Theories Concerning the Pathogenesis of the Acute Charcot Foot Suggest Future Therapy

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The acute Charcot foot is characterized by bone fracture and dislocation, and is a rare complication of distal symmetrical neuropathy in diabetes. The cause is unknown, but it cannot be attributed solely to loss of protective sensation. However, recent advances in understanding the mechanisms of osteoclast activation have suggested that the key abnormality may lie in an enhanced inflammatory response to injury, which is itself linked to increased bone lysis. The recognition that the acute Charcot foot is essentially an inflammatory arthropathy suggests new options for the management of this potentially devastating condition.

Introduction

The acute Charcot foot (diabetic neuropathic osteoarthropathy) is a complication of denervation, in which there is progressive fracture and dislocation of bones and joints of the foot without significant preceding trauma. The condition has been well reviewed in recent years [1,2]. The acute Charcot foot is rare, and although there are no precise estimates of cumulative incidence, it probably affects less than 1% of all people with diabetes [3]. Partly as a result of its rarity, it is a condition of which many health care professionals are ignorant and this may result in considerable delay in diagnosis. The delay allows the condition to worsen while the foot is unprotected, and can lead to catastrophic consequences—with secondary ulceration affecting up to 50% [4,5], an appreciable risk of major amputation and poor overall survival [6,7]. But even though prompt diagnosis—with early institution of effective offloading—is essential for the minimization of the eventual damage, the acute Charcot foot can be very difficult to manage. The main reason for this difficulty is that the pathogenesis of the condition is not understood and that apart from offloading there is currently no treatment of proven efficacy.

History of the Condition

The earliest cases of neuropathic osteoarthropathy were reported in 1831 by the American physician, Mitchell [8], in patients with "caries of the spine." The priority of this work was acknowledged by Charcot when he reported the results of detailed clinicopathologic studies of his own patients, most of whom had tabes dorsalis. His original description was of neuropathic arthropathy affecting more major joints [9], but he described involvement of the bones and joints of the foot in later work [10]. It was the presentation of these later studies at the International Medical Congress in London in 1881 that prompted the eminent English surgeon, Paget, to suggest that the condition be called "Charcot's disease" [11]. It was later recognized that neuropathic osteoarthropathy could complicate any cause of dense peripheral denervation, including trauma, leprosy, and syringomyelia. It was first described in diabetes in 1936 [12] and, worldwide, this is almost certainly the most common cause today.

Clinical Features

The typical clinical features are well recognized. The patient with neuropathy presents with inflammation of the foot or ankle, which has been present for a variable number of days or weeks, and which may have been triggered by an injury. Such injury is often trivial and in many cases no precipitating event is recalled at all. The foot itself may be simply inflamed at first, and without obvious structural damage, but in some cases there is clinical and radiologic evidence of dislocation or fracture even at the time of presentation. If there is no obvious structural damage, the lesion is most likely to be diagnosed as a sprain or soft tissue infection by a nonspecialist, although the specialist diabetologist will have a low threshold for making the correct diagnosis in any patient with established neuropathy. The part of the foot that is affected may be the forefoot, but the condition is most commonly recognized in the midfoot and ankle. A good case can be made for suggesting that isolated fractures of the metatarsals ("stress fractures") represent a limited manifestation of the same condition. It is not clear why some patients present with minimal and relatively non-

progressive disease, whereas in others the damage is continued and extensive.

The inflammation persists for a period of time, which may extend for weeks, months, or even years; the condition remained active for 18 months or more in 23% of one large series [5]. Although the inflammation persists, there is a persistent risk of damage to the joints and bones of the foot, and every effort should be made to rest the foot and to minimize weightbearing during this period. The disease eventually enters a phase of resolution, or "coalescence," with restoration of bone strength and decreasing inflammation. Although the condition may affect the contralateral foot, most believe that it recurs only rarely on the same side, if at all.

