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Review

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Rheumatological and Musculoskeletal Complications in Diabetes Patients

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Abstract

Musculoskeletal disorders are common in individuals with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). It is associated with significant morbidity and hampered quality of life. Hyperglycemia-induced aberrant levels of insulin or insulin growth factors may lead to neuropathic complications, which enhances pain through central sensitization. Evidence suggests that diabetes is associated with numerous musculoskeletal disorders and inefficient control of diabetes may cause persistent musculoskeletal pain over time. Neuropathic joints are commonly observed in the foot and ankle of patients. Diabetic polyneuropathy, rheumatoid arthritis (RA)-associated pain are other complications. In diabetic patients with osteoarthritis (OA), factors including advanced glycation end-stage products (AGEs) and markers of oxidative stress could contribute to pain associated with low-grade inflammation. In obese individuals with T2DM, uncontrolled glycemic status can lead to mechanical stress-induced calcification and ossification of ligaments, and oxidative damage. In individuals with diabetes and OA, synovitis in the tissues is evidenced by the presence of higher levels of prostaglandins, leukotrienes, and adipokines. The pathogenesis of cheirarthritis remains largely unknown and is attributed to increased AGE, chronic hyperglycemia, dysregulated function of extracellular and some intracellular proteins. Advancing age, hormonal changes during adolescence, disorderly secretion of growth hormone and insulin-like growth factor-1 (IGF-1) are other possible contributing factors. Early assessment and strict control of diabetes can prevent other long-term micro and macrovascular complications. These measures can reduce the term of enduring pain and morbidity in susceptible individuals. This article reviews the prevailing knowledge and the mechanistic role of underlying diabetes on rheumatological and musculoskeletal disorders.

Keywords: Diabetes; Musculoskeletal disorders; Complication; Early assessment; Strict control

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Introduction

Diabetes mellitus (DM) perceived as a multisystemic and multi-organ disease remains a global health issue and is predicted to affect 4.4% of population by 2030 [1, 2]. Depending on the duration of disease, the extent of control and associated end organ damage, DM may pose diverse musculoskeletal manifestations of both clinical or subclinical nature and rheumatic disorders. Evidence suggests that diabetes coexists with musculoskeletal disorders [3-5]. Such disorders may cause significant pain and disability and have implications on the quality of personal, social, and occupational life of affected individuals [4, 6-10].

Limited joint mobility disorders are increasingly prevalent in diabetic patients and are associated with microvascular changes and increasing age [11]. As a consequence of aging, there is a decreeing trend in the number of tendon cells resulting in degenerative disorders [8, 12]. Prolonged uncontrolled diabetes and hyperglycemia may result in the accumulation of less soluble glycosylated collagen in connective tissues. This in turn alters the structure of extra cellular matrix and collagenase activity [13]. Frozen shoulder (FS) or periarthritis of shoulders, a complex group of various shoulder cuff abnormalities is common amongst diabetic individuals. Hyperinsulinemia over several years precipitate degenerative tendinitis particularly impacting supraspinatus tendons and sub acromial bursa [14]. These changes lead to a progressive capsular contraction with restrictive rotator action. This article reviews the prevailing knowledge on the effects of diabetes on such musculoskeletal disorders and the possible underlying mechanisms establishing the link. The rest of the article delves into details, the complications of musculoskeletal origin in DM classified according to the presentation.

Classification

Muscle-related disorders

Causes of musculoskeletal disorders in diabetes

DM patients are prone to risk of musculoskeletal disorders linked to hyperglycemia, increased advanced glycation end-stage products (AGEs), inflammatory cytokines, and connective tissue disorders [15, 16].

1) Hyperglycemia

Hyperinsulinemia and hyperglycemia of long duration in diabetes gradually leads to accentuated degenerative changes in weight bearing joints leading to osteoarthritis (OA) [17-21]. Hyperuricemia is often noticed in patients with metabolic syndrome or established diabetes [22].

2) AGEs

The AGEs have profound adverse impact on the basement membrane of many end organs besides affecting cartilaginous part of joint surfaces [23]. There are several changes attributable to AGE such as increasing osteoporotic tendency and loss of cartilaginous integrity [24]. Generally, AGEs cause structural malformations of collagenous and other proteins which gradually lead to evolution of osteoporotic and osteoarthritic changes.

3) Inflammation

Diabetes is known to be a metabolic inflammatory disorder [25]. The body organs that are susceptible to wear and tear are highly prone to have a greater trigger due to gradually evolving hyperinsulinemia or frank type-2 diabetes. This fact is obvious in patients with OA, psoriatic arthritis, and rheumatoid arthritis (RA) [24, 26-30].

Tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and IL-1β are found to be elevated in patients with osteopenia and/or severe cases of myalgia. TNF-α is often found to be associated with increased bone mineral loss and osteoclastic activity [31-33]. Hyperinsulinemia and hyperglycemia have a direct impact on the trigger of inflammatory markers to induction of several intracellular signaling pathways [34, 35].

4) Connective tissue

Much of the terminal portions of the muscles and various connecting fibrous structures are also prone to wear and tear and inherent proneness to mild grade inflammation. This mild grade inflammation gets further accentuated by the degenerative changes triggered by various mechanisms described earlier in patients with diabetes or prediabetes and obesity [5, 9, 15, 36-39]. AGEs are also implicated in the destruction of collagen with excessive hydration and impairment of synthesis [38-40].

Types of musculoskeletal disorders

1) Diabetic amyotrophy (diabetic cachexia)

Diabetic amyotrophy, although rare often involves degenerative changes of proximal muscles mostly in the lumbosacral and pelvic regions with complaints of pain and reduced ability to perform routine activities. Some patients show loss of weight, in addition. A tight glycemic control with emphasis on continued physical activity and physiotherapy offer benefits, albeit slow [41, 42].

2) Diabetic muscle infarction

It is quite a logical extension of micro and macrovascular disease that occur in diabetes with involvement of small muscular blood vessels, endothelial damage, and diffuse atherosclerotic changes. It usually manifests with edematous large muscles of the lower limb with sudden onset of severe myalgia [43]. Peripheral vasodilators, anti-atherosclerotic measures, tighter glycemic control, adequate management of hypertension along with analgesics benefit most patient, however, with high chances of recurrence, if treatment adherence is low [23, 44].

Skeletal disorders

Osteoporosis

Osteoporosis like T2DM is a chronic illness that is affected due to increasing age [45, 46]. Diabetes is an added risk factor for osteoporosis and consequent fractures in women and elderly [47]. Hip fracture risk is heightened by about 6 - 9 times in patients with diabetes [47-49]. Immobility of the patients caused by diabetic peripheral neuropathy and decrease in bone mineral density (BMD) along with autonomic neuropathy enhances hypotension-induced risk of fractures.

The general view is that T2DM affects bone mineral metabolism, strength, and bone quality. T1DM leads to low BMD although BMD is normal or increased in T2DM. In the case of T1DM, reduced insulin, insulin-like growth factor (IGF) levels and cachexia, pancreatic amylin and preptin levels may contribute to reduced BMD. Localized osteopenia, visual neuropathic complications, episodes of hypoglycemia could lead to greater frailty [50].

Hyperglycemia affects all aspects of bone metabolism. The resulting hypercalciuria, which induced dysregulated vitamin D metabolism and diabetic nephropathy, impairs the healing of fractures. It also affects the bone quality and BMD [51]. However, a recent meta-analysis did not find a significant relation between diabetes status and low bone density [52]. Due to the variable diverse manifestation of diabetes and osteoporosis in different patients and the contribution of other confounding factors including age, comorbidities, duration of diabetes, and medication history, the precise inter-relationship in general patient population could not be established.

Fibroproliferative disorders of the soft tissue

Limited joint mobility syndrome

A restricted joint mobility syndrome (cheiroarthropathy) severely hampers the ability to fully extend or flex the fingers.

This is prevalent in 10-50% and 25-75% of individuals with T1DM and T2DM, respectively [53, 54]. Mechanical trauma, overuse, immunological, biochemical, and genetic factors contribute to the diverse manifestations of diabetic cheiroarthropathy. These among others contribute to flexion contractures observed at the proximal joints of the hand and foot that starts usually in the early decades of life [53]. Clinically, in the dorsum of the hand, there is a thin waxy appearance. The presentation is evidenced as a "praying-hands sign" position, i.e., when two hands are juxtaposed facing and touching each other, unlike a normal scenario, the surfaces do not touch at all expected points of contact. Frequently, cheiroarthropathy concurs with either of the carpal tunnel syndrome (CTS) or FS, or occasionally with all of them [41].

Despite the frequent observation in the clinical practice, due to lack of standardized guidelines and recommendations, the incidence of these pathologies have gained limited attention and remains underestimated. Although there is no definitive cure, adoption of practices towards effective glycemic control, physiotherapy towards releasing contractures and mitigating the symptoms can be useful. Alternatively, local steroid administration has been considered to resolve contractures. Since the pathogenesis of several joint diseases and their relapse are associated with a low-grade persistent inflammation, for favorable short-term results, anti-inflammatory drugs and corticosteroids (CSs) are frequently considered [55]. In advanced cases, surgery can be considered [56].

FS/adhesive capsulitis (AC)

FS in diabetics is characterized by sharp pain, and stiffness of shoulder joints that could eventually over time severely impede the mobility of the shoulder. The prevalence estimate of FS is about 10-20% of T1DM and 7-32% of T2DM patients [57]. FS is often observed in people above the age of 50 years, and its incidence increases with age and duration of diabetics. FS is frequently co-associated with other joint problems including DC and cheiroarthropathy [58]. There is increased infiltration and proliferation of fibroblasts in the tissue mediated by inflammatory response, increased accumulation of type I as well type III collagen. Studies have also reported all these events cause hyperproliferation of capsular and synovial membranes with fibrotic changes leading to contractures and reduction in the volume of the joint cavity [59].

For preliminary diagnosis, physical examination or radiographic observations indicative of any impaired range of motion of the glenohumeral joint are useful. Magnetic resonance imaging techniques and ultrasound examinations are useful for differential diagnosis. Although complete recovery of joint movement is time consuming (period of months), physiotherapy, CS injections or medications, hydro dilatation are alternate options [60].

Dupuytren's contracture (DC)

DC is characterized by development of a thick hardened collagen cord that upon contractions inflicts flexion deformity. It is a heritable disorder affecting the palmar side of the hand. This impairs flexible finger and hand movements. Also prevalent in nondiabetic individuals and equally prevalent in T1DM (5-15%) and T2DM (10-15%) individuals. The incidence is frequently associated with microvascular complications and microalbuminuria [61, 62]. Increasing age and extended prolonged duration of diabetes are risk factors contributing to progression of the disease. Occupation-related risk factor is overuse of hand motion in compression including drill operations [61]. Genetic studies have identified gene polymorphism in *Zf9* gene, a transcription factor facilitating expression of TGF-β. Diagnosis is based on the presence of symptoms including palmar or digital nodule, palmar tissue adhesion, pretendinous band, digital contractures.

Promising treatment options include splinting and collagenase injection into the lesions. CS injections into the lesions does not seem to have any significant improvement. Common surgical options are fasciotomy and fasciectomy which is cutting or removal of affected areas of palmar fascia, respectively. As a short-term benefit-rendering, minimally invasive option, percutaneous needle fasciotomy is considered. But in diabetic, recurrences are frequent [63].

Carpal Tunnel Syndrome (CTS)

CTS manifests as pain, altered sensation most often ascribed median nerve getting compressed at the hand forearm junction. The flexor tendons transverse carpal ligament and carpal bones make up the tunnel and any minor hyperproliferation or small swelling arising in this fibromuscular structure due to frictions can lead to a nerve compression. The vascular supply to the nerves is affected due to this compression which triggers loss of myelin coverage and progressive degeneration of nerve endings [64]. Due to all day activities demanding the involvement of fingers leads to worsening of paresthesia disturbing the quality of sleep at night. Sometimes there could be additional motor involvement affecting coordination. Clinical history, physical examination, and provocative tests, such as Phalen and Tinel tests are used in the diagnosis of CTS. The provocative tests evaluate the extent of CTS that are provoked by wrist flexion and direct manual compression of the carpal tunnel. Definitive diagnosis is achieved by nerve conduction studies and or electromyography. These tests mainly detect prolonged latency and delayed transmission in the median nerve of the wrist [65].

Fibrous hyperproliferation of tendons is commonly observed. Additionally, CTS development due to underlying diabetic neuropathy or microvascular complications is evidenced by increased endoneural ischemia. Noninflammatory tenosynovial fibