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REVIEW

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Musculoskeletal manifestations of diabetes mellitus

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Abstract

The prevalence of Type 1 and Type 2 diabetes are increasing significantly worldwide. Whilst vascular complications of diabetes are well recognized, and account for principle mortality and morbidity from the condition, musculoskeletal manifestations of diabetes are common and whilst not life threatening, are an important cause of morbidity, pain and disability. Joints affected by diabetes include peripheral joints and the axial skeleton. Charcot neuroarthropathy is an important cause of deformity and amputation associated with peripheral neuropathy. A number of fibrosing conditions of the hands and shoulder are recognized, including carpal tunnel syndrome, adhesive capsulitis, tenosynovitis and limited joint mobility. People with diabetes are more prone to gout and osteoporosis. Management of these conditions requires early recognition and close liaison between diabetes and rheumatology specialists.

Introduction

Diabetes mellitus affects nearly 387 million people worldwide.[1] The number of adults with diabetes in Europe is estimated to be over 50 million with a prevalence of 7.9%, and it is estimated that around 17.2 million people remain undiagnosed. Around 90% of patients with diabetes have Type 2 diabetes (T2D), characterized by variable degrees of insulin resistance and deficiency. Type 1 diabetes (T1D) is an autoimmune condition, characterized by the destruction of the insulin-producing beta cells, resulting in lifelong insulin deficiency. In developed countries, T1D is increasing at a rate of around 4% a year.[2]

Whilst diabetes is widely recognized as causing significant morbidity and premature mortality due to myocardial infarction, stroke, renal failure, visual impairment and foot ulceration, it is less widely known that diabetes is associated with a number of musculoskeletal conditions. Patients with diabetes may develop several musculoskeletal syndromes or symptoms, many of which are associated with the severity and duration of the disease. These conditions may affect joints, soft tissues, nerves, muscles or tendons. Some conditions are unique to people with diabetes, while others are seen in the general population but have a higher prevalence in the diabetic population. While some of these conditions stem from other complications of diabetes, such as peripheral neuropathy, others seem to be directly caused by the metabolic abnormality, with direct glycosylation damaging tissues. Though musculoskeletal complications of diabetes are rarely life threatening, they usually occur in patients who have other complications, such as cardiovascular, neuropathic, nephropathic or retinal conditions, and can cause significant disability. This article aims to review some of the musculoskeletal manifestations of diabetes that may be seen in clinical practice.

Diabetic neuropathic arthropathy (Charcot neuroarthropathy)

It is estimated that around one-half of all patients with diabetes develop some degree of peripheral neuropathy.[3] Peripheral neuropathy may lead to loss of protective sensation, which increases risk of foot ulceration. Distal motor neuropathy also

causes atrophy of the intrinsic muscles of the feet leading to claw toe deformity, and as a result callus may form over the now weight-bearing metatarsal heads, with further collapse of the mid foot arch adding to the deformity and disability. An uncommon sequel of severe diabetic peripheral neuropathy is the development of Charcot neuroarthropathy. Jean-Martin Charcot was the first to give a detailed description of arthropathy associated with neuropathy in 1868, in a patient suffering from tabes dorsalis.[4] In diabetic neuropathy-associated neuroarthropathy, the joints involved in order of frequency are ankle, metatarsophalangeal and tarsometatarsal joints. This distribution differentiates diabetic neuroarthropathy from tabes dorsalis, in which the knee is more commonly involved.

The pathogenesis of this condition is thought to be primarily caused by neuropathy of the sympathetic fibres, leading to an increase in the blood flow to subchondral bone and a consequent increase in osteoclastic activity, bone resorption, fragmentation, disorganization and destruction (Figure 1).[5] A proposed mechanism is that advanced glycation end-products (AGE) bind to receptors for AGE (RAGE) on chondrocytes up-regulating matrix metalloproteinase, leading to more damage and degeneration. It is thought that increased numbers of RAGE receptors in diabetes may be responsible for inflammation and accelerated atherosclerosis.[6]

Generally, patients with diabetic Charcot neuroarthropathy are relatively pain free, and even when they suffer pain, the severity is much less than what would be expected from the clinical and radiologic appearance of the affected areas. The condition should be considered in a diabetic patient with unilateral, red and warm ankle or foot, especially if the patient is known to have a peripheral sensory neuropathy. Early recognition is crucial in preventing deformity and reducing progression of the condition.

