Diabetic bone disease and Charcot joints: A review

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Article points

1. Both type 1 and type 2 diabetes are associated with increased risk of bone disease and fractures.
2. Preventing fractures requires a balance of achieving good glycaemic control whilst mitigating the risks of fracture associated with certain antidiabetes drugs.
3. Diabetic, or Charcot, neuroarthropathy needs to be identified early and treated aggressively in order to prevent the substantial long-term disability that can result from it.

Key words

- Charcot joints
- Diabetic bone disease
- Diabetic neuroarthropathy
- Fracture

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The relationship between diabetes mellitus and bone fragility is complex. Whilst osteoporosis is common in the ageing general population, people with diabetes have additional risk factors for bone fragility due to diabetes itself, its complications such as renal impairment and the drugs used in treatment. In addition, an increased risk of falls due to neuropathy, poor vision and cerebrovascular disease may increase the risk of fracture independent of bone quality and quantity. Diabetic neuropathy can result in localised bone loss at the foot and ankle, increasing the risk of fracture. Metabolic abnormalities of bone in combination with neuropathy, vasculopathy and minor trauma can lead to diabetic neuroarthropathy, otherwise referred to as Charcot joints. This article is a review of diabetic bone disease, including the rarer diabetic neuroarthropathy, and its aetiology, prevention and management.

There are many issues other than blood glucose levels which the diabetes clinic has to deal with in order to give quality care to people with diabetes. As well as screening for retinopathy, microalbuminuria and neuropathy and reducing cardiovascular risk, consideration needs to be given to long-term skeletal health. The importance of foot care in the prevention of ulceration and infection has long been recognised, but occasionally the diagnosis of diabetic neuroarthropathy is delayed. This article covers the increased risk of fracture common in people with diabetes, along with the possible causes, as well as the rarer diabetic neuroarthropathy, prompt recognition and treatment of which is important in preserving the patient's quality of life.

Bone metabolism in type 1 and type 2 diabetes

Although both conditions result in raised blood glucose, the pathology of type 1 diabetes, which is characterised by insulin deficiency, is different from that of type 2 diabetes, in which there is insulin resistance, hyperinsulinaemia and raised levels of insulin-like growth factor-1 (IGF-1). Most studies in people with type 1 diabetes show low bone turnover (Bouillon, 1991), with low levels of insulin and IGF-1 probably impairing the function of osteoblasts, the cells that synthesise bone (Epstein and Leroith, 2008). In both type 1 and type 2 diabetes, the accumulation of advanced glycation end-products in collagen, as a result of hyperglycaemia, may further reduce bone turnover and increase fragility (Krakauer et al, 1995). Loss of calcium in the urine also occurs (Raskin et al, 1978). The effects of type 1 and type 2 diabetes on bone are summarised in *Table 1*.

Bone mineral density in type 1 and type 2 diabetes

As type 1 diabetes commonly starts in adolescence, peak bone mass may be reduced, particularly if glycaemic control is suboptimal (Hui et al, 1985;

Table 1. The effects of type 1 and type 2 diabetes on bone. Adapted from Hordon (2015). Copyright © 2016 UpToDate, Inc.

	Type 1 diabetes	Type 2 diabetes
Pathology	Insulin deficiency	Insulin resistance Hyperinsulinaemia Raised IGF-1
Age of onset	Younger May affect peak bone mass	Older Usually maturity-onset
BMI	May be low	Usually high Increased load on skeleton May protect against impact Increased oestrogen, leptin and adiponectin production in adipose tissue
Mechanism	Hyperglycaemia may cause increased urinary calcium loss and inhibit bone formation Bone turnover is usually low Advanced glycation end-products may affect bone fragility	Hyperglycaemia may cause increased urinary calcium loss and inhibit bone formation Bone turnover is usually low Advanced glycation end-products may affect bone fragility Anabolic effect of insulin resistance
BMD	May be low	May be increased
Fracture risk	Increased	Increased
Treatment	Insulin has anabolic effect	Different effects of drugs on fracture risk (reduction with metformin; increase with TZDs; possible reduction with DPP-4 inhibitors and GLP-1 receptor agonists; possible increase with SGLT2 inhibitors) Insulin has anabolic effect but use marks long-standing or severe diabetes
Complications	Microvascular and macrovascular complications may increase fracture risk by effects on bone (e.g. by metabolic effects of nephropathy) or by association with an increased risk of falling (e.g. secondary to visual loss, cerebrovascular disease or neuropathy). Neuropathy-related local bone loss may increase fracture risk at the foot and ankle	

BMD=bone mineral density; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; IGF-1=insulin-like growth factor-1; SGLT2=sodium–glucose cotransporter 2; TZD=thiazolidinedione.

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Parthasarathy et al, 2016). In contrast, people with type 2 diabetes may have normal or increased bone mineral density (BMD) independent of obesity (Rishaug et al, 1995; van Daele et al, 1995). However, dual-energy X-ray absorptiometry (DXA) scanning, as a way to measure BMD, may not detect changes in cortical bone, while cortical porosity, as detected by high-resolution peripheral quantitative computed tomography, may contribute to fracture risk in type 2 diabetes (Burghardt et al, 2010).

The risk of fracture in diabetes

Despite the differences in BMD between type 1 and type 2 diabetes, the majority of studies show that fracture risk is increased in both conditions (Vestergaard, 2007; Janghorbani et al, 2007). The risk of hip fracture in type 1 diabetes is

Page points

1. Fracture risk increases with the duration of diabetes and is associated with its long-term complications.
2. Retinopathy, neuropathy, cerebrovascular disease and nephropathy can all increase the risk of fractures in people with diabetes, whether directly or indirectly.
3. Metformin and, possibly, the incretin-based therapies are associated with reduced risk of fracture, while pioglitazone and, possibly, the sodium–glucose cotransporter 2 inhibitors are associated with increased risk.
4. Healthcare providers need to be aware of the relatively uncommon form of diabetic bone disease, Charcot neuroarthropathy, as early diagnosis and treatment can prevent severe long-term disability.

higher than that in type 2 diabetes, but in both conditions the risk is greater than in the general population, with a relative risk of 6.3 in people with type 1 diabetes, and 1.7 in those with type 2 diabetes (Janghorbani et al, 2007). Fracture risk increases with the duration of diabetes and is associated with its long-term complications (Vestergaard, 2007).

The complications of diabetes may affect the risk of fracture by several different mechanisms. Renal impairment may affect BMD and bone quality; neuropathy, cerebrovascular disease and visual impairment may affect the risk of falling; and localised bone loss secondary to neuropathy may increase the risk of ankle fracture. In addition, the presence of complications can be seen as a marker of microvascular disease, which may itself have an adverse effect on bone. In one study, diabetic retinopathy was associated with fracture risk, even when adjustments were made for visual acuity (Ivers et al, 2001). These factors are important when assessing the risk of fracture using DXA or the World Health Organization's Fracture Risk Assessment Tool (FRAX), as for a given BMD or FRAX score the risk of fracture is higher in people with diabetes than in the general population (Giangregorio et al, 2012).

Drugs and fracture risk in diabetes

While poor glycaemic control increases the risk of fracture, antidiabetes drugs from the thiazolidinedione group, such as pioglitazone, may also increase fracture risk in women with type 2 diabetes by increasing bone loss (Meier et al, 2016). The risk in men is less clear. Metformin, however, has been associated with reduced fracture risk in some studies, and sulfonylureas do not appear to affect bone mass or fracture rate.

Preliminary biochemical data show that incretin-based therapies (e.g. sitagliptin and liraglutide) may potentially have beneficial effects on bone (Meier et al, 2016). In contrast, sodium–glucose cotransporter 2 inhibitors, such as dapaglifozin and canagliflozin, may be associated with an increased risk of fracture. However, further work is needed on these more recent groups of drugs to clarify their effects on bone.

The effects of insulin on bone are complex. Animal studies suggest that insulin promotes bone formation, with insulin receptor signalling in osteoblasts controlling osteoblast development and osteocalcin expression (Fulzele et al, 2010). Osteocalcin itself appears to have a role in glucose homeostasis, enhancing both insulin secretion by the pancreas and insulin sensitivity. Bone remodelling is, therefore, linked to energy regulation (Rosen and Motyl, 2010). However, insulin use by people with type 2 diabetes is associated with severe or long-standing disease, which itself has an adverse effect on bone.