Early Theories Concerning the Pathogenesis of the Acute Charcot Foot

Although it has been traditional to suggest that theories concerning pathogenesis divide into two camps (the French [or "nutritive"]—after Charcot, and German [or "neurotraumatic"]—attributed to Volkmann [13] schools), this distinction may relate as much to nonmedical chauvinism in the 20th century than to true differences of scientific opinion. Charcot [9] himself was well aware of the importance of the loss of protective sensation, and his speculation concerning abnormal vasomotor regulation leading to abnormal bone "nutrition" merely reflected the breadth of his vision and the realization that multiple factors were likely to be involved. The neurotraumatic theory cannot on its own explain the pathogenesis of the disorder; if it did, the condition would be a more common complication of dense neuropathy. The etiology is much more multifaceted.

One factor that suggests a multiplicity of pathologic processes is the similarity of the clinical presentation in a wide range of different diseases—diseases linked only by the presence of a fairly marked degree of peripheral denervation. The type of denervation is not uniform—whether affecting distal nerves (diabetes, leprosy, or alcohol induced), trauma to major nerves or nerve roots, or disease of the spinal cord. Tabes dorsalis is primarily a disorder of the dorsal columns with loss of deep pain, unconscious proprioception, and vibration sense, but intact perception of fine touch and superficial pain (or pinprick). Syringomyelia is most likely to affect the spinothalamic tracts with impairment of fine touch and superficial pain, whereas function of the dorsal columns may be intact. Deep pain sensation is also often preserved in distal symmetrical neuropathy, which explains why the acute Charcot foot is not always painless in diabetes. Attempts to link the occurrence of the acute Charcot foot with degrees or spectra of denervation in diabetes have produced no consistent results [14,15]. Thus, there is no identified single aspect of the nerve damage itself that may indicate why the condition affects only a small minority of those with distal symmetrical neuropathy.

Factors Associated with Neuropathy that May Predispose to the Acute Charcot Foot

Hyperemia

It has long been recognized that denervation is associated with distal hyperemia. Charcot [9] wrote that the increase in distal limb blood flow he observed was most likely to be the result of involvement of vasomotor nerves, and his observations were extended by von Leyden and Brissaud, as quoted by Henderson [16], as well as by workers (both French and German) who concluded that the hyperemia was the result of loss of sympathetic innervation [17,18]. Writing in the middle of the 20th century, Foster and Bassett [19] and Martin [20] demonstrated that loss of sympathetic innervation was a feature of the Charcot foot, and was also a relatively early manifestation of diabetic neuropathy [21]. Archer *et al.* [22] later demonstrated that diabetic neuropathy was associated with impairment of peripheral vasoconstriction.

Therefore, it is established that peripheral denervation (from tabes, distal symmetrical neuropathy of diabetes, or other disease) may be associated with loss of sympathetic innervation and increased peripheral limb blood flow. But such changes will inevitably be symmetrical, and affect both legs equally. It follows that this process cannot be responsible for the asymmetrical increase in blood flow that characterizes the acute Charcot foot—with a clinically obvious difference between the affected and nonaffected feet. Moreover, the hyperemia of the acute Charcot foot is self-limiting, and this would not be expected if it was solely the consequence of underlying neuropathy, which is essentially irreversible. It follows that other mechanisms must be involved, although the underlying hyperemia that results from sympathetic denervation may be a predisposing factor.

Osteopenia

Because the acute Charcot foot is associated with bone fracture, it is possible that the condition is particularly likely in those with a premorbid reduction in bone mineral density. There is evidence that patients with diabetes have an increased prevalence of osteopenia, and this tendency is most marked in those with type 1 disease [23–25]. It is possible that the factors leading to osteopenia in type 2 disease are opposed by the effect of increased body mass index in this population, although a variety of other mechanisms may be involved [26••]. In type 1 disease, however, the association is generally accepted and has been shown to correlate with the presence of peripheral neuropathy [27,28]. The mechanism whereby peripheral denervation may be associated with osteopenia was not previously clear, although it has been thought that it may relate in some way to the increase in blood flow that results from sympathetic denervation. However, major advances in understanding of the factors that regulate the activity of osteoclasts in other circumstances have suggested the key involvement of the RANKL/OPG signaling system.

