Musculoskeletal disorders in diabetes mellitus

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ABSTRACT

Diabetes mellitus is associated with a great variety of musculoskeletal manifestations, many of which are subclinical and correlated with disease duration and its inadequate control. They should be recognized and treated properly, because their management improves the patients' quality of life. This review discusses the major musculoskeletal manifestations found in diabetes mellitus.

Keywords: diabetes mellitus, Dupuytren’s contracture, trigger finger, bursitis, carpal tunnel syndrome.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease of high morbidity and mortality,1 which has become a public health problem. In 1985, the world prevalence of DM was approximately 30 million cases, increasing to 177 million in 2000.2

Based on current tendencies, more than 360 million individuals will have the disease by 2030.2

Type 1 DM results from a complete deficiency of insulin due to the autoimmune-mediated destruction of insulin-producing β cells in the pancreas; in type 2 DM, which represents most of the DM cases (around 95%), there is insulin resistance, excessive hepatic production of glucose, and abnormal fat metabolism, resulting in a relative deficiency of that hormone.2,3

The prevalence of type 2 DM increases more than that of type 1 DM, because of the increase in obesity and the reduction in physical activities as countries become more industrialized.2

Diabetes mellitus accounts for a number of vascular complications, which impair patients’ survival.2 Musculoskeletal complications are also found, and, although less valued than the vascular ones, they significantly compromise the patients’ quality of life.4 The incidence of DM and the life expectancy of diabetic patients have both increased, resulting in an elevation in the prevalence and clinical importance of those osteomuscular changes. The following have been described in diabetic patients: stiff hand syndrome; Dupuytren’s contracture; trigger finger; shoulder capsulitis; calcific periartitis of the shoulder; carpal tunnel syndrome; muscular infarction; diffuse idiopathic skeletal hyperostosis (DISH); and Charcot’s arthropathy.5,6 In addition, a higher prevalence of the following has been reported: crystal arthritides; infections; osteoporosis; and osteoarthritis.6 Several authors have tried to classify the articular manifestations of DM,5,7 which is a hard task, because most of the pathophysiological mechanisms remain obscure. Table 1 shows the classification proposed by Arkkila et al.5

LIMITED JOINT MOBILITY SYNDROME

Limited joint mobility syndrome (LJMS) is a painless non-inflammatory limitation of the mobility of hands, feet, and large joints.3 The following biochemical abnormalities seem to be related to the appearance of LJMS: an increase in the non-enzymatic glycosylation of collagen fibers; an increase in collagen crosslinking and its consequent resistance to...
enzymatic digestion; an increase in the hydration mediated by aldolase reductase pathway; and an increase in the formation of advanced glycosylation end products (AGEs).5,8

The increase in the formation of AGEs might associate the occurrence of LJMS with micro- and macrovascular complications of DM.3,5 The AGEs result from the rearrangement of Amadori products or early glycosylation products. They accumulate in tissues, depending on time and glucose concentrations, and damage extra- and intracellular proteins. On cell surface, there is a receptor for AGEs (RAGEs), which is a transmembrane receptor of the family of the immunoglobulins, signaling events that lead to cell dysfunction. Experimental studies have shown that there is a reduction in the vasodilating response to nitric oxide, and that AGEs decrease vascular elasticity.5,9

The influence of a genetic component on the development of the syndrome is controversial.10,11 Some authors10 have reported that diabetic children with LJMS had more relatives with the same findings than children without that syndrome. However, Rosembloom et al.11 have not been able to confirm those findings when assessing 204 individuals with type 1 DM and their 336 first-degree relatives.

