CHARCOT OSTEOARTHOPTHY: ONE DISEASE, TWO PRESENTATIONS

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Charcot osteoarthropathy or Charcot foot is a disabling complication of diabetes and is associated with poor prognosis and high mortality. Its pathogenesis is not fully understood and its treatment is at best symptomatic. Furthermore, it is not known whether there is a specific type of neuropathy which affects osteoclastic activity, and thereby leads to reduction of bone mineral density and the development of Charcot osteoarthropathy. Recently it has been proposed that there is a difference in the presentation of Charcot osteoarthropathy between type 1 and type 2 diabetes.

This article reviews the link between underlying osteopenia, abnormal biomechanical forces and type of neuropathy, and their varying interaction in the pathogenesis of Charcot osteoarthropathy in type 1 and type 2 diabetes. Further attention is drawn to the newly discovered osteoprotegerin/receptor activator of nuclear factor kappaB ligand (OPG/RANKL) cytokine system, which controls bone resorption. Increased osteoclastic activity in the acute Charcot foot may be associated with altered expression of OPG/RANKL signaling pathway and modulation of the OPG/RANKL equilibrium in Charcot osteoarthropathy may provide additional therapeutical option to manage this difficult condition.

**Key words:** Charcot osteoarthropathy, diabetes, fracture, neuropathy, OPG/RANKL, osteopenia

INTRODUCTION

Charcot osteoarthropathy or Charcot foot is a major complication of diabetes and its pathogenesis remains poorly understood (1). It often presents without warning and can rapidly deteriorate into severe and irreversible foot deformity leading then to ulceration and amputation. Prognosis of this condition is poor and mortality is high (2,3). There is considerable controversy regarding its pathogenesis and the treatment is at best symptomatic. Natural history studies have indicated that the important initial lesions are fractures which are spontaneous in most cases. Due to underlying peripheral neuropathy, the fractures are not painful and the patient who is unaware of the condition is able to tolerate walking. Eventually a stage with multiple fractures and loss of normal foot architecture develops, that is, the Charcot foot (4).

Fractures are often juxta-articular and can cause the joint to become unstable and subject to abnormal stresses which will result in erosion of bone and cartilage. Fractures of significant magnitude were responsible for initiating joint changes in the majority of the 118 cases of Charcot foot reported by Johnson (4). In this classical review, he was convinced that fractures are the harbinger of the Charcot foot (5). However, the reason for

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these fractures is not fully understood. It is possible that there is increased fragility of bone associated with a reduction of bone density in the foot that would increase susceptibility to fracture. Alternatively, these may be stress fractures, occurring in bones with normal bone density but subjected to abnormal biomechanical forces. Furthermore, it is not known whether there is a specific type of neuropathy which by affecting osteoclastic activity, leads to reduction of bone mineral density and the development of Charcot osteoarthropathy.

**IS THERE UNDERLYING OSTEOPENIA THAT PREDISPOSES TO FRACTURES AND THEN TO THE DEVELOPMENT OF THE CHARCOT FOOT?**

Previous studies have suggested that reduced bone mineral density in diabetic patients predisposes to fracture, leading to Charcot osteoarthropathy. A reduced bone mineral density in the lower limbs of Charcot patients compared with non-Charcot neuropathic patients has been reported (6) as well as reduced stiffness in the calcaneum in the Charcot and non-Charcot foot compared with controls (7). However, these studies did not differentiate between type 1 and type 2 diabetes and we demonstrated that at the onset of Charcot osteoarthropathy, there is a pre-existing osteopenia only in type 1 but not in type 2 diabetes as indicated by a reduced bone mineral density in the non-Charcot foot compared with controls (8) and a recent study has shown a link between type 1 diabetes, osteopenia and fractures (9).

Thus the association between diabetes and osteopenia is more marked in type 1 rather than type 2 diabetes and interestingly a relatively high preponderance of patients with longstanding type 1 diabetes developing Charcot osteoarthropathy at a young age has been reported (10). This overrepresentation of type 1 diabetes suggests that there may be additional predisposing factors to Charcot osteoarthropathy in type 1 diabetes and underlying osteopenia may be one of them.