Two recent observations suggest that premorbid osteopenia is important in the pathogenesis of the acute Charcot foot. The first is that Petrova *et al.* [29] have shown that bone mineral density may be reduced at presentation in the contralateral (nonaffected) foot at the time of presentation, although this observation was most strongly associated with type 1 diabetes. In addition, Herbst *et al.* [30] have suggested that patients with reduced bone density at presentation are more likely to have fractures of the foot, as opposed to joint dislocation without fracture. Although these observations indicate the possible importance of premorbid osteopenia, it should be noted that they are not completely compatible because together they suggest that those with type 1 diabetes should present with fractures whereas those with type 2 disease present with dislocations, but this is not the case.

Abnormal loading and foot biomechanics

Distal symmetrical neuropathy is associated with well-recognized changes in the shape of the foot and the distribution of forces during normal standing and walking. These abnormalities may be exaggerated by shortening of the Achilles tendon, and contraction of the plantar fascia as a result of glycation of connective tissue. Exaggerated clawing of the foot may lead to spontaneous dislocation in the non-Charcot neuropathic foot, principally of the metatarsophalangeal and interphalangeal joints. Each of these changes can result in increased forces being applied to the bones of the foot and may, therefore, play a part in initiating or exaggerating the cascade of damage that occurs once the Charcot process starts.

The RANKL/OPG Cytokine Pathway and the Manifestations of Diabetic Neuropathy

Osteopenia

It is now established that bone lysis is generally dependent on activation of osteoclasts by the nuclear transcription factor, nuclear factor-κB (NF-κB), and that expression of NF-κB is itself induced by the locally acting polypeptide cytokine, RANKL [31–34,35••]. The involvement of this pathway has been demonstrated in a wide variety of conditions associated with osteopenia, including idiopathic, hypogonadal, and glucocorticoid-induced osteoporosis, Paget's disease, inflammatory arthritides, and malignancy. The expression of RANKL is accompanied by increased production of a glycoprotein, osteoprotegerin (OPG), and this serves as a decoy receptor for RANKL and may act to neutralize its effects. Although there is no direct evidence, it is very possible that increased expression of RANKL mediates any osteopenia that is associated with diabetic neuropathy [26••]. Increased activation of the RANKL system (as reflected in increased circulating concentrations of OPG) has been shown in diabetes [36], and early evidence suggests that this may be especially marked in those with microvascular complications [37]. Suzuki *et al.* [38] have recently reported increased circulating concentrations of OPG in male patients with type 2 diabetes, and that there was an associated inverse correlation between OPG and bone mineral density.

Vascular calcification

Calcification of the smooth muscle cells of small- to medium-sized arteries (Mönckeberg's sclerosis) is common in diabetic neuropathy. This calcification had been noted to be associated with clinical evidence of sympathetic denervation [39] and is induced by therapeutic sympathectomy [40]. Vascular calcification is especially common in those patients affected by neuropathic osteoarthropathy [41,42], even though these patients tend to be otherwise without evidence of peripheral arterial disease and pedal pulses are typically easy to feel [43]. Despite this, the nature of the mechanistic link between denervation and calcification remained obscure until very recently. However, it now appears that calcification of smooth muscle cells of the arterial wall is triggered by the expression of the same cytokine system that stimulates maturation of osteoclasts—the RANKL/OPG system [44–48]. Thus, increased expression of RANKL leads to both osteolysis and vascular calcification.