Diabetic stiff hand syndrome or cheiroarthropathy (from the Greek, cheiros = hand) is the name reserved to the LJMS that affects that extremity, being its most studied form. Typically, the diabetic stiff hand syndrome begins as cutaneous changes around the metacarpophalangeal and proximal interphalangeal joints of the fifth finger, progressing to involve all fingers.3 The patients have changes in the skin, which becomes thick, rigid and waxy, similarly to that in scleroderma. Skin changes in the hands and forearms, with no changes in joint mobility, can also be found.3,12 Arterial calcifications are commonly seen on those patients’ hand radiographs.3 The histological exam shows dermal thickening, accumulation of connective tissue in the reticular dermis with increased collagen crosslinking, and small amounts of mucin.12 The cutaneous changes should be differentiated from those of scleroderma, and the lack of the following help that differentiation: Raynaud’s phenomenon; dermal atrophy; telangiectasia; and autoantibodies.12 The frequency of the development of skin changes is associated with the duration of diabetes, although they have also been reported in children with recent-onset DM.13 Nailfold capillaroscopic changes are found in diabetic patients with microangiopathy. Spiraling capillary loops with decreased density and apical dilations, as well as dilations in the venous branch, have been described.14 Kuryliszyn-Moskal et al.14 have found an association between the severity of periungual morphological changes and disease duration, metabolic control and systemic involvement.

The prevalence of stiff hand syndrome varies from 38% to 58% of type 1 DM patients and from 45% to 76% of type 2 DM patients.3,15,16 Patients can be asymptomatic or complain from pain, which increases with the use of the extremity, or from paresthesia.3

The stiff hand syndrome is diagnosed based on its characteristic findings and physical examination. The patients’ inability to press their palms together completely without a gap remaining between opposed palms and fingers is known as the “prayer sign” (Figure 1).3 One alternative manner to test reduced joint mobility is with the so-called “table top test”, in which the patient places an open hand on a table top with fingers spread apart. When positive, the fingers and palm cannot lie completely flat on the table top.3 Passive mobility reduction is confirmed by lack of extension of proximal interphalangeal and metacarpophalangeal joints (lower than 180° and 60°, respectively).3

Both type 1 and type 2 DM patients with LJMS have a higher prevalence of diabetic retinopathy and nephropathy.1

Figure 1
Prayer signal.
The LJMS is believed to be influenced by a poor glycemic control, although the association between that musculoskeletal complication and glycemic control, or even \( \text{HbA}_{1c} \) levels, is controversial.\(^3,5,15,17\) However, it is worth noting that glycemia and \( \text{HbA}_{1c} \) levels do not reflect past periods of hyperglycemia, which might have existed years before the diagnosis of type 2 DM.

The recommended treatment is physical therapy and non-steroidal anti-inflammatory drugs.\(^3,5\) However, prior to prescribing such drugs, it is worth noting the association of that syndrome with diabetic nephropathy, to avoid its undesired side effects. In the presence of cutaneous involvement, the only treatment proposed is glycemic control.\(^8\)

**DUPUYTREN’S CONTRACTURE**

Dupuytren’s contracture (DC) is characterized by palmar fascia thickening, palmar and digital nodules, skin thickening and adherence, pretendinous band formation, and digital flex contracture.\(^3,5\) It affects 16%–32% of the patients,\(^3,5,18,19\) being more common among the elderly and those with longer DM duration.\(^3,19\)

The DC of diabetic patients have some peculiarities. The first is its tendency to mainly affect the third and fourth fingers,\(^19,20\) rather than the fourth and fifth fingers, as typically occurs in cases associated with other etiologies (Figure 2).\(^19,20\) The second is that, differently from other cases of DC affecting preferentially the male sex, in DM there is a higher prevalence of women, although that manifestation is still more severe among men.\(^3,19,20\)

The histological examination shows a dense collagenous matrix containing fibroblasts longitudinally aligned along the lines of stress. The nodules contain myofibroblasts and collagen bands, and local blood vessels are narrowed.\(^21\) There is an increased amount of glycosaminoglycans, and the local collagen has a higher proportion of type 3 fibers as compared with type 1 fibers.\(^21\)

A theory about the DC origin is that the condition results from local hypoxia followed by the release of free radicals, which affect the function of fibroblasts that produce altered collagen fibers.

Dupuytren’s contracture has been treated with intralesional infiltration of corticosteroid, surgery, and physical therapy.\(^3\) Recently, the injection of collagenase from *Clostridium histolyticum* has been claimed to be an alternative non-surgical treatment. A study\(^22\) with 308 patients, 6.5% of whom were diabetic, has reported an improvement in the flexion contracture and range of motion of finger joints with three or more collagenase injections. In that study, two patients had tendon rupture and one developed reflex sympathetic dystrophy.

**TRIGGER FINGER OR STENOSING FLEXOR TENOSYNOVITIS**

Stenosing flexor tenosynovitis presents typically as fingers locked in flexion, extension or both, more commonly involving the thumb, the third finger and/or the fourth.\(^3,5\) It results from fibrosis, with tendon thickening as it passes through the pulley or one bone prominence, limiting its motion inside the sheath. A volume increase distal to the constriction point causes pain and difficulty in flexing and extending the corresponding finger, which might become locked.\(^3\)

The prevalence of trigger finger in patients with DM ranges from 5% to 36% in those with type 1 or type 2 DM as compared with 2% in the general population.\(^23,24\) Its development being associated with longer disease duration.\(^3,5\) When compared with non-diabetic patients, those with DM have a tendency to the simultaneous involvement of multiple fingers.\(^19,25\) According to Koh et al.,\(^26\) the involvement of three or more fingers is highly suggestive of the association with DM, which should be investigated if not yet diagnosed.

The treatment of stenosing flexor tenosynovitis comprises a change in activities, use of non-steroidal anti-inflammatories, splinting, infiltrations, and, in more severe cases, surgery.\(^3,5\)

**CARPAL TUNNEL SYNDROME**

Carpal tunnel syndrome (CTS) is caused by compression of the median nerve beneath the transverse carpal ligament.
The syndrome is characterized by pain and paresthesia in the territory from the thumb to the middle portion of the fourth finger, which worsens during the night and can radiate to the forearm.\(^5,27\) In advanced cases, atrophy of the thenar musculature and grip strength loss can occur\(^27\) (Figure 3). Clinical diagnosis is established by use of the Phalen’s maneuver and Tinel’s test.\(^27\) In dubious cases, electrophysiological study might help.\(^28\)

The prevalence of CTS in patients with DM ranges from 11% to 25%, being more common in women\(^19,29\) and in patients with polyneuropathy.\(^30\) In contrast, DM is found in 5%–8% of the individuals with CTS.\(^29,31\) However, some authors believe that the real predisposing factor to CTS is obesity, common in patients with type 2 DM.\(^32\) A study of 791 patients with CTS referred for electrophysiological study\(^33\) has shown that a diagnosis of DM, female sex, obesity and age between 41 and 60 years were risk factors for CTS; however, when data were stratified according to the patients’ body mass index, the association with DM disappeared.

The management of CTS is based on the use of splints and analgesics. Infiltrations with corticosteroids can be performed, although their effect is temporary and the response of patients with DM is poorer.\(^34–36\) Release surgery might be required, at a 4–14-times greater frequency in diabetic patients than in the general population.\(^36\) The post-operative recovery of those patients is worse. That less favorable response results from the fact that DM impairs peripheral nerve regeneration due to microangiopathy, macrophagic and Schwann cell dysfunction, and reduced expression of neurotrophic factors and their receptors.\(^26,37\)

**CALCIFIC TENDINITIS AND ADHESIVE CAPSULITIS OF THE SHOULDER**

In DM, impairment of the shoulder has been described as the most disabling musculoskeletal manifestation.\(^38\)

Adhesive capsulitis of the shoulder (also known as frozen shoulder) presents as an almost complete limitation on passive and active mobility of the shoulder, mainly on adduction and external rotation.\(^3\) That condition occurs in a progressive and painful manner, leading to contracture of the joint capsule, which adheres to the humeral head, reducing the joint volume.\(^3\) The histological exam of the capsule shows proliferation of fibroblasts and their transformation into myofibroblasts, which produce an excessive amount of type 1 and type 3 collagen. Those findings are similar to those of DC.\(^3,39\) The pain appears at night initially and installs gradually.\(^3\) The natural history of adhesive capsulitis of the shoulder can be divided into the following three phases: (a) pain; (b) stiffness; and (c) recovery.\(^3\)

The prevalence of adhesive capsulitis of the shoulder is five-fold higher in the diabetic population than in the general population, being identified in 10%–29% of the former.\(^3,40,41\) It appears in both type 1 and type 2 DM, is more common in the elderly, and can be bilateral.\(^3\)

Pal et al.\(^40\) have proposed criteria for diagnosing adhesive capsulitis of the shoulder that include shoulder pain for at least one month, impossibility of lying on one’s shoulder, and limited active and passive mobility in at least three planes.

