

Musculoskeletal problems in diabetes mellitus

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Abstract

Diabetic patients may suffer from a wide range of musculoskeletal disorders that can cause pain and some dysfunctions in the patient and affect the treatment negatively or reduce the quality of life by causing problems in the implementation of exercise programs, which are very important in the treatment of patients with Diabetes Mellitus. Although most of these problems are also seen in non-diabetics, they are more frequently observed but are not specific to diabetics. Their pathophysiology is not fully understood; there is some evidence suggesting that macro- and microvascular complications of diabetes are responsible. A diagnosis of musculoskeletal dysfunctions in diabetic patients is made by clinical findings, and there is currently no specific treatment. If the treatment of problems requires corticosteroid use, diabetes can be hard to manage. In this review, we summarized the general features, diagnosis, and treatment modalities of frequent and important musculoskeletal disorders in diabetic patients.

Keywords: Diabetes mellitus, connective tissue, carpal tunnel syndrome

Introduction

Various skeletal and muscular system problems arise in Diabetes Mellitus (DM). Those problems can cause pain and loss of function at the involved sites and limit the exercise programs that are part of the treatment program of the diabetic patient in maintaining and managing body weight. If rheumatoid complaints and use of non-steroidal antiinflammatory drugs (NSAIDs) and/or corticosteroids (CS) are present, the kidney functions as well as the glycemic control can be adversely affected. Musculoskeletal changes in DM are classified in Table 1.

Fibroproliferative disorders of the soft tissue

a) Limited joint mobility syndrome (cheiroarthropathy)

Cheiroarthropathy (derived from Greek *cheiro*, which means “hand”) or limited joint mobility syndrome presents itself with the restriction of joint mobility due to contractures. Prevalence is not affected by gender and race, which is 8% to 58% in Type 1 DM (T1DM) and 25% to 76% in Type 2 DM (T2DM), whereas it is 1% to 20% in non-diabetics (1). Reduced prevalence with optimal glucose control shows that glycemic control is important (2). The flexion contractures begin around the first or second decades and are rare before the first decade of life. Pathogenesis of cheiroarthropathy is not fully known. Increased advanced glycosylation end products (AGE), due to chronic hyperglycemia, change the structure and function of extracellular proteins such as collagen, and some of the intracellular proteins. Binding of AGE to their specific receptors (receptors for AGE; RAGE) reduces vascular elasticity by changing intracellular signaling (3). Old age, puberty, and disorders along the axis of growth hormone and insulin-like growth factor-1 (IGF-1) may also play some role in the pathogenesis (4). In the dorsum of the hand, waxy and stiff appearance accompanies the painless limitation of the joint, which is usually seen at the proximal interphalangeal and metacarpophalangeal (MCP) joints of the hand, wrists, ankles, and elbows. When patients bring their palms together in the praying position, palmar surfaces cannot touch each other completely, which is called the “praying-hands sign.” Cheiroarthropathy frequently is seen with frozen shoulder (FS), Dupuytren’s contracture (DC), or carpal tunnel syndrome (CTS), or all of them (5). The physiotherapy can be effective preventing or opening of the contractures. CS injections to flexor tendon sheaths can resolve contractures in two-thirds of the cases. The glycemic control is important. There is no complete cure. Interventions for pain relief and NSAIDs, stretching exercises, and steroid injections are usually not satisfactory. In advanced cases, surgery can relieve the sensorial disturbances (6).



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b) Frozen shoulder (FS)/adhesive capsulitis (AC)

Frozen shoulder is frequently bilateral in diabetics and is characterized by severe pain, increased tightening, and stiffness, and it restricts the range of motions of the shoulder. The incidence of FS is 10%-20% and 7%-32% in T1DM and T2DM, respectively; the prevalence is 11%-19% and 2%-3% in diabetics versus normal controls of the same age (7). It has been reported that the incidence of adhesive capsulitis increases with age and duration of the disease, in both patients with T1DM and T2DM. FS has shown to be associated with shoulder trauma and cerebral, cardiac, and respiratory diseases as well.