It has been suggested that any increased activation of RANKL expression may be the indirect result of loss of nerve-derived peptides, such as calcitonin gene-related peptide, which are known to influence the RANKL/OPG system [26••]. It is also possible that conflicting influences of peptides, such as leptin and islet amyloid polypeptide (amylin), may explain some of the difference observed between type 1 and type 2 diabetes [26••]. Despite the attractiveness of the circumstantial evidence in support of this hypothesis, one group has recently confirmed a strong correlation in patients (both with and without diabetes) between vascular disease and reduced bone mineral density, while reporting no relationship with circulating concentrations of either RANKL or OPG [49]. There have been no other relevant studies of circulating concentrations of either RANKL/OPG, or of RANKL gene expression, and no studies to examine whether differences exist between type 1 and type 2 diabetes in terms of the prevalence of vascular calcification in neuropathy.

The Onset of the Acute Charcot Foot

Although the above mechanisms relate to manifestations of neuropathy, they do not explain why a small subset of affected patients goes on to develop an acute Charcot foot. Whatever puts this group at risk, the process itself requires some form of trigger. As mentioned earlier, this is usually some form of injury—often surprisingly minor. In those cases in which no precipitating trauma is noted, it may be because loss of protective sensation left the patient unaware of what had happened. In other cases the precipitating factor appears to have been local surgery, including

revascularization [50,51]. It is also possible, but very difficult to prove, that the Charcot foot may be triggered by pre-existing ulceration, or infection, of the affected foot. In our unit we have observed cases in which Charcot arthropathy was apparently triggered by pre-existing osteomyelitis, as well as by crystal synovitis.

Dislocation and microfracture

It is generally accepted that the trigger, or episode of trauma, causes microfracture of one or more pedal bones and that this (or any accompanying dislocation) increases the forces applied to adjacent bones and joints, leading to further damage. Although the foot may feel uncomfortable at this stage, the pain perceived is minor in comparison with the structural damage, and if the patient continues to take weight on the affected foot, its condition will worsen and the distortion can quickly become gross. This process, in effect, summarizes the basis of the "neurotraumatic" theory and is important in the development of the condition, even though it ignores the likely part played by the accompanying inflammation.

The Role of Inflammation

The role of inflammation is critical. Charcot [9] likened the onset of the process to an acute exacerbation of rheumatoid arthritis. It is accepted in clinical practice that the signs of inflammation (redness, warmth, and swelling) are the best guide available to the activity of the disease. When there is no difference in temperature between the affected and nonaffected limbs, it is accepted that the process has gone into remission and weightbearing can be allowed.

Inflammation is a normal response to fracture or dislocation, and is mediated through the release of proinflammatory cytokines—principally of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). This leads to local vasodilatation, which constitutes part of the healing process. TNF-α and IL-1β are also necessary for chondrogenic differentiation in the first phases of new bone formation [52]. It is also highly relevant that these proinflammatory cytokines have a close functional relationship with RANKL and NF-κB, leading to their increased expression [53–55]. The increase in NF-κB will in turn cause activation of osteoclasts, which will enable lysis of unwanted bone fragments. In an acute uncomplicated fracture, the expression of proinflammatory cytokines reaches a peak in the first 48 hours, before gradually declining [56]. It is possible that the factor leading to this early resolution of the acute inflammatory reaction is pain, and the resultant splinting of the fractured bone. However, in the acute Charcot foot, pain perception is limited and the process of inflammation, with associated osteolysis, continues. This predisposes to further fracture, which will in turn maintain the activation of the inflammatory cycle [57••].

The central role of inflammation and of exaggerated hyperemia highlights the importance of one more factor in the etiology of this disorder. Thus, the acute Charcot foot will not occur if any inflammatory response is inhibited by the limited capacity of the vessels of the foot to vasodilate. This factor helps explain why the condition is relatively rare in a disease like diabetes, which is associated with an increased risk of macrovascular disease. It is relevant that Shapiro *et al.* [58] have shown that those who have previously had a Charcot foot have a particular pattern of vasomotor neuropathy, and retain the capacity to increase foot blood flow in response to warming, whereas neuropathic control subjects did not. The capacity to increase limb blood flow is presumably relevant to the reported case of acute Charcot foot complicating revascularization [50].