Some researchers, studying patients with frozen shoulder, have reported a higher prevalence of myocardial infarction in those with type 1 DM, and of autonomic neuropathy in those with types 1 and 2 DM.\(^3\)

The treatment of adhesive capsulitis of the shoulder consists of analgesics, corticosteroid infiltrations, and physical therapy. Most patients recover normal function.\(^3\) In the adhesive phase, capsule release can be performed via manipulation under anesthesia or surgery.\(^3,5\) Surgical release is preferably performed via arthroscopy rather than open surgery, because the former reduces the post-operative recovery period.\(^3,42\)

Calcific tendinitis results mainly from the deposition of hydroxyapatite in periarticular areas, such as the rotator cuff.\(^3,4\) It is more common in type 2 DM and can coexist with adhesive capsulitis of the shoulder. A case-control study with radiographs of the shoulder has shown calcifications in 31.8% of the patients with DM as compared with 10% of those without DM.\(^41\) Many patients with DM and calcifications are asymptomatic.\(^3\)
MUSCULAR INFARCTION

That is a relatively rare complication, mainly found in patients with type 1 DM and disease duration over 15 years.3 Clinically, the condition presents as muscle edema and pain of sudden onset.7 A palpable mass can be detected in 34%-44% of the cases.1,44 Thigh muscles are involved in approximately 80% of the cases, but more than one infarction point can appear simultaneously.45

The diagnosis is established based on clinical history and imaging, especially magnetic resonance imaging. Muscle enzymes, such as CPK, are slightly increased.5 On magnetic resonance imaging, isointense edema on T1 and hyperintense edema on T2 are found in muscle areas, with subcutaneous and subfascial edema. Usually, gadolinium is not required, but, when used, a non-enhanced area surrounded by another hyper-enhanced is observed.46 Biopsy shows necrosis of muscle fibers, edema, phagocytosis of necrotic fibers, granulation tissue and collagen deposits. Older lesions might show regeneration of muscle fibers, replacement by fibrous tissue and mononuclear infiltration.44

Because most patients with muscular infarction have diabetic retinopathy, neuropathy and nephropathy, those diagnoses are believed to be associated with local ischemia. Hypercoagulable states with changes in the coagulation-fibrinolysis system and endothelial dysfunction have also been proposed as potential pathogenic mechanisms.47 Another hypothesis would be the contribution of antiphospholipid antibodies, but that has not been proven.48

Muscular infarction resolves spontaneously in weeks or months, but half of the patients have recurring episodes. Treatment consists of rest and analgesia.5

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH)

Also known as Forester’s disease or ankylosing hyperostosis, DISH is characterized by entheseal ossification.49 The involvement of spinal ligaments forming bridges of confluent osteophytes between the vertebrae is the most striking feature of the disease, which can also involve peripheral entheses.49

The definition of DISH has been created by Resnick et al.50 and requires the involvement of four contiguous vertebral segments with preservation of intervertebral disc spaces and lack of degenerative apophyseal involvement and of sacroiliac inflammatory changes. Later, that notion was modified by Utsinger51 to include peripheral involvement. That author has proposed that the continuous anterolateral involvement of two or more vertebrae and a symmetrical peripheral enthesopathy support the probable diagnosis of DISH.

DISH affects mainly the thoracic spinal column, but the lumbar and cervical segments might also be involved.49 It is more common in patients with type 2 DM and in obeses.3 In type 2 DM, DISH has prevalence of 13%-40%.52,53 However, some authors challenge that association with DM, crediting it to obesity.52,54

Its pathophysiology is unknown. Some authors believe that hyperinsulinemia is the link between DM, DISH and obesity. The levels of growth hormone (GH) and of insulin-like growth factor-1 (IGF1) are increased in patients with DISH and might favor soft tissue ossification by stimulating osteoblast proliferation and function.3,49 Serum levels of matrix GlA protein, which inhibits bone formation, are paradoxically higher than in controls.55

Clinically, patients can be asymptomatic or have pain in the affected sites, column stiffness, dysphagia, and odynophagia, in the presence of large cervical osteophytes.49,51 Neurological complains might result from spinal cord compression due to ossification of the posterior longitudinal ligament. Peripheral pain results from peripheral enthesal involvement.39