Other risk factors include past myocardial infarction, retinopathy, and peripheral neuropathy. FS is also associated with other hand problems such as DC and cheiroarthropathy (8). Imaging, histological, and histochemical studies have revealed the presence of fibroblasts with heavy proliferation in the tissue due to cytokine-mediated inflammation, T-cells, macrophages, and chronic inflammatory infiltration comprising mast cells, and accompanying Type I and Type III collagen accumulation. This proliferation leads to thickening of the capsule and synovium, capsular contractures, and contraction of the joint cavity (9). Diagnosis can be made by a careful history review and physical examination demonstrating a reduced range of motion of the glenohumeral joint; plain radiographies are normal, and magnetic resonance imaging or ultrasound can exclude other problems and give some diag-

nostic information. Although the disease usually spontaneously improves, some patients continue to have persistent shoulder pain and restricted joint movements. Full recovery of the joint movements takes months. Non-surgical interventions such as physical therapy, oral, or intraarticular CS, hydrodilatation or surgery are the other treatment options (10). Usually, the approach depends on the stage of the disease, and it consists of dulling the pain, increasing the arm movements, reducing the duration of the symptoms, and recovering the patient's normal activity. If tolerated, NSAIDs and analgesics are used for the pain during the freeze phase. In the early phase, intra-articular CS have a positive effect on the prognosis. Although oral CS provide a feeling of well-being for a short period during the painful phase, they are not routinely recommended due to their ineffectivity and adverse effects in the long term. More intensive physiotherapy is required in the adhesion phase. Transcutaneous electrical nerve stimulation and short-wave diathermy can be performed between electrotherapies (10). Hydrodilatation or arthroscopic relief under anesthesia directed by radiography should be considered in patients who do not benefit from physiotherapy and who have shoulder restriction (11). In diabetic patients, treatment is more difficult due to persistence, and the rate of recovery after surgery is lower.

c) Dupuytren's contracture (DC)

This highly heritable fibrotic disease of the palmar aponeurosis progresses to peripheral structures with thickening, hardening, and

contraction of the fingers, restricting joint movements. Incidence ranges between 5% and 14% in T1DM and 12% and 14% in T2DM. The disease progresses with age and the duration of diabetes, and its relationship with metabolic control has not been shown. Risk factors include old age, male gender, smoking, and alcohol use (12). It is frequently observed in people who professionally use their hands in compression, such as compressor operators, drill operators, and oarsmen (13). The genetic aspect of DC includes polymorphism in the ZF9 gene, which is a transcription factor for the tumor growth factor (TGF) beta expression (14). DC is frequently bilateral in diabetic individuals compared to the non-diabetics. In non-diabetics, it is observed in the 4th and 5th fingers, whereas in diabetics, it is rather observed in the 3rd and 4th fingers. It is claimed that it accompanies microvascular complications in T1DM and microalbuminuria in T2DM (12). The diagnosis is made if one or more of the following symptoms are present:

- Palmar or digital nodule
- Digital or palmar adhesion to the tissues below
- Pre-tendinous band and digital contracture

Splinting and collagenase injection into the lesion are promising treatment modalities. CS injections into the lesions failed to show any improvement (15). Surgical approaches performed for contractures are fasciotomy (cutting the affected part of the palmar fascia) and fasciectomy (removal of the affected palmar fascia). Percutaneous needle fasciotomy is a minimally invasive procedure, and it shows good short-term results, but recurrences are frequent especially in diabetics (16).

d) Carpal tunnel syndrome (CTS, trap neuropathy)

Carpal tunnel syndrome is a neuropathy that occurs frequently, when the median nerve that passes through the carpal tunnels of the flexor tendons is contracted by the transverse carpal ligament and carpal bones. DM is the most common metabolic disease that causes CTS, found in 14%-16% of patients. In a study performed, CTS was 11% in T1DM, 12% in T2DM, and 8% in control individuals. It is seen more frequently in women, with an incidence of 8% in women vs 0.6% in men (17). The disease manifests itself with paresthesia that worsens in the evenings in the thumb, index, and middle fingers of the hands, which wakes the patient up from sleep. Pain in the wrist and hand can cause clumsiness in hand movements. Clinical examination can be normal, and denervation of the median nerve and atrophy of the tenar muscles, sen-

Table 1. Musculoskeletal changes in diabetes

Musculoskeletal System	Complication Type
Fibroproliferative disorders of the soft tissue	Limited joint mobility syndrome
	Frozen shoulder (FS; adhesive capsulitis)
	Dupuytren's contracture (DC)
	Carpal tunnel syndrome (CTS; trap neuropathy)
	Stiff hand syndrome
	Flexor tenosynovitis (trigger finger)
Joint disorders	Charcot joint (Charcot osteoarthropathy; COA)
	Gouty arthritis
	Osteoarthritis
	Rheumatoid arthritis
Muscle-related disorders	Diabetic amyotrophy
	Diabetic muscle infarction
Skeletal disorders	Diffuse idiopathic skeletal hyperostosis (DISH)
	Osteoporosis
	Osteoporosis-related fractures

sory deficiency in the range of median nerve, and weakness in the abduction of the thumb are observed in chronic cases. Provocative tests such as positive Phalen and Tinel tests are very specific for CTS. Diagnosis becomes definite in the nerve conduction test, typically when there is prolonged latency and delayed transmission in the median nerve in the wrist (18).

In addition to the thickening and fibrosis of the flexor tendon sheaths in the carpal tunnel leading to nerve compression, increased endoneurial ischemia due to diabetic neuropathic factors and microvascular disease may also play a role in the CTS development in diabetes. Pathologic specimens commonly show noninflammatory tenosynovial fibrosis, which is accompanied by increased transforming growth factor, fibroblast proliferation induced by TGF-beta-RI and basic fibroblast growth factor, and increased Type III collagen. Compression in the carpal tunnel destroys the microvascular circulation of the nerve, leading to demyelination and axonal degeneration (19). The severity of the disease is not related to its duration, but rather to its association with microvascular complications such as polyneuropathy, retinopathy, and nephropathy. Treatment approach is similar to that in non-diabetic patients, which is keeping the wrist in neutral position with a wrist splint preventing nocturnal paresthesia, and it is sufficient for the relief of mild symptoms. CS injections provide relaxation. A meta-analysis has shown that locally injected steroids provide a significant temporary relief and that vitamin B6 is ineffective, steroids are more effective than NSAIDs and diuretics, ultrasound application is effective, laser therapy gives conflicting results, exercise therapy is ineffective, and splints are effective, especially in sustained use (20). Surgical intervention under local anesthesia is performed in those who do not respond to conservative treatment or in those with severe symptoms and when there are symptoms of nerve compression (21).

e) Stiff hand syndrome

Stiff hand syndrome is an uncommon condition causing restriction of the hand function. It is more common in patients who had diabetes for more than 20 years, and it is suggested that it is related with circulatory failure (22). Unlike cheiroarthropathy, the skin is hard in the palmar but soft in the dorsal region, affecting all fingers at the same time. The symptoms may progressively increase and lead to vessel calcifications, which are radiologically detectable. The prickling and burning sensation and pain in rare cases may be other complaints of the patients in long-lasting disease. Cheiroar-

thropathy and reflex sympathetic dystrophy should be considered in the differential diagnosis. A previous history of trauma, arm fracture, stroke, herpes zoster, and myocardial infarction and presence of pain are important to distinguish stiff hand syndrome from reflex sympathetic dystrophy. Immobilization is not necessary, and physical therapy may preserve the hand functions (23).

f) Flexor tenosynovitis (trigger finger)

The flexor tenosynovitis, known as a "trigger finger," is a noninfectious inflammation of the flexor tendon sheaths of the thumb or other fingers. The flexor tendon passes through the fibroosseous tunnels between the MCP and the distal IP joints; the surface tendon adheres to the middle and the deep tendon to the distal phalanx. The tunnel provides mechanical stability to the tendons and facilitate their nourishment. Inflammation or irritation develop as a result of repeated use of the fibroosseous tunnel. Proximal to the MCP joint, the tunnels become swollen, and nodules form on the tendons of the flexor. Tendon is arrested in the MCP joint and causes the finger to be locked flexed. The duration of illness is long, and incidence is higher in poorly controlled T1DMs (20%) than in well-controlled ones (3%) (12) and in T2DMs (3.8%) than in controls (13). The use of the affected hand causes pain in the finger, and the pain spreads distally and also to the palm of the hand, and frequently the finger becomes triggered and locked up in a flexed position. Patients awaken due to pain at night with the finger flexed toward the palm, and the locking gradually dissolves during the day. The diagnosis is based on the patient's description of locked fingers and detection of the locking during the examination. The flexor tendon should be palpated on the MCP joint to check for local tenderness or swelling, which is usually present at the base of the finger where the metacarpal head of the tendon is located. Isometric resistance during the stretching of tendon for extension or flexion increases the pain. When the patient is asked to open and close his hand, comfortable, painless movement of the fingers excludes the trigger finger. The symptoms of tenosynovitis may improve when the patient uses his or her finger less frequently to prevent triggering, and the pain decrease during triggering as well, in some cases. Sometimes, mechanical triggering can be so severe that it may not be possible to recover the finger from the flexion state, which is referred to as "locked fixed finger." Rarely, a local anesthetic application is necessary to solve this fixation. Microvascular complications such as retinopathy, nephropathy, and neuropathy are more frequent in these patients. The studies with ex-