Recent work has shown that the inhibitory effect of ethanol on fracture healing in experimental animals is attenuated by the administration of IL-1 and TNF antagonists. This indicates the possible central role of these proinflammatory cytokines in the pathogenesis of ethanol-related bone disease, and suggests that distal symmetrical neuropathy may not be the only factor involved in the occasional cases of acute Charcot foot that complicate alcohol abuse [59].

The Evolution of the Charcot Process

Thus, it is possible to envision how the process is triggered in a foot that is put at risk of microfracture or dislocation by multiple overlapping effects of denervation. Metabolic factors that lead to the consequences of increased premorbid expression of NF-κB (ie, reduced bone mineral density) may also apply in diabetes. The occurrence of microfracture or dislocation has two main effects. The first is that it increases the forces applied to other bones and joints of the foot, and the second is that it initiates an inflammatory cascade. The inflammation is accompanied by increased expression of NF-κB and the resultant bone lysis increases the likelihood of further fracture. Such fracture will exacerbate the inflammatory process and a complex vicious cycle is established. This does not happen after acute uncomplicated traumatic fracture because pain leads to splinting and this in turn leads to reduction in local blood flow, but it will occur when denervation results in the absence of significant pain. When the process is established, however, it is not clear what factor leads to remission, and why this occurs relatively early in some, whereas it is late in others.

Multiple Causative Factors and the Final Common Pathway

Acceptance of the central role of inflammation, and of the RANKL/NF-κB system, in the evolution of this condition serves to explain how the presentation is essentially similar (although varying in severity), irrespective of the nature of the underlying disease (eg, diabetes, alcohol abuse, syphilis, leprosy, syringomyelia) and the type of underlying nerve damage. Even within a population with diabetes and

distal symmetrical neuropathy, there will be differences in the extent to which there is increased premorbid expression of RANKL and osteolysis, but these will be obscured by the overriding effects that follow the initiation of the inflammatory cascade. The only difference that is relevant to the underlying pathology is the site: the foot is most likely to be affected in distal neuropathies with a metabolic cause (diabetes, ethanol) because of the relative sparing of more proximal nerves. This is not the case when the primary defect is in the spinal cord.

This hypothesis also explains why osteopenia increases in the affected foot during the course of the condition (although disuse from splinting and non-weightbearing may also play a part), as well as possibly the very high reported prevalence of vascular calcification in the Charcot foot. It would be of interest to study whether the degree of vascular calcification increases during the time course of the disease.

Therapeutic Implications

The potential therapeutic implications of this hypothesis are obvious. If the requirement is to interrupt the vicious cycle of augmentation between structural skeletal damage and inflammation, then this should be the target of therapeutic interventions. Bisphosphonates may play a role by virtue of their capacity to strengthen bone by chelation as well as, conceivably, their reported effect in reducing microvascular flow. However, they do not have a direct effect on the RANKL/OPG system. Agents that do reduce the expression of RANKL and that may be of particular therapeutic benefit are calcitonin and inhibitors of TNF-α, such as glucocorticoids and nonsteroidal anti-inflammatory agents. Other potential options may include synthetic OPG and RANKL antagonists, as well as inhibitors of NF-κB (ie, the experimental agent, curcumin) or of TNF-α (including commercially available preparations [ie, infliximab and etanercept]).

Conclusions

It is suggested that a variety of factors may predispose to the development of the acute Charcot foot in patients with distal symmetrical neuropathy, as well as other causes of denervation. However, the condition is triggered by any episode that leads to local inflammation and will not occur in those with a limited capacity to increase foot blood flow. Once the process is initiated, a vicious cycle is established whereby proinflammatory cytokines lead to increased expression of NF-κB and thus of increased osteolysis. The increased osteolysis predisposes to further fracture, leading to further release of proinflammatory cytokines. The process is facilitated by reduced pain sensation and continued weightbearing on the weakened foot. Understanding of the central part played by proinflammatory cytokines suggests the possibility of effective new therapies.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Jeffcoate W, Lima J, Nobrega L: **The Charcot foot.** *Diabet Med* 2000, **17:**253–258.
2. Rajbhandari SM, Jenkins RC, Davies C, Tesfaye S: **Charcot neuroarthropathy in diabetes mellitus.** *Diabetologia* 2002, **45:**1085–1096.
3. Nabarro JD: **Diabetes in the United Kingdom: a personal series.** *Diabet Med* 1991, **8:**59–68.
4. Fabrin J, Larsen K, Holstein PE: **Long-term follow-up in diabetic Charcot feet with spontaneous onset.** *Diabetes Care* 2000, **23:**796–800.
5. Saltzman CL, Hagy ML, Zimmerman B, *et al.*: **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.
6. Sinacore DR, Withrington NC: **Recognition and management of acute neuropathic (Charcot) arthropathies of the foot and ankle.** *J Orthop Sports Phys Ther* 1999, **29:**736–746.
7. Gazis A, Pound N, Macfarlane R, *et al.*: **Mortality in patients with diabetic neuropathic osteoarthropathy (Charcot foot).** *Diabet Med* 2004, **21:**1243–1246.
8. Mitchell JK: **On a new practice in acute and chronic rheumatism.** *Am J Med Sci* 1831, **8:**55–64.
9. Charcot JM: **Sur quelques arthropathies qui paraissent dépendre d'une lésion cerveau ou de la mouelle épinière.** *Arch Physiol Norm Pathol* 1868, **1:**161–178.
10. Charcot JM, Féré C: **Affections osseuses et articulaires du pied chez les tabétiques (pied tabétique).** *Arch Neurol* 1883, **6:**305–309.
11. **Transaction of the International Medical Congress [no authors listed].** 1881, **8:**128–129.
12. Jordan WR: **Neuritic manifestations in diabetes mellitus.** *Arch Intern Med* 1936, **57:**307–366.
13. **Berliner medicinische Gesellschaft [no authors listed]. Sitzung vom 17 November.** *Berliner Klinische Wonchenschr* 1886.
14. Stevens MJ, Edmonds ME, Foster AV, Watkins PJ: **Selective neuropathy and preserved vascular responses in the diabetic Charcot foot.** *Diabetologia* 1992, **35:**148–154.
15. Young MJ, Marshall A, Adams JE, *et al.*: **Osteopenia, neurological dysfunction, and the development of Charcot neuroarthropathy.** *Diabetes Care* 1995, **18:**34–38.
16. Henderson VE: **Joint affectations in tabes dorsalis.** *J Pathol* 1905, **10:**211–263.
17. Leriche R: **Sur quelques maladies osseuses et articulaires d'origine vaso-motrice et sur leur traitement.** *Bull Mem Soc Nat Chir* 1927, **53:**1022–1030.
18. Marinescu G, Bruch H: **Zur kenntnis der gelenkstörungen bei tabes.** *Zeitschr F Klin Med* 1937, **132:**178–182.
19. Foster DB, Bassett RC: **Neurogenic arthropathy associated with (Charcot joint) with diabetic neuropathy: report of two cases.** *Arch Neurol Psychiat* 1947, **57:**173–185.
20. Martin MM: **Charcot joints in diabetes mellitus.** *Proc Roy Soc Med* 1952, **45:**503–506.
21. Martin MM: **Involvement of autonomic nerve fibres in diabetic neuropathy.** *Lancet* 1953, **1:**560–565.
22. Archer AG, Roberts VC, Watkins PJ: **Blood flow patterns in diabetic neuropathy.** *Diabetologia* 1984, **27:**563–567.
23. Ziegler R: **Diabetes mellitus and bone metabolism.** *Horm Metab Res Suppl* 1992, **26:**90–94.
24. Cundy T, Edmonds ME, Watkins PJ: **Osteopenia and metatarsal fractures in diabetic neuropathy.** *Diabet Med* 1985, **2:**461–464.