The diagnosis is made by use of radiological exams, and the treatment consists of analgesics and therapeutic exercises.5

CHARCOT’S JOINT

Charcot’s arthropathy, or diabetic neuropathic arthropathy, results from a likely combination of mechanical and vascular factors secondary to diabetic neuropathy.56 Lack of proprioception has been postulated to cause ligament looseness, joint instability and joint lesion from small traumas. Another possibility is that autonomic neuropathy causes vasomotor alterations with the formation of arteriovenous shunts and a reduction in the effective blood flow to the skin and bones, despite the good amplitude of peripheral pulses.57 The third hypothesis is an excessive inflammatory response to traumas, mediated by pro-inflammatory cytokines.58

Regardless of the cause of the problem, there is an initial phase, which is resorptive, followed by a repair or hypertrophic phase.59

Tarsal and tarsometatarsal joints are the most affected, followed by metatarso-phalangeal joints and ankles.60

The clinical manifestations of Charcot’s arthropathy vary. The patient can present with sudden-onset erythema and unilateral edema of the foot or ankle. Recurring attacks might follow, and chronic arthropathy, characterized by plantar arch collapse and bony prominences, develops.56 Complications, such as...
ulcers that infect easily, might develop. In 20% of the patients, Charcot’s arthropathy is bilateral. The arthropathy is either painless or the pain is disproportionally milder than expected. The differential diagnosis with septic arthritis is mandatory.

Diagnosis is established via imaging, which shows, at an initial stage, only osteopenia, a reduction in joint space, and soft tissue edema. With progression, areas of osteolysis develop, with phalangeal and metatarsal head resorption. Luxations, bone fragmentation, sclerosis and neoformation can be seen at the final stages. Contrast-enhanced magnetic resonance imaging might be required to discard associated osteomyelitis (Figures 4 and 5).

Treatment consists in preventing weight bearing on the affected joint, with the use of appropriate shoes, and foot orthoses. The use of bisphosphonates (alendronate and pamidronate) might be useful. Calcitonin has been used in patients with renal failure who cannot receive bisphosphonates, but its benefits are yet to be proven.

OTHER DISEASES

Other musculoskeletal diseases possibly associated with DM are osteoporosis, osteoarthritis and crystal arthritis. The association of DM with osteoporosis is controversial. Patients with DM have low bone metabolism with reduced bone formation and, to a lesser extent, reduced resorption. The mechanism is likely multifactorial and includes, in type 1 DM, low levels of insulin and IGF-1, which inhibit osteoblast activity. In types 1 and 2 DM, the accumulation of AGEs is associated with a reduction in bone formation. Bone mass is reduced in type 1 DM and increased in type 2 DM, but the risk of fractures is increased in both types of DM.

Obesity can be a common factor to DM and osteoarthritis. Although there are some studies attempting to implicate AGEs in cartilage degeneration, there is no clear evidence implicating DM in early osteoarthritis.

Hyperuricemia and consequent gout can be found in type 2 DM as part of the metabolic syndrome. Renal failure, a common complication in DM, also predisposes to crystal arthritis. The association of DM with calcium pyrophosphate deposition disease, although suggested, remains to be proven.
ON THE USE OF CORTICOSTEROID INFILTRATION IN DIABETIC PATIENTS

The effects of the systemic use of corticosteroids on glucose metabolism are well known. However, the effects of intra-articular injections of corticosteroids on glucose metabolism have been less studied. There has always been the concern that their absorption might lead to systemic effects. Three studies, two with epidural infiltration\textsuperscript{69,70} and another with infiltration for trigger finger,\textsuperscript{71} have shown a temporary increase in glycemia, which returned to its baseline level in two to five days. Another study\textsuperscript{72} with shoulder infiltrations has not shown that increase.

CONCLUSION

Diabetes mellitus has been associated with a number of musculoskeletal manifestations. These associations have been mainly supported by epidemiological studies, because their pathophysiological mechanisms have not been completely clarified. The upper limbs (hand and shoulder) are most commonly involved. Identification and treatment of those lesions are important to improve the patients’ quality of life. On the other hand, knowing those associations might enable the diagnosis of DM in patients not yet recognized as such, and, thus, lead to the institution of proper therapy that will prevent the development of diabetic complications.
REFERENCES