**IS THERE A BIOMECHANICAL ABNORMALITY THAT MAY LEAD TO FRACTURES IN BONES WITH NORMAL BONE MINERAL DENSITY AND THUS LEAD TO THE DEVELOPMENT OF THE CHARCOT FOOT?**

It is possible that fractures in type 2 diabetes are result of abnormal biomechanical forces on the background of global neurological deficit. Indeed, stress fractures of the bone were the most frequent cause of Charcot osteoarthropathy in one series of patients (5). Fractures may result from alteration of weight bearing and load in the foot. Armstrong reported elevated peak plantar pressures in the Charcot foot and interestingly also in the non-Charcot foot in type 2 diabetic patients (11) and patients with Charcot osteoarthropathy who presented with dislocation pattern of osteoarthropathy had a higher bone mineral density compared with patients who presented with fractures (9). Weight-bearing on a neuropathic foot with weak ankle dorsiflexors causes the triceps surae to forcefully plantarflex the foot resulting in increased pressure over the metatarsal-phalangeal joints, a slapping gait and stress at the tarsometatarsal, naviculo-cuneiform and midtarsal joints once calf contracture occurs (1). Achilles tendon shortening may predispose to Charcot foot collapse (12) by pulling the hind foot into planter flexion which results in markedly increased load in the forefoot (13). Thus high peak pressure and sensory neuropathy in the forefoot coupled with a relative equinus deformity may predispose to Charcot osteoarthropathy (11) as a consequence of an increased pressure in the mid-foot. Recent studies have shown that the equinus foot alters the normal profile of footfall, moving initial contact away from the lateral aspect of the heel to the forefoot area, in essence missing the load response phase of gait (the first rocker). This will result in forces of approximately 1.5-2 times body weight being transmitted to a region with limited extrinsic shock absorption properties. Furthermore, due to the foot’s normal pronation profile, a forefoot impact may result in excessive stress at the articulations of the medial cuneiform, resulting in micro- and eventual macrotrauma (14). This may explain why the tarsometatarsal joint (Lisfranc joint) is the commonest site of involvement of Charcot osteoarthropathy (1) and increased pressure in the forefoot may result in fracture/dislocation of the tarsometatarsal joint and eventual collapse of the medial longitudinal arch. Thus abnormal foot biomechanics in the insensitive neuropathic limb may lead to repetitive trauma and result in fractures and development of Charcot foot.

Although both osteopenia and abnormal biomechanical forces in the background of neuropathy may have varying interaction in the pathogenesis of Charcot osteoarthropathy in type 1 and type 2 diabetes, the final common precipitating event is usually trauma, which determines the site of involvement on the background of peripheral neuropathy, which has been demonstrated in both type 1 and type 2 patients with Charcot osteoarthropathy.

**IS THERE A SPECIFIC TYPE OF NEUROPATHY THAT MAY LINK OSTEOPENIA AND DIABETES?**

Several investigations have shown that neuropathy may aggravate the deficit of bone mass in type 1 diabetes. A decreased bone mineral density in the femoral neck and distal limb in association with peripheral neuropathy has been
Charcot osteoarthropathy

has been reported in post-teen age years in patients with type
mass at adolescence and indeed reduced bone mineral density
impair osteogenesis and impede achievement of peak bone
density in both type 1 and type 2 diabetes, once Charcot
osteoarthropathy has developed, are unknown but this may
be related to a specific type of neuropathy.

Clinical observations have indicated that local innervation
plays a modulating role in bone growth, repair and remodeling.
Patients with neurological disorders such as spinal cord injury
and arthritis exhibit localised osteopenia, bone fragility,
excessive callus formation and altered fracture healing.
Identification of the nerve-derived signalling molecules,
using immunohistochemistry has enabled the identification
of these nerve fibres of osseous tissues. Calcitonin gene-
related peptide (CGRP) and substance P (SP) have been
of much interest because these neuropeptides are found in
unmyelinated (C type) and small myelinated (A- type)
primary sensory neurons, namely nociceptive fibres (17,18).
The terminal structure of the osseous CGRP-containing nerves
reaches directly osteoblasts, osteoclasts, and perioseal lining
cells, and are a source of local CGRP which act as a local
modulator of bone metabolism. CGRP increases osteoblastic
cyclic adenosine monophosphate via acting on their specific
CGRP receptors (19,20) and thus stimulating osteogenesis
(21). Osseous CGRP-containing fibres are also involved in
pathologic events of bone. The density of CGRP fibres is
increased near the sites of postfracture osteogenesis (healing
callus) (22) and is decreased at the stumps of non-union (23).
Damage to the CGRP-releasing terminals may result in loss
of the trophic and modulatory factors provided by the peptide
transmitters (19-21,24,25). CGRP positive nerve fibres are
crucial element of bone metabolism during growth and
development and their impairment at a young age may lead
to impaired bone formation (26).

Thus small fibre neuropathy may play two possible roles in
the pathogenesis of Charcot osteoarthropathy. Firstly, CGRP
deficiency, as a result of small fibre neuropathy presenting
at young age in patients with type 1 diabetes, may lead to
impaired osteogenesis and impede achievement of peak bone
mass at adolescence and indeed reduced bone mineral density
has been reported in post-teen age years in patients with type
1 diabetes (27). Secondly, the loss of CGRP containing nerve
fibres and their modulatory effect on bone, may lead to impaired
healing of microfractures resulting from a minor trauma in the
insensate foot in both type 1 and type 2 diabetes, thus triggering
the development of Charcot osteoarthropathy.

A distinct syndrome has been described in young insulin
dependent diabetic subjects in their twenties and thirties, often
women, who develop small fibre neuropathy in association
with Charcot osteoarthropathy (28,29). This is often associ-
ated with symptomatic autonomic neuropathy. Despite their
youth these patients demonstrate medial calcification of the
arteries of the feet, yet do not experience numbness of their
feet, retaining normal light touch and near-normal vibration
perception. The clinical manifestations are almost solely due to
small nerve fibre damage. This striking syndrome is not rare, is
highly destructive, and is clearly different from the commoner
problem of numb, ulcerated feet. We have previously described
an association of neuropathy with vascular calcification but
the mechanism is not fully understood (30).

Thus in type 1 diabetes, there appears to be a syndrome of
small fibre neuropathy, vascular calcification and peripheral
osteopenia which then results in pathological fractures and
Charcot osteoarthropathy whilst in type 2 diabetes periph-
eral neuropathy and autonomic neuropathy associated with
vascular calcification may be present at the time of diagnosis
of type 2 diabetes and thus subsequently increase the risk of
Charcot osteoarthropathy.

WHAT THEN COULD EXPLAIN THE LINK BETWEEN SMALL
FIBRE NEUROPATHY, CALCIFICATION, OSTEOPENIA AND
CHARCOT OSTEOARTHROPATHY?

A recently described cytokine system, which controls bone re-
sorption may provide this link. This is the osteoprotegerin(OPG)/
receptor activator of nuclear factor-kappaB ligand (RANKL)
signaling pathway which may be disturbed in diabetic neu-
ropathy (31). A small pilot study has demonstrated increased
concentrations of OPG in patients with neuropathy compared
with non-neuropathic patients and healthy controls (32).

The RANKL has been identified as an essential cytokine
for the formation and activation of osteoclasts. RANKL
activates its receptor, which is expressed on osteoclasts,
thus promoting osteoclastogenesis. RANKL is expressed
on bone forming osteoblasts and thus bone resorption and
bone formation are coupled through RANKL. The effects of
RANKL are physiologically counterbalanced by OPG, which
acts as a decoy receptor (a soluble receptor that acts as an
antagonist) for RANKL. The balance between RANKL and
OPG determines osteoclast functions. Expression of RANKL

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and OPG is coordinated to regulate bone resorption and density and negatively by controlling activation state of RANK on osteoclasts. Alterations of the OPG/RANKL ratio are critical in the pathogenesis of bone diseases that result from increased bone resorption (33). Transgenic mice overexpressing OPG develop osteoporosis and, conversely, OPG knockout mice develop severe osteoporosis (34). These mice also develop arterial calcification which may also be influenced by the OPG/RANKL cytokine system (35). It is well known that there is a high clinical prevalence and coincidence of arterial calcification and cardiovascular disease in patients with osteoporosis thus supporting the hypothesis that the OPG/RANKL system may influence both osteoporosis and calcification. (36-38). Furthermore, there is a significant correlation of serum OPG levels with diabetes and with cardiovascular mortality and this raises the possibility that OPG may be a cause of or a marker for arterial calcification (39).

Recent studies on the OPG/RANKL signaling pathway provide a deeper understanding of how diverse physiological and pathophysiologival signals exert their effect on this cytokine pathway to induce osteoclastogenesis, bone resorption and skeletal remodeling, and so control bone mass. Mutations in the genes encoding RANK and OPG cause bone diseases and therefore inhibition of the RANKL signaling pathway may be a viable therapeutic strategy for treatment of diseases with excessive resorption (40). In a recent study in Charcot osteoarthropathy we demonstrated raised levels of OPG in type 1 and type 2 patients with Charcot osteoarthropathy compared with type 1 and type 2 diabetic control patients (41). It is possible that the increased OPG levels reflect a protective mechanism to inhibit osteoclast formation and thus compensate for increased osteoclastic activity resulting from an increased activity of RANKL in acute Charcot osteoarthropathy. The RANK/RANKL signaling pathway has been shown to be essential for osteoclast differentiation in inflammatory arthritis. Furthermore, imbalance between RANKL and OPG has recently been shown to lead to osteoarticular pathologies in inflammatory arthritis and in severe osteolysis (42).

Expression of OPG/RANKL is known to be modulated by various factors including tumour necrosis factor-alpha, interleukins, calcitonin, and CGRP. The latter inhibits osteoclast function and stimulates bone formation. CGRP is a neuropeptide that acts as a neurotransmitter in small fibres (C-fibres) (43,44). CGRP is deficient in small fibre neuropathy and this may result in osteopenia via the OPG/RANKL cytokine pathway. Small fibre neuropathy may enhance the ratio of RANKL to OPG and thus promote osteoclastogenesis and accelerate bone resorption. Furthermore in Charcot osteoarthropathy, there is early fracture which itself stimulates increased expression of RANKL. In the presence of neuropathy, with deficiency of CGRP, this may lead to overexpression of RANKL and an increased OPG/RANKL ratio may result in excessive osteoclastic activity leading to Charcot osteoarthropathy.

Thus altered expression of OPG/RANKL secondary to small fibre neuropathy may have two roles: (i) by promoting osteopenia in type 1 diabetes to increase susceptibility to Charcot osteoarthropathy, and (ii) by stimulating osteoclastogenesis in the actual development of Charcot osteoarthropathy in both type 1 and type 2 diabetes.

CONCLUSION

Thus the observed difference in bone mineral density in the background of sensory deficit may lead to different pathways in the development of Charcot osteoarthropathy in type 1 and type 2 diabetes, as determined by the neurovascular and neurotraumatic theories of its pathogenesis (1,45). In type 1 diabetes, the underlying osteopenia secondary to increased blood flow and autonomic neuropathy may lead to pathological fractures and Charcot neuropathic osteoarthropathy as described in the neurovascular theory (46). In contrast, in type 2 diabetes, where bone mineral density is normal, repetitive trauma in the insensitive foot with elevated plantar pressure (11,47) as a result of the increased body mass index and abnormal biomechanical forces may lead to stress fractures and Charcot osteoarthropathy in accordance with the neurotraumatic theory. Increased osteoclastic activity in the acute Charcot foot may be associated with altered expression of OPG/RANKL signaling pathway and modulation of the OPG/RANKL equilibrium in Charcot osteoarthropathy may provide additional therapeutical target to manage this difficult condition.

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