25. Kayath MJ, Dib SA, Vieia JG: **Prevalence and magnitude of osteopenia associated with insulin-dependent diabetes mellitus.** *J Diabet Complications* 1994, **8:**97–104.

26.•• Jeffcoate W: **Vascular calcification and osteolysis in diabetic neuropathy—is RANK-L the missing link ?** *Diabetologia* 2004, **47:**1488–1492.

Reviews the evidence suggesting the importance of the OPG/RANKL signaling pathway in diabetic neuropathy, and includes speculation on possible mechanisms underlying abnormal activation of NF-κB in type 1 and type 2 diabetes, with and without nerve damage.

27. Forst T, Pfutzner A, Kann P, *et al.*: **Peripheral osteopenia in adult patients with insulin-dependent diabetes mellitus.** *Diabet Med* 1995, **12:**874–879.

28. Rix M, Andresaasen H, Eskilden P: **Impact of peripheral neuropathy on bone density in patients with type 1 diabetes.** *Diabetes Care* 1999, **22:**827–831.

29. 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.

30. Herbst SA, Jones KB, Saltzman CL: **Pattern of diabetic neuropathic osteoarthropathy associated with the peripheral bone mineral density.** *J Bone Joint Surg Br* 2004, **86:**378–383.

31. Hofbauer LC, Heufelder AE: **The role of receptor activator of nuclear factor kappaB ligand and osteoprotegerin in the pathogenesis and treatment of metabolic bone diseases.** *J Clin Endocrinol Metab* 2005, **85:**2355–2363.

32. Khosla S: **Minireview: the OPG/RANKL/RANK system.** *Endocrinology* 2001, **142:**5050–5055.

33. Schoppet M, Preissner KT, Hofbauer LC: **RANK ligand and osteoprotegerin. Paracrine regulators of bone metabolism and vascular function.** *Arterioscl Thromb Vasc Biol* 2002, **22:**549–553.

34. Ashcroft AJ, Davies FE, Morgan GJ: **Aetiology of bone disease and the role of bisphosphonates in multiple myeloma.** *Lancet Oncol* 2003, **4:**284–292.

35.•• Rogers A, Eastell R: **Circulating osteoprotegerin (OPG) and receptor activator for NFkappaB ligand (RANKL): clinical utility in metabolic bone disease assessment.** *J Clin Endocrinol Metab* 2005, Aug 16; [Epub ahead of print].

An up-to-date review of current knowledge of the role of the OPG/RANKL signaling pathway in bone.

36. Browner WS, Lui LY, Cummings SR: **Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women.** *J Clin Endocrinol Metab* 2001, **86:**631–637.

37. Knudsen ST, Foss CH, Poulsen PL, *et al.*: **Increased plasma concentrations of osteoprotegerin in type 2 diabetic patients with microvascular complications.** *Eur J Endocrinol* 2003, **149:**39–42.

38. Suzuki K, Kurose T, Takizawa M, *et al.*: **Osteoclastic function is accelerated in male patients with type 2 diabetes mellitus: the preventive role of osteoclastogenesis inhibitory factor/osteoprotegerin (OCIF/OPG) on the decrease off bone mineral density.** *Diabetes Res Clin Pract* 2005, **68:**117–125.

39. Edmonds ME, Morrison N, Laws JW, Watkins PJ: **Medial arterial calcification and diabetic neuropathy.** *BMJ* 1982, **284:**928–930.

40. Goebel FD, Fuessl HS: **Monckeberg's sclerosis after sympathetic denervation in diabetic and non-diabetic subjects.** *Diabetologia* 1983, **24:**347–350.

41. Sinha S, Munichoodappa C, Kozak GP: **Neuro-arthropathy (Charcot joints) in diabetes mellitus: a clinical study of 101 cases.** *Medicine (Baltimore)* 1972, **51:**191–210.

42. Clouse ME, Gramm HF, Legg M, Flood T: **Diabetic osteoarthropathy: clinical and roentgenographic observations in 90 cases.** *AJR Am J Roentgenol* 1974, **121:**22–33.