tracellular matrix and fibroblasts obtained from the involved area showed connective tissue changes, such as increased intra- and intermolecular crosslinking making them less soluble and resistant to the effect of collagenase enzyme to break down. It was also shown that collagen accumulates in connective tissue, and the amount of collagen crosslinking in T1DM shows correlation with the disease duration, skin changes, limitation of joint movements, retinopathy, and microalbuminuria (24).

The goal of the treatment is to reduce the swelling and inflammation of the flexor tendon sheath to allow the comfortable movement of the tendon in the A1 channel and to prevent the recurrent tenosynovitis with extensor stretching exercises.

Immobilization is a preferred treatment in the acute phase of the first 4-6 weeks, taking advantage of CS injection in the event of severe locking. Antivibratory gloves can be used when utilizing vibrating instruments. When the acute symptoms disappear, the prevention of recurrence with stretching exercises, which include extension of the fingers, should be started. Local CS injections with lidocain are better than lidocain only, being found effective for 1 year. This treatment can be used if the immobilization is not effective, although it is less effective in diabetics (25).

Joint disorders

a) Charcot osteoarthropathy (COA; Charcot joint, neuropathic arthropathy)

Charcot osteoarthropathy (COA), first described by the French neurologist Jean-Martin Charcot, is a progressive, denervating, and degenerative disease of the foot and ankle joints, which causes damage and deformities of the joint if left untreated. COA is also seen in a variety of other diseases, but it is more common in diabetic patients. The COA prevalence was reported as 1/680 in diabetics, and recent radiologic studies showed that the incidence of arthropathy in the foot and ankle in diabetic neuropathy was approximately 10% (26). A recent increase in the incidence of COA was explained by availability of better diagnostic modalities and increased awareness of the disease among physicians. Many minor or major traumatic injuries result in microfractures, causing macrofractures, and eventually destructed joint presents typical appearance. Initially, there is swelling, warmth, and acute inflammation with erythema in the foot; frequently seen in the middle part of the foot, most commonly in the tarsal and tarso-metatarsal area, rarely in the knee, wrist, shoulder and intervertebral

joints, and/or dislocations of the damaged joints with loss of joint function, ulceration, osteomyelitis, and fever, subsequent sepsis, and pain. Leucocytosis and high erythrocyte sedimentation rate and C-reactive protein may be predictive for osteomyelitis.

Although the pathogenesis is not fully understood, widely accepted opinion is the loss of protective proprioceptive mechanisms secondary to neuropathy causing damage in the joint, (neurotraumatic hypothesis) and relaxation of the ligaments. It is assumed that repeated microtraumas due to continuous loading on the foot precipitate the disease, and subclinical bone injuries trigger an inflammatory event that is not expected under normal conditions. Another suggested hypothesis (neurovascular hypothesis) is that vasodilation causes arteriovenous shunts and hyperemic bone resorption. In spite of the peripheral neuropathy, the lesion might be painful sometimes. It was shown that beside the lack of proprioception, an involvement of autonomic nervous system is responsible for the COA formation as well (26). In COA patients with uncomplicated foot ulcers, it was reported that the incidence of vascular calcification in the peripheral arteries of the foot is 54%, and this incidence increases to 66% in the presence of osteomyelitis, but peripheral pulses might be palpable. In some series, calcifications reach up to 90% (27).

The progressive bone resorption, fractures, and dislocation increase deformity and destabilizes the foot, and classical "rocker-bottom" appearance is observed in the middle part of the foot. In both acute and recovery phases, bone deformity may cause abnormal bearing on the foot, causing ulceration and secondary osteomyelitis in surface tissues. COA seen in DM is clinically and radiologically classified into four stages and types of foot involvement (Table 2) (28).

The patients symptoms are inappropriately significant to correlate the severity of the radiologic findings, which causes a delay in the referral to the specialists until the later stag-

es of advanced soft tissue ulcerations and deformities (5, 29). The cycle of osteopenia, osteolysis, abnormal loading, and bone instability increases fracture risk. Uncontrolled inflammation in COA damages vascular tissues and bones. When vascular smooth muscle cells are treated with sera from COA patients, their mineralization capacity increases, as well as the secretions of the mediators (including proinflammatory cytokines, etc.) that directly induce osteoblastic changes in vascular smooth muscle cells and increase calcification in COA. Indeed, when compared with controls, the hypersensitive C-reactive protein (hsCRP), tumor necrosis factor alpha (TNF- α), IL-6, and bone resorption and formation markers (Type 1 C terminal telopeptide, collagen and alkaline phosphatase) were found increased in these patients.

Recent in vitro studies have shown an increase in newly formed osteoclast counts in the peripheral blood collected from patients with COA. Interaction between inflammation, TNF- α IL-6, and receptor activator of nuclear factor kappa B ligand (RANKL) modulates osteoclastogenesis. In COA, TNF- α increases bone resorption because proinflammatory cytokines do not only increase RANKL expression, but increase osteoclastogenesis in the presence of RANKL. All these observations suggest that proinflammatory cytokines play a role in COA. This suggests that a treatment, targeting prevention of RANKL-induced osteoclastogenesis by pro-agents, may be appropriate treatment (30). Early diagnosis may prevent catastrophic consequences such as amputation. The fever, pain, and leucocytosis may be alarming for osteomyelitis. COA is seen more in patients with poor glycemic control, and diabetic control should be an important part of the treatment (4, 31). The bone scanning with technetium diphosphonate and magnetic resonance imaging detect early bone changes and diagnose of COA.

The COA treatment is based on the disease stage. Immobilization with total contact plaster and rest can prevent the joints of feet from being overloaded, might reduce inflam-

mation in the acute phase, and stabilize the joint in a way that will cause minimum deformation (32). The treatment should continue until the swelling and temperature return to normal, and no more bone damage is detected with imaging technics (33). Other applications include the use of appropriate orthosis and crutches to reduce the load on the foot during movement. Bisphosphonates were used in the treatment. It has been shown that the use of a single 90 mg pamidronate infusion for 6 months followed by 70 mg alendronate weekly alleviates symptoms, corrects bone markers, and relieves pain (34). Surgery should not be the first choice of treatment and should be preferred in those particularly susceptible to chronic foot ulcers and joint instability-related deformities. Arthrodesis or other surgical methods such as exostomy, osteotomy, intramedullary rodding, and amputation are used according to the anatomical diversity and the presence of local infection. Infection and triggering of nonunion or acute Charcot reaction are important postoperative complications. Chronic recurrent ulcers in the initial phase increase the risk of amputation. The gradual reduction of amputations may result from a better patient care. The prognosis is generally poor. Non-operative follow-up results in a 2.7% amputation rate per year (35).

b) Gouty arthritis

Gout is an inflammatory arthritis with accumulation of monosodium urate crystals in the joints, which is accompanied by acute inflammatory attacks that can terminate itself in the early stages of the disease. It is the most common inflammatory arthritis in adult males, with the incidence rate in caucasians of 1%-2%. The prevalence of gout in T2DM patients was found to be 22% (36). The disease frequently affects the first metatarsophalangeal (MTP) joint located at the middle part of the foot and in the wrist. In cases of prolonged hyperuricemia, it manifests itself as recurring episodes or disease with chronic tophus or erosive arthritis. The risk factors are male gender, excessive alcohol consumption, seafood or meat consumption, diuretic use,

Table 2. Classification of charcot arthropathy by modified eichenholtz system (28)