Prevention and treatment of fracture in people with diabetes

Optimal control of blood glucose is important for the prevention of complications in diabetes. Good diabetes control also appears to be beneficial to skeletal health, although this has to be balanced against the risks of hypoglycaemia, which may contribute to falls, and the possible adverse effects of some drugs. In the absence of specific guidelines for people with diabetes, standard guidelines for the prevention and treatment of osteoporosis in the general population should be applied. Reassuringly, bisphosphonate drugs and raloxifene have been shown to be effective in the prevention of fracture in people with diabetes (Keegan et al, 2004; Vestergaard et al, 2011). Although the FRAX algorithm may underestimate the risk of fracture in people with diabetes (Giangregorio et al, 2012), further research is required before the algorithm can be adjusted for this condition.

Diabetic neuroarthropathy

This condition is known by several other names, including Charcot arthropathy or neuro-arthropathy, diabetic osteoarthropathy, Charcot osteoarthropathy and the simpler Charcot foot. It is important for medical and nursing staff in primary care to be aware of this uncommon condition, which can be mistaken for several others affecting the diabetic foot, as prompt diagnosis and treatment can prevent substantial long-term disability.

Pathogenesis

The predisposing factor for diabetic neuroarthropathy is the neuropathic diabetic foot. The exact mechanism triggering the onset of

neuroarthropathy is uncertain, but it is postulated that lack of sensation and proprioception leads to ligamentous laxity, instability and minor trauma (Wukich and Sung, 2009). This leads to structural damage, change in weight-bearing and further trauma. This in turn causes an exaggerated local inflammatory response mediated by proinflammatory cytokines, leading to bone resorption, which is then followed by hypertrophic repair. If not promptly identified and treated, progressive damage occurs, leading to foot deformity, plantar ulceration and a high risk of infection, leading in some cases to amputation. Autonomic as well as peripheral neuropathy may play a role, with vasomotor changes altering blood flow to skin and bone, despite the good foot pulses that are commonly found.

Epidemiology

Diabetic neuroarthropathy is uncommon. The exact incidence is difficult to ascertain, as many case series come from specialist centres treating more severe cases of diabetes. One specialist centre reported an incidence of 0.3% per year among the population with diabetes studied (Fabrin et al, 2000), while a study of 561 597 inpatients and outpatients with diabetes (predominantly type 2) in the US showed the annual incidence to be 0.12% (Stuck et al, 2008).

People with either type of diabetes are at risk. One study showed that people with type 1 diabetes tended to present with Charcot neuroarthropathy in their fifth decade with an average diabetes duration of 24±8.4 years, while those with type 2 diabetes presented later, in their sixth decade, with a shorter duration of 13±8.1 years (Petrova et al, 2004). Obesity increases the risk of diabetic neuroarthropathy (Stuck et al, 2008).

Box 1. Case report of diabetic neuroarthopathy.

Mr M was a 68-year-old man referred to the rheumatology department by his GP at the request of his podiatrist. The GP felt he had plantar fasciitis of the left foot, as well as multiple joint pains, and commented that his bloods were normal.

When he was seen in clinic in October, Mr M described pain in his shoulders, knees and neck, but his main problem was pain in his left ankle and heel. The heel had started to hurt in February and the rest of the foot and ankle followed in March. He had a history of recurrent cellulitis, with episodes 14 months and 2 years previously, and he had had type 2 diabetes for 18 years, treated with insulin and metformin.

On examination, Mr M weighed 121.6 kg and was 1.73 m in height (BMI, 40.7 kg/m^2). He had difficulty weight-bearing on his left foot and was using elbow crutches. He was pain-free when laid on the couch and had no plantar fascia tenderness. His left foot was warm, pink and not particularly tender, with non-pitting oedema and some mid-tarsal osteoarthritis. There was no ulceration. In addition, he had reduced neck movement, mild osteoarthritis of the knees and bilateral supraspinatus tendonitis. The X-ray of his left foot in June was normal, but an MRI at the end of October showed changes consistent with Charcot arthropathy, with bone marrow oedema affecting the calcaneum and talus and some fragmentation of the navicular.

He was treated by offloading the foot with a weight-bearing total contact cast for several months until resolution of the temperature difference between his feet. This gave good symptom relief. He then progressed to a special walking boot. He continues under the care of the specialist diabetic foot clinic over the long term.

Clinical presentation

Classically, the patient presents with a sudden

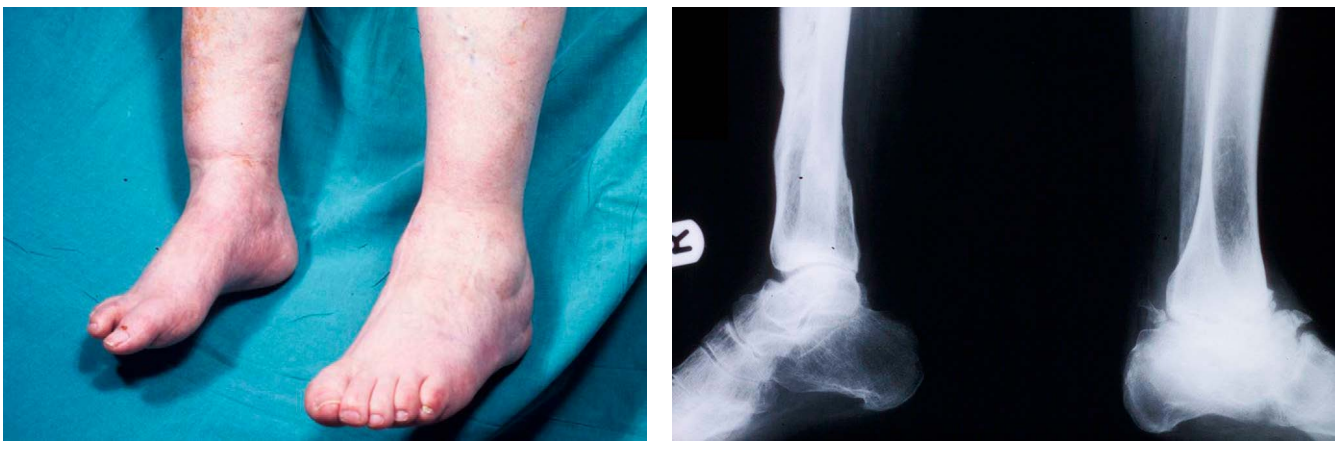

Figure 1. Photograph and X-ray of a case of late-stage Charcot arthropathy of the left ankle. The patient was a 72 year old lady with a delayed diagnosis of Charcot arthropathy leading to severe and irreversible bony damage to the left ankle, leaving her with chronic pain.

Box 2. Modified Eichenholtz classification of diabetic neuroarthropathy (Wukich and Sung, 2009).

Stage 0: Early or inflammatory
Localised swelling, erythema and warmth with little or no radiological abnormality.

Stage 1: Development
Swelling, redness and warmth persist, and bony changes such as fracture, subluxation/dislocation and bony debris are seen on plain X-ray.

Stage 2: Coalescence
Clinical signs of inflammation decrease and radiological signs of fracture healing, resorption of bony debris and new bone formation are seen.

Stage 3: Remodelling
Redness, warmth and swelling have resolved and bony deformity, which may be stable or unstable, is present. X-rays may show mature fracture callus and decreased sclerosis.

onset of warmth, redness and oedema over one foot or ankle, often with a history of minor trauma (Slowman-Kovacs et al, 1990). The affected foot is usually warm to the touch and has a temperature several degrees higher than the other foot. Most commonly, the joints affected are the tarsus and the tarsometatarsal joints, followed by the metatarsophalangeal joints and the ankle. It used to be thought that the neuroarthropathy was painless, but the majority of patients do report pain, although perhaps less than might be expected from the appearance of the foot (Armstrong et al, 1997). As an example, a real-life case is reported in *Box 1*. A photograph and X-ray of another case are presented in *Figure 1*.

Differential diagnosis

It is important to distinguish neuroarthropathy from gout, cellulitis, osteomyelitis and inflammatory arthritis with a careful history and examination. A temperature, raised white cell count and elevated inflammatory markers are suggestive of infection or gout rather than neuroarthropathy. An episode of very severe pain, redness, marked tenderness and inability to bear weight, resolving in 7–10 days, often with a history of previous similar attacks, is suggestive of gout. The presence of a foot ulcer, particularly a deep one that can be probed to bone, raises the suspicion of osteomyelitis. Unfortunately, both foot ulcers and osteomyelitis can coexist with neuroarthropathy in a minority of patients (Game et al, 2012). Septic arthritis should also be considered, particularly in the hot, swollen ankle, and joint aspiration undertaken if appropriate.

Investigations

As well as the blood tests mentioned above, blood cultures may be performed, along with swabs of any ulcers. A plain X-ray is often normal in the early stages of neuroarthropathy, and a non-contrast MRI is recommended in such cases. Contrast MRI using gadolinium, whilst giving extra information, may be contraindicated in a person with diabetes, particularly in the presence of renal impairment. Discussion with an experienced musculoskeletal radiologist is very helpful in deciding on the most appropriate imaging for the individual patient.

Treatment

Treatment should be performed by a multidisciplinary team experienced in the treatment of diabetic neuroarthropathy. The team usually includes a consultant in diabetes, a podiatrist, a physiotherapist and an expert in orthotics, with input from rheumatology, radiology and orthopaedics where needed.

The mainstay of treatment is avoidance of weight-bearing, usually offloading the affected foot with either a total contact or removable cast until signs of inflammation subside and the temperature of the affected foot is within 1 or 2 degrees of the non-affected foot, and any radiological signs improve (Frykberg et al, 2006).

The duration of casting may be many months. The treatment has to be tailored to the individual patient, taking into account balance, comorbidities, mobility and risk of falls. For example, an elderly, overweight person with diabetes may struggle with crutches and weight-bearing through the non-affected (but also neuropathic) foot, and in some cases a wheelchair is necessary for non-weight-bearing.

Bisphosphonates, both intravenous and oral, have been used in the past as an adjunct to the primary treatment of offloading in the hope of speeding the resolution of acute diabetic neuroarthropathy. However, evidence for their benefit is limited, and their use does not appear to shorten the period of immobilisation, although some centres still use these drugs in selected patients (Game et al, 2012; Richard et al, 2012).

Outcomes

If diagnosis is made at an early stage (Eichenholtz stage 0; see *Box 2*), and treatment by offloading is instituted rapidly, the outcome of neuroarthropathy is good (Rogers et al, 2011; Petrova and Edmonds, 2013). Delay in diagnosis can lead to irreversible joint disorganisation, and the main aim of treatment in these cases has to be to maintain a stable, plantigrade foot free of infection and ulceration. It is important to realise that diabetic neuroarthropathy can have a significant adverse effect on quality of life (Raspovic and Wukich, 2014).

Surgery is best avoided. However, in the occasional carefully selected patient, procedures such as the removal of exostoses, lengthening of the Achilles tendon to reduce forefoot pressure or arthrodesis to improve stability and pain may be helpful if performed by a foot and ankle surgeon experienced in the treatment of diabetic neuroarthropathy (Rogers et al, 2011).

Conclusions

There is increasing interest in the effects of diabetes and the drugs used in its treatment on bone strength and quality and the risk of fracture, with accumulating evidence that a person with diabetes may be at greater risk of fracture than a person without diabetes with similar BMD. Whilst the relationship between BMD, bone quality and fracture risk is complex, it is reassuring that bisphosphonate treatment appears to be as effective in the diabetes population as in people without the condition for the prevention of fracture.

The effects of diabetic neuropathy on bone leading to Charcot neuroarthropathy are equally complex, and poorly understood. Treatment is largely based on expert opinion but is effective if instituted at an early stage. A high index of suspicion and rapid investigation and treatment is required to ensure a good outcome for people with this uncommon but serious diabetic complication. ■

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