43. Purewal TS: **Charcot's diabetic neuroarthropathy: pathogenesis, diagnosis and management.** *Pract Diab Int* 1996, **13:**88–91.

44. Bucay N, Sarosi I, Dunstan CR, *et al.*: **Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification.** *Genes Dev* 1998, **1:**1260–1268.

45. Hofbauer LC, Schoppet M: **Osteoprotegerin: a link between osteoporosis and arterial calcification?** *Lancet* 2001, **358:**257–259.

46. Demer LL, Tintut Y, Parhami F: **Novel mechanisms in accelerated vascular calcification in renal disease patients.** *Curr Opin Nephrol Hypertens* 2002, **11:**437–443.

47. Schoppet M, Al-Fakhari N, Franke FE, *et al.*: **Localization of osteoprotegerin, tumor necrosis factor-related apoptosis-inducing ligand, and receptor activator of nuclear factor-kappaB ligand in Mönckeberg's sclerosis and atherosclerosis.** *J Clin Endocrinol Metab* 2004, **89:**4101–4112.

48. Collin-Osdoby F: **Regulation of vascular calcification by osteoclast regulatory factors RANKL and osteoprotegerin.** *Circ Res* 2004, **95:**1046–1057.

49. Pennisi P, Signorelli SS, Riccobene S, *et al.*: **Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels.** *Osteoporosis Int* 2004, **15:**389–395.

50. Edelman SV, Kosofsky EM, Paul RA, Kozak GP: **Neuro-arthropathy (Charcot's joints) in diabetes mellitus following revascularisation surgery.** *Arch Intern Med* 1987, **147:**1504–1508.

51. Fleischli JE, Anderson RB, Davis WH: **Dorsiflexion metatarsal osteotomy for treatment of recalcitrant diabetic neuropathic ulcers.** *Foot Ankle Int* 1999, **20:**80–85.

52. Gerstenfeld LC, Cho TJ, Kon T, *et al.*: **Impaired fracture healing in the absence of TNF-alpha signaling: the role of TNF-alpha in endochondral cartilage resorption.** *J Bone Miner Res* 2003, **18:**1584–1592.

53. Hofbauer LC, Lacey DL, Dunstan CR, *et al.*: **Interleukin-1 beta and tumor necrosis factor-alpha, but not interleukin-6, stimulate osteoprotegerin ligand gene expression in human osteoblastic cells.** *Bone* 1999, **25:**255–259.

54. Saidenberg-Kermanac'h N, Bessis N, Cohen-Salal M, *et al.*: **Osteoprotegerin and inflammation.** *Eur Cytokine Netw* 2002, **13:**144–153.

55. Lam J, Abu-Amer Y, Nelson, *et al.*: **Tumour necrosis factor superfamily cytokines and the pathogenesis of inflammatory osteolysis.** *Ann Rheum Dis* 2002, **61(suppl 2):**ii82–ii83.

56. Kon T, Cho TJ, Aizawa T, *et al.*: **Expression of osteoprotegerin, receptor-activator of NF-kappaB ligand (osteoprotegerin ligand) and related proinflammatory cytokines during fracture healing.** *J Bone Miner Res* 2001, **16:**1004–1014.

57.•• Jeffcoate WJ, Game F, Cavanagh PR: **The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes.** *Lancet* 2005, Aug 10; [Epub ahead of print].

This hypothesis outlines the evidence to suggest a central role on inflammation in the development of the acute Charcot foot.

58. Shapiro SA, Stansberry KB, Hill MA, *et al.*: **Normal blood flow response and vasomotion in the diabetic foot.** *J Diabetes Complications* 1998, **12:**147–153.

59. Perrien DS, Wahl EC, Hogue WR, *et al.*: **IL-1 and TNF antagonists prevent inhibition of fracture healing by ethanol in rats.** *Toxicol Sci* 2004, **82:**656–660.