 3 weeks. As the physical properties of the bones, including the "breaking strength", did not change, he concluded that trauma was very important in the genesis of CN [44]. Also dogs with hind limb neuropathy due to L4-S1 dorsal radicular ganglionectomy have shown degenerative changes in the anterior section of the knee cruciate ligament [45]. This shows that neuropathy and trauma interact in the genesis of CN. More recently, a rat CN model has been developed in which typical CN characteristics are produced by injecting immunotoxins into the joints to cause the selective destruction of sensory innervation [46]. The precise role of trauma in the genesis of CN is unclear. Charcot's neuroarthropathy is known to progress very quickly in humans after trauma [47-49]. However, the observation that CN can develop in the non-load-bearing upper limb joints, where there is very little trauma [50,51], suggests that trauma may not be a necessary prerequisite. Unfortunately, due to the presence of sensory neuropathy, the detection of trauma remains difficult.

Table 1
Trepman CN classification.

Type	Localization	Joint
1	Plantar	Tarsometatarsal, naviculocuniform
2	Medio plantar	Subtalar, talonavicular
3A	Bassi ankle	Calcaneocuboid tibiotalar
3B	Calcaneus	Tuberosity fracture
4	Multi regions	Sequential, simultaneous
5	Forefoot	Metatarsophalangeal

Table 2
CN neurotraumatic theory.

CN Neuro-traumatic theory				
In favor		Carpintero J Bone Joint Surg Br	Holmes GB Foot Ankle Int	Slowman-Kovacs Arthritis Rheum
Against	Location other than the lower limb			

B. Neuro-bone-inflammatory theory

In a previous review, Childs showed the existence of an association between diabetes mellitus and osteoporosis that could contribute to the development of CN [52]. People with CN have been shown to have a lower bone density in the lower limbs compared to neuropathic participants [53]. Studies using bone markers to assess the bone formation and resorption have shown that there is an increase in osteoclastic activity compared to osteoblastic activity in acute and chronic forms of CN [54,55]. In 2007, Jeffcoate [56] described CN as an increased inflammatory response to a lesion inducing increased bone lysis. Since the emergence of this theory, a significant number of studies have evaluated inflammatory factors and bone modelling in people with CN, like C-reactive protein, TNF-α, and IL6. Three studies have shown an increase in the rate of CN [57-59]. In parallel, a new series of experiments was carried out on the evolution of bone modelling factors in the appearance of CN by trying to associate the receptor activator of nuclear factor-B ligand (RANKL) and its natural antagonist, osteoprotegerin (OPG). The results of these studies were very heterogeneous; in some, there was no difference in the expression of RANKL/OPG in CN compared to participants without CN [60], while other studies confirmed the disturbance of this system during the development of CN [61,62]. In this area, it is interesting to cite a study, which described the presence of genetic polymorphism of OPG, RANKL, and RANK in patients with CN; this evaluation indicates that this polymorphism can be studied as a means of the genetic predisposition for CN development [63].

Always in the role of inflammatory factors, Connors noted [60] that interleukin-1β and interleukin-6 play important roles by inducing an overproduction of receptor activator of nuclear factor kappa-B ligand (RANKL).

The other theories only describe factors associated with the diagnosis of CN

Murchison [64] described a sudden onset of CN after significant weight loss in three people with diabetes. CN has also been described after a kidney transplant linking the onset of CN to the high dose of corticosteroid therapy given after transplantation [65]. Another cohort has shown that participants who have had a double kidney–pancreas transplant have an increased risk of developing CN. However, this cohort does not indicate whether this increased risk is related to the correction of blood sugar, which seems to be more present in people with normalized blood glucose levels than in participants with only

kidney transplantation [66]. More recently, the rapid glycaemic regulation in poorly controlled patients living with diabetes was described as a new associated factor in the pathophysiology of Charcot's acute neuroarthropathy, but this was in a retrospective study [67]. However, few studies have linked the appearance of CN to glycaemic control; an evaluation carried out in 164 participants showed that the presence of diabetic nephropathy (high level of micro-albuminuria) is a predictive factor that is more sensitive to the appearance of CN than the level of HbA1c [68].

Another interesting fact of the appearance of CN is that which has been described after performing a biopsy on bone, suggesting that this can induce the local inflammation that is responsible for triggering CN [69]. The low prevalence of CN in people with diabetes, along with its almost exclusive presence in patients with sensory neuropathy of the lower limbs, suggests that CN has its own neuropathy, which is selective in its sensory disorder (hot and cold perception) [70], an element which contrasts with the so-called lambda sensory neuropathy found in people with diabetes complicated by foot sores. The excess of glycation products in people with diabetes, inducing a shortening of the posterior ligament chains of the knee and the appearance of hyper-support zones, is also considered to be a contributing factor in the pathophysiology of CN [71-73].

The clinical presentation of acute CN

The diagnosis and management of Charcot neuroarthropathy poses many clinical challenges. The often asymptomatic nature of the condition is very similar to ankle sprain, cellulitis, venous thrombosis, inflammatory arthritis, In semiology, CN generally evolves in two phases: (i) acute, and (ii) chronic; the signs and symptoms of the two phases can mix. Petrova has shown that signs of inflammation (CRP, leukocytes) are often normal in the active phase [75]. The typical clinical picture of acute Charcot's foot is a swollen red joint, with a temperature difference greater than 2 °C compared to the joint that is not affected. These symptoms may go unnoticed because the pain may be absent or disproportionate depending on whether or not there are lesions on the foot [17,74]. The description that is most commonly used in the literature is that of Eichenholtz [76] (evaluation based on clinical and radiological signs). Stage 0 is characterized by mild inflammation, soft-tissue edema and normal X-rays, but abnormal results of magnetic resonance imaging show signs of microfracture, edema of the bone marrow and bone contusion. The recognition and management in step 0 could stop the disease activity and prevent foot deformity [77,78]. In a recent series in which magnetic resonance imaging was performed very early, 69% of patients with CN at stage 0 healed without deformities, in contrast with only 7% of participants with a delayed presentation at stage 1 [79]. Stage 1 is characterized by severe inflammation, soft-tissue oedema, abnormal X-rays with macro-fractures and an abnormal result of magnetic resonance imaging showing signs of macro-fracture and edema of the bone marrow, with bone resorption starting with the presence of articular dislocation. Stage 2: coalescence – the end of bone resorption and the start of remodelling with the healing of fractures, and the resorption of debris; and Stage 3: definitive bone remodelling with bone reconstruction and the frequent appearance of ulcers, followed by installation in the chronic phase of CN, which is synonymous with the appearance of ulcers following significant modification of the arch of the foot.

It is important to mention that the F-fluoride PET/CT helps in the characterization of the extent of underlying CN [80].

Treatment of CN

Off-loading: Due to the potentially devastating consequences of CN, early identification and treatment are essential. The current treatment of CN consists of prolonged immobilization, for example, amovible system like Aircast®; [81-84]. The sooner the off-loading starts, better will be the results [85]; the off-loading gives the affected foot time to heal by reducing inflammation. It stops lesions and progressive deformation of the bone structure and is maintained for as long as the foot shows signs of inflammation, especially the temperature difference between the affected joint and the contralateral one. The entire affected joint must also be evaluated according to the presence or absence of fractures, with the average duration of off-loading varying in the data sets from 3 to 12 months [86-88]. As the treatment must be scrupulously respected in the long-term to ensure its success, the observance of treatments by the patient is an important and delicate problem [89]. In addition to the off-loading, people will often need a long control to prevent the foot ulcers and to propose a surgical reconstruction in cases of deformation or disabling bone or joint instability, when the foot is in remission [74,81,82]. A thorough follow-up is necessary to provide correct orthopedic shoes and to watch for signs of reactivation, which justifies the establishment of off-loading. Risk factors for recidivism remain somewhat unexplored [85,90] and rarely identified.

• medical treatment:

Due to the osteodegenerative nature of acute CN, all attempts at pharmacological treatment have focused on anti-osteoporotic drugs. Since CN is rare, only a few randomized trials are available, and these tend to be underpopulated. In addition, their execution is hampered by the fact that it is difficult to define solid clinical evaluation criteria for the resolution of CN. A useful endpoint would be a clinical resolution or the duration of off-loading, but these are based on individual clinical assessments and are therefore difficult to quantify. For all available studies, pharmacological interventions are used as a supplement to off-loading therapy. Anti-resorptive treatment with bisphosphonates has been extensively studied in randomized controlled trials. A single dose of pamidronate was evaluated by Jude et al. [91], who found a transient reduction in the markers of bone turnover as well as symptoms evaluated by patients. Pitocco et al. [92] found similar results when using alendronate treatment once a week for six months. In an open design, Anderson et al. [93] found that a single dose of pamidronate could lower foot temperature and bone-specific alkaline phosphatase levels. However, none of the studies contained data on resolution time or relapse; in addition, without a more recent study, Pakarinen et al. [94] evaluated a three-dose regimen of zoledronic acid, which resulted in an increase in the total downtime required for patients treated with the active drug compared to the placebo.