Classification	Clinical Features	Radiological Features
Stage 0-Early/inflammatory	Localized swelling, erythema, and warmth	Little or no radiological abnormalities
Stage 1-Development	Swelling, redness, and warmth	Fracture, subluxation/dislocation, bony debris
Stage 2-Coalescence	Decreased inflammation signs	Fracture healing, resorption of bony debris, and new bone formation
Stage 3-Remodelling	No inflammatory sign Bony deformity (stable or unstable)	Mature fracture callus and decreased sclerosis

hyperuricemia, hypertension, obesity, metabolic syndrome, coronary artery disease, and nephropathy. In diabetic patients, hyperglycemia causing uricosuria along with polyuria reduce uric acid concentrations and decrease gout attacks; conversely, the gout episodes may increase with less glycosuria when blood glucose is reduced with treatment (37). A strong association between serum urate concentrations, gout, abdominal obesity, and diabetes is well known. In patients with gout, co-occurrence of diabetes and metabolic syndrome is much higher than in healthy individuals (38).

In acute episodes, NSAIDs, corticosteroids, or colchicine are used for treatment. Patients with frequent episodes, gouty tophi, and radiological damage are treated with long-term urate-reducing agents. The serum urate level should be lowered to 6 mg/dl for the prevention of attacks and tophus regression, and xanthine oxidase inhibitor allopurinol is used for this purpose. The dosage change may be considered if the administered dosage is not effective, or uricosuric agents such as probenecid or benzobromarone or new xanthine oxidase inhibitor febuxostat are added to the treatment. The episodes may be precipitated when an urate-reducing treatment initiated. To prevent the attack, treatment might be delayed until the episode is over, and doses of the treatment must be gradually increased, or colchicine should be added to the treatment. The intake of alcohol or purine-rich foods triggers the gouty attacks, and these should not be included in the diet. Gout episodes can interfere with the exercise programs of the diabetics. Diuretic treatments should not be used unless it is necessary, because they may increase the urate levels. In diabetics, losartan and fenofibrate should be preferred because they are mild urate-reducing drugs (39).

c) Osteoarthritis

The pressure of heavy weight on the joint cartilage is an important risk factor for the formation of osteoarthritis. The close correlation between osteoarthritis and obesity is well known (23). Although there are studies that found that osteoarthritis occurs frequently in T2DM, whether this relationship is due to diabetes or diabetes related obesity is not clear since no corrections to body mass index was performed in these studies.

d) Rheumatoid arthritis (RA)

Common genetic characteristics were found in some studies of RA and T1DM (PTPN22, HLA-DR9, 4q27 chromosome, IDDM5, and IDDM8

regions). The occurrence of T1DM was reported to be 2.8% in the first-degree relatives of patients with RA, suggesting the existence of familial cluster, but there is no evidence that RA is common in T1DM patients (40).

Muscle-related disorders

a) Diabetic amyotrophy (diabetic cachexia)

Diabetic amyotrophy is an important cause of disability that is different from other diabetic neuropathies and causes muscle weakness and atrophy. Particularly, proximal muscles of the lower extremities affected with loss of tendon reflexes and diffuse pain, being more common in older males with T2DM. A significant weight loss observed with diabetic amyotrophy alarms the patient that it is related to malignancy of some kind. Then it is important to diagnose the amyotrophy at once to prevent money- and time-consuming unnecessary work up to rule out the malignancy, which the patient is going to be subjected to. Its pathogenesis is obscured.

Treatment involves improving the glycemic control and physiotherapy. Although spontaneous recovery occurs in most patients, it is slow and usually incomplete (5, 41).

b) Diabetic muscle infarction

Muscle infarction is a very rare complication of diabetes with unknown etiology; it is observed in long-term disease. Diffuse diabetic microangiopathy, thromboembolism, hypercoagulability, vascular endothelial damage, and advanced atherosclerosis are considered as responsible mechanisms (42). Diabetic muscle infarction usually manifests itself with an acute onset of pain and localized swelling in the lower extremities. Calf muscles, vastus lateralis of quadriceps femoris, and adductor muscles of the femur are the commonly affected muscles. There are no systemic findings. Soft tissue tumor, deep vein thrombosis, cellulitis, hematoma, and myositis ossificans should be considered in differential diagnosis. In addition to characteristic clinical picture, magnetic resonance can contribute diagnosis by showing isointense swelling, and the loss of muscle fiber borders in T1 increases in diffuse heterogeneous at the center after contrast injection. Histopathologically, there are necrotic fibers surrounded by necrotic fibrous tissue and inflammatory tissue reaction. Treatment includes resting the affected muscle group and analgesics for the pain (23, 43). It usually lasts for several weeks and recovers by itself in a couple of weeks or months, but recurrences are common in 50% of the patients.