The main aim of treatment is to maintain a stable plantigrade foot that is free of ulceration and infection. Even with good podiatry and the use of specialized footwear and orthoses, this can be difficult to achieve. Avoiding weight bearing on the affected joint is important and must be continued until the erythema and swelling settles with improvement in radiologic appearance. A difference in temperature between the legs may be useful in monitoring activity of the condition. Immobilization with total contact casting or air-cast boots may be used. Some clinical trials have suggested using intravenous bisphosphonates, but systematic reviews suggest there is insufficient evidence for their routine use.[7] Involvement of the ankle and hind foot has a worse outcome than disease of the mid foot, and in patients presenting with late in the disease, the deformity can be difficult to treat, and lead to high risk of skin ulceration. Surgical intervention has little to offer in management of the Charcot joint, apart from debridement or amputation in severe infection.

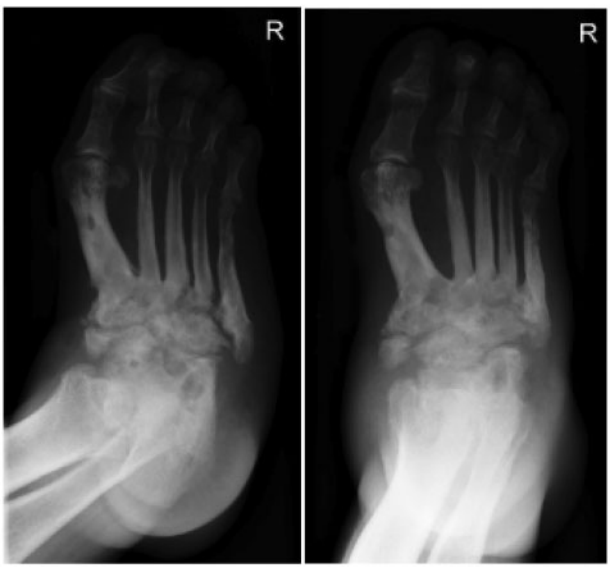

Figure 1. Plain radiographs of a 67-year-old patient with diabetic neuroarthropathy of the right ankle and foot showing soft tissue swelling, bone resorption, fragmentation, disorganization and destruction. There is also some sclerosis.

Gout, hyperuricaemia and metabolic syndrome

Obesity and metabolic syndrome are risk factors for the development of T2D. After adjusting for age, body mass index, smoking, family history of T2D, alcohol intake, dietary factors and presence of individual components of the metabolic syndrome, the multivariate risk for T2D among men with gout at baseline compared with men without gout was 1.34 [95% confidence intervals (CI): 1.09–1.64].[8] These findings from men with a high cardiovascular risk suggest that men with gout are at a higher future risk of developing T2D, independent of other known risk factors.

Co-occurrence of rheumatoid arthritis and T1D

It has long been recognized that people with rheumatoid arthritis (RA) have a higher risk of T1D, and vice versa, but a recent study from Sweden has concluded that the association of RA and T1D appears to be limited and specific to those RA patients with positive anti-citrullinated peptides antibodies.[9] The risk in patients with T1D of developing RA in later life was attributed partly to the presence of a specific allele 620 W PTPN22, possibly representing a common pathway for both autoimmune diseases.

Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) or Forestier's disease was originally described as confined to the axial skeleton, but is now recognized as a condition that involves ossification of tendon and ligament attachments in both spinal and extraspinal locations as well as hyperostosis at bony prominences (Figure 2). Nearly one-half of patients with DISH have diabetes, and it is more common in elderly diabetic subjects.[10] Glycaemic control or presence of other diabetic complications does not appear to be related to the onset or extent of DISH. Whilst many patients may be asymptomatic and DISH noted on routine radiology, DISH may present with back stiffness and pain, or even dysphagia due to exostoses. Atlanto-axial subluxation in DISH has been described. Physiotherapy and anti-inflammatories drugs may help with symptomatic relief and function, although prolonged courses of anti-inflammatories is not desirable due to the renal and cardiovascular risks with these drugs in diabetic subjects.

Fibrosing syndromes

Diabetes is associated with a number of fibrosing syndromes including adhesive capsulitis of the shoulder, tenosynovitis of

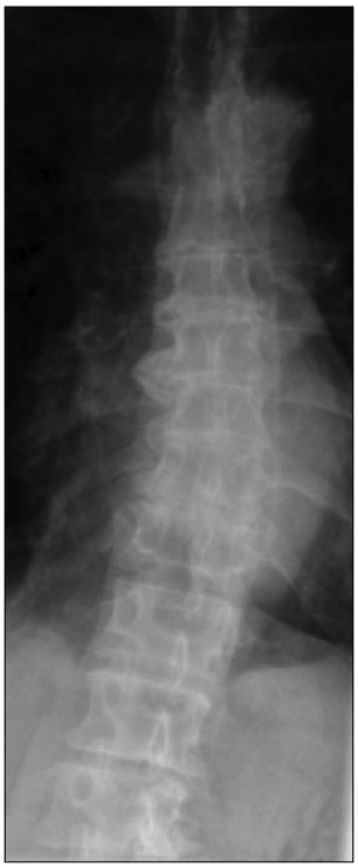

Figure 2. Plain radiograph of a 60-year-old man with T2 and DISH. Bridging osteophytes are seen on four consecutive vertebrae on the right side of the mid dorsal spine.

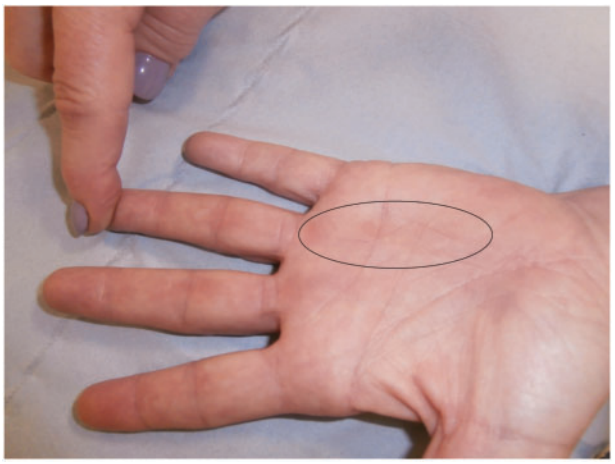

Figure 3. Tendinopathy of the long flexor tendon of the ring finger. The finger has to be pushed back to be straightened. Note the thickened tendon inside the black oval. Also note the scar of carpal tunnel release.

the long flexor of the fingers and thumbs (trigger finger/thumb) (Figure 3), or the long abductor and the short extensor of the thumbs (De Quervain's tenosynovitis), carpal tunnel syndrome, Dupuytren's contracture (Figure 4) and diabetic stiff hand syndrome (cheiroarthropathy).[11–15] The prevalence of hand or shoulder disorders is higher in people with diabetes compared with non-diabetic subjects, and correlates with the duration,

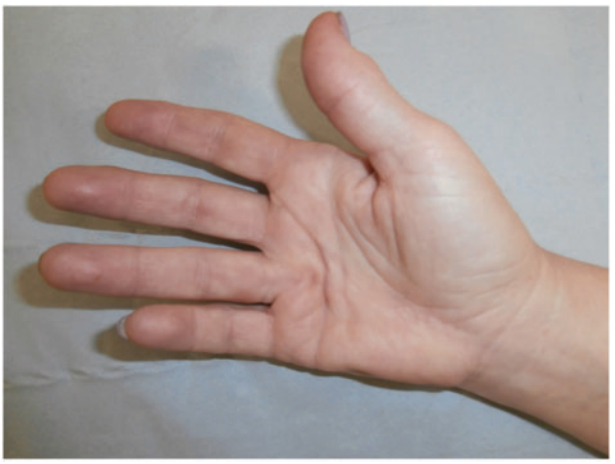

Figure 4. Dupuytren's contracture.

Figure 5. Pathogenesis of limited joint mobility.

but not the type, of diabetes.[16] In patients with diabetes, adhesive capsulitis of the shoulder can occur at a much earlier age than a non-diabetic frozen shoulder, which rarely occurs before the age of 40 years.

The aetiology of these syndromes is at least in part due to abnormal collagen deposition in the periarticular connective tissues. In addition, glycosylation increased hydration and abnormal cross-linking of collagen may be important.[17] Microangiopathy and neuropathy aggravate the problem (Figure 5). These conditions are therefore not strictly inflammatory in nature, and their natural history is that they generally tend to improve with time. The joints involved are particularly those of the upper limbs, although the feet may also be involved.

Limitation of joint movement is most marked in the small joints of the hands with thickening and waxiness of the skin, particularly on the dorsal surface of the fingers, but these skin changes may occur in the absence of limited joint mobility. It

can occur early in the course of the disease. The prevalence also increases with age and cigarette smoking. Whilst previous studies suggested a prevalence of anywhere between 20 and 50% of people with diabetes, more recent studies suggest a reduction in incidence by around 50%, although the cause of this reduction is unclear.[18] The patient shows a positive 'prayer sign' (Figure 6) and may be unable to place his hand and fingers flat on a table (tabletop sign). The condition is usually painless and may be asymptomatic.

Management strategies for fibrosing syndromes related to diabetes are guided towards symptomatic relief and improvement in function. There is no evidence that tightening of glycaemic control or cessation of smoking will help limited joint mobility, although as the pathogenesis may be related to glycosylation, poor glycaemic control is undesirable. Physiotherapy with passive palmar stretching and occupational therapy may improve function. In patients with carpal tunnel syndrome, electromyography is important diagnostically and prognostically, and management involves resting wrist splints, physiotherapy, anti-inflammatories and injection of local corticosteroid. Cases not responding to these measures or with evidence of progressive neurological changes should be considered for surgical decompression, which can be performed endoscopically.

A resting wrist, hand and finger splint for patients with limited joint mobility or a thumb splint for patients with De Quervain's tenosynovitis may be helpful. Corticosteroid injections may also be used, but they tend to be less effective in people with diabetes compared with people without diabetes. Adhesive capsulitis of the shoulder may be treated with mobilization and corticosteroid injection if there is pain. Recurrence is common.

Complex regional pain syndrome Type 1 (reflex sympathetic dystrophy)

Though it is thought to be common in patients with diabetes, the evidence for this association is not well-documented.[19] Sudek's atrophy (reflex sympathetic dystrophy or 'shoulder–hand syndrome') can occur in association with shoulder pathologies. As in other cases, the complaint is of pain with evidence of skin changes, hyperasthesiae and vasomotor instability.

Osteoporosis

In patients with diabetes, fracture risk appears to be increased in patients with vascular, nephropathic and neuropathic complications of the disease.[20–22] Hyperglycaemia itself may cause increased urinary calcium loss, leading to reduced bone mineral density. In T2D, there is a paradox of increased fractures despite normal bone mineral density (BMD) because of increased porosity of cortical and trabecular bone. A meta-analysis of 12 studies reported a relative risk (RR) of 1.7 (95% CI:1.3–2.2) for hip fracture in both men and women with T2D.[22] The risk of all clinical fractures was also increased with a summary RR of 1.2 (95% CI:1.0–1.5). There appears to be a direct association between the duration of diabetes and increased fracture risk, although poorer glycaemic control has not consistently been found to be a risk factor. Pioglitazone, an oral hypoglycaemic agent, may increase risk of fractures in postmenopausal women.[23]

Figure 6. Positive 'prayer's sign' in a patient with diabetic cheiroarthropathy.

Diabetic muscle infarction (aseptic myonecrosis, infarcted myonecrosis)

Diabetic muscle infarction is a rare complication that mainly occurs in patients with long-standing and poorly controlled disease with microvascular complications, particularly diabetic nephropathy related end-stage renal failure. It presents with acute muscle pain and swelling, most commonly in the thigh with mild constitutional symptoms. Diagnosis is made with magnetic resonance imaging without the need for a biopsy.[24,25] Creatine kinase may be elevated in around 50% of patients, and the elevation may be modest. It generally improves with conservative treatment, and surgical treatment may only be needed if compartment syndrome develops.

Conclusions

The musculoskeletal complications of diabetes are common and, though not life threatening, can lead to significant pain and disability. They usually occur in patients with poorly controlled diabetes of long duration and in those who have other more serious complications such as vascular, neuropathic, renal and retinal problems. Early recognition of these complications, and multidisciplinary management between diabetes and rheumatology specialists is necessary to reduce morbidity from these complications.

Conflict of interest: None declared.

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