Overall, there is little evidence to suggest that bisphosphonates have a positive effect on relevant clinical outcomes of resolution time in participants with CN [95]. This may be due in part to the fact that zoledronic increases the level of RANK-L in animal models [96], inducing a significant decrease in bone resorption. In the class of anti-resorptive drugs, calcitonin has also been tested. Bem et al. [97] reported that treatment with intranasal calcitonin once daily resulted in reduced markers of bone turnover. However, no data regarding resolution times were presented. Regarding anabolic treatment, a few studies have been carried out on recombinant parathyroid hormone (rhPTH; 1–34). In an open-label pilot study, Brosky et al. [98] described an improvement in healing fractures of the feet, however, the results are presented in a 2005 summary and have never been published in a peer-reviewed journal. In a recent and larger double-blind study, Petrova et al. [99]; abstract presentation of the 'EASD (2016), there was no difference in resolution time or the healing of fractures when using rhPTH (1–85), so there appears to be no effect of anabolic therapy on the resolution time of Charcot's feet. Another study very recently demonstrated the effectiveness of a therapy (rhPTH; 1–34) on the acceleration of bone modelling in diabetic patients with a CN phase in the chronic phase [100]; an interesting double-blind trial to test a therapeutic effect of methylprednisolone or zoledronic acid on the resolution of active CN vs. placebo, unfortunately, did not give a faster remission of an active phase of CN despite a marked reduction in inflammatory cytokines

[101].

Thus, the pharmacological treatment of CN with bisphosphonates, calcitonin, and rhPTH (1–84) may have an effect on biomarkers for bone turnover and lowering the temperature of Charcot's affected joint, but there is no evidence of faster healing or better relevant clinical outcomes. On the contrary, treatment with zoledronic acid can prolong immobilization and recovery time. As is now known, the markers of inflammation and bone resorption (IL-6 and the RANK-L/OPG ratio) are increased in CN. Therefore, the optimal medical treatment of Charcot's acute foot can go through the inhibition of bone resorption and inflammation by targeting the RANK-L/OPG system. This could be done with Denosumab®, a monoclonal antibody against RANK-L, which inhibits bone resorption. Denosumab® is approved for the treatment of osteoporosis as well as the prevention of skeletal events in patients with bone metastases. In a recent open study with Denosumab® [102], 11 participants with a Charcot acute foot were treated with Denosumab® 60 mg as a single subcutaneous injection; the total average time for treatment by contact plastering was 18 weeks, while the time resolution of fractures on imaging was 16 weeks. This is significantly less ($p < 0.01$) than 26 and 25 weeks, respectively, in a historical control group of 11 participants with one-joint acute Charcot receiving standard treatment, which had significant methodological limitations as it was an underpowered study, not a randomized controlled trial. In addition, preliminary results from 10 participants in an open, uncontrolled trial of acute CN treated with Denosumab® (single subcutaneous injection of 60 mg) also appear promising, with < 12 weeks of remission [103].

Remission for acute CN

Multiple techniques have been used to evaluate remission in acute CN, but the quality of published studies to support any particular technique has been very low. Uncertainty, therefore, remains about the effectiveness of the different monitoring techniques, and whether the different monitoring techniques influence time to remission and recurrence rates. Therefore, there are no formal recommendations for clinical practice; the key finding is the lack of a consistent approach to monitoring in CN. Common techniques included X-ray, temperature monitoring, and MRI. Techniques were poorly described, and where the information was reported, there was variability in the devices used and how the technique was applied. It is not clear whether the devices used were validated for the temperature ranges commonly found in feet. Some studies still relied on subjective measures of the temperature difference between feet to monitor CN. It is interesting to note that the PET scan was also used as a means of diagnosis and remission in CN [104,105]

The risk of amputation and mortality associated with CN

In the presence of CN and in order to avoid amputation of the standing limb (especially if the joint affected by CN is located at the level of the leg), it is essential to prevent the appearance of an ulcer on the joint [106]; CN by itself does not pose a serious amputation risk, but ulcer complication increases the risk of joint amputation [107], so the implication of CN by increasing the mortality risk is now also shown. People with Charcot neuroarthropathy have an almost three times higher risk of mortality, despite being younger at presentation [108]; however, this risk remains lower than the mortality risk observed in people with diabetic foot ulcer [109].

In conclusion, CN remains a serious complication, the appearance of which remains controversial; therapeutic success requires an early diagnosis and rapid management. The involvement of bone modelling factors seem to be the best method of treatment for this complication in the future.

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Declaration of Competing Interest

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