Skeletal disorders

a) Diffuse idiopathic skeletal hyperostosis (DISH)

In DISH, also known as the Forestier disease or ankylosing hyperostosis, new bone is formed in the anterior longitudinal ligament entheses, which is predominantly found in the thoracic and lumbar vertebrae. It is a systemic condition, not a reaction to local mechanic factors. In T2DM, hyperostotic changes are frequent in the form of hyperostotic spondylosis, osteitis condensans ilii, and tendon or ligament calcification. The prevalence of hyperostosis over the age of 50 is 15% in women and 25% in men. It is more common in individuals with DM (13-49%) compared to the general population of the same age (1.6-13%), and the incidence of diabetes is increased in patients with hyperostosis as well (4, 44). Hyperuricemia, dyslipidemia, obesity, elevated serum insulin, and growth hormone (GH) levels were also found to be higher in diffuse idiopathic skeletal hyperostosis patients compared to control groups. It has been suggested that the chronic elevation of serum insulin and IGF-1 leads to calcification and ossification in ligaments and entheses regions exposed to mechanical stress (45).

However, in a recent study that was conducted in our country, the DISH was found to be higher in diabetic patients compared to the control group, but the difference was not statistically significant (46).

Obesity causes mechanical pressure on entheses, and obese patients usually have an increased bone mineral density (BMD). It was shown that besides increased insulin resistance in obesity, the GH and IGF-1 levels, RANKL, and platelet derived growth factor (PDGF) and TGF- β may be responsible for osteoblast activation and new bone formation and high BMD in DISH (45, 47).

The calcifications can be found outside of the spine as well. Back pain and a feeling of stiffness is present in the patients, but it is doubtful whether this is related to calcifications, because many people who have no complaints may be detected radiologically by chance. Dysphagia, paralysis in vocal folds, compression to inferior vena cava, and neurological compression syndromes have been reported in patients with extreme hyperostosis. There may be spinal fractures with weak trauma causing neurological problems. The diagnosis is radiologic and classified according to the Resnick criteria (Table 3) (48). There are no controlled studies for DISH treatment, and pain control with analgesics and physiotherapy are standard treatment

Table 3. Resnick Criteria for Diffuse Idiopathic Skeletal Hyperostosis Diagnosis (48)

1. Presence of ossifications and calcifications in the anterolateral parts of at least four sequential vertebrae
2. Relatively preserved height of the intervertebral discs and absence of common degenerative disc disease
3. Absence of spondyloarthropathy

Table 4. Causes of Bone Fragility Increase in Patients With DM

Type 1 DM	Type 2 DM
Decreased BMD	Localized Osteopenia
<ul style="list-style-type: none"> • Cachexia • Lack of insulin • Lower IGF levels • Local osteopenia due to neuropathy 	<ul style="list-style-type: none"> • Related to neuropathy
Increased Fall Risk	Increased Fall Risk
<ul style="list-style-type: none"> • Due to complications (visual, neuropathic, etc.) • Hypoglycemia • Other medications 	<ul style="list-style-type: none"> • Due to complications (visual, neuropathic, etc.) • Hypoglycemia • Medications
Defective of Bone Quality	Defective Bone Quality
<ul style="list-style-type: none"> • Increased AGEs 	<ul style="list-style-type: none"> • Increased AGEs
	Medications of DM
	<ul style="list-style-type: none"> • Tiazolidinediones

AGEs: advanced glycosylated end products; BMD: bone mineral density; DM: Diabetes Mellitus; IGF: insulin-like growth factor

options for symptomatic patients. Surgery is rarely necessary, and it is only performed when there are pressure syndromes.

b) Osteoporosis

Predisposing osteoporosis factors and associated fractures can be divided into two groups (Table 4):

1. Factors decreasing the bone strength
 - A. Factors diminishing bone mineral density (BMD)
 - B. Factors affecting the bone quality (mineralization, material properties, geometry, macro and microarchitecture of the bone, etc.)
2. Increased frequency of falls and traumas

BMD is normal or increased in T2DM, whereas T1DM leads to low BMD, but in some studies, there was no difference found in BMD. Since insulin is an anabolic hormone increasing bone formation, in T1DM beside absolute insulin and IGF-1 deficiency, pancreatic amylin and preptin are probably responsible for low BMD. In T2DM, the presence of excessive insulin along

with insulin resistance is the issue (49). The bone quality is deteriorated in both types of diabetes along with hyperglycemia causing increased glycosylation of structural proteins such as collagen as well others, by changing the structure and function of these proteins, affecting the material properties and the quality of bone. Increased AGE and RAGE play an important role as well in the bone metabolism and strength, making the bone vulnerable to fractures (49).

All aspects of bone metabolism are affected by hyperglycemia, such as functional inappropriate hypoparathyroidism and osmotic diuresis causing natriuresis and accompanying hypercalciuria, leading to negative calcium balance and diabetic nephropathy responsible from abnormal vitamin D metabolism. These changes not only affect the bone quality and BMD, but also cause impairment and difficulties in the healing of fractures. It is also known that high glucose has adverse effects on bone formation (50).

c) Osteoporosis and fractures

In addition to low BMD, some other problems such as age, gender, body weight, previous

fracture history, smoking, use of corticosteroids, and rheumatoid arthritis are considered the risk factors of osteoporotic fractures. Recently, absolute fracture risk algorithms were developed using these risk factors to predict a hip fracture or any other fracture in 5-10 years (51). According to some researchers, both types of diabetes should be accepted as a risk factor for fragility fractures. Adding diabetes as a risk factor to the algorithm is being considered, which is called the fracture risk assessment tool. For example, it is thought that in patients with T1DM, a nonvertebral fracture risk increases 1.3-3.0 times for any fracture and 2.4 times for foot fracture. The occurrence mechanism of these fractures is probably different from each other.

There are two meta-analyses of observational studies of hip fractures in T1DM. In these meta-analyses, it has been found that the hip fracture risk is increased by 6 to 9 times (51, 52). In an observational study of Women Health Initiative, an increased risk of hip, foot, and upper-arm fracture was found in women with T2DM (53).

Tiazolidinediones (TZD) (peroxisome proliferator activated receptor ligand; PPAR), which are insulin sensitizers and used in the treatment of T2DM patients, enhance insulin sensitivity and achieve glycemic control in T2DM, but it was reported that they increase fractures (hip, humerus, and forearm) in both men and women. TZDs directly reduce bone formation by directing mesenchymal stem cells to be adipocytes instead of osteoblasts. This condition decreases IGF-1 in stromal stem cells, accelerating the transformation of osteoclast precursors into resorptive osteoclasts, as a net effect bone resorption that causes fractures (54).

An increase in bone resorption, reduction in BMD due to secondary or tertiary hyperparathyroidism in diabetic nephropathy and in transplant patients make diabetic patients predisposed to fractures. On the other hand, diabetic peripheral neuropathy causes immobility of the patients and decrease in BMD, and autonomic neuropathy increases the risk of fractures as a result of falls due to postural hypotension.

Osteoporosis management in DM

Taking into consideration a higher risk of osteoporosis and fractures in diabetics, necessary precautions should be taken to minimize the risk of falls. Even though there are only few randomized, controlled, prospective studies with

osteoporosis prevention drugs in diabetics, bisphosphonates are used for therapeutic purposes (55). Resistive exercises were applied to a group of patients to accompany weight loss, which is desired as a part of their treatment in T2DM patients through diet therapy, and it was shown that despite losing weight, the BMD levels of these patients have not changed. These results show that in addition to weight loss diet therapies, resistance exercises maintain their BMD (56).

Healing of fractures in patients with DM

An increasing number of publications are added to literature stating that fracture healing is abnormal in diabetic patients. In rats, when compared with non-diabetic rats, bone healing was found to be more degenerate in T1DM models. The callus sizes, collagen contents, and properties were found to be different and decreased.

Conclusion

Diabetes Mellitus is a systemic disease that not only causes metabolic problems, but also a wide variety of musculoskeletal problems leading to disability and decreased life quality. Assessment and early management of musculoskeletal problems in diabetic patients can prevent pain, morbidity, and also mortality in this patient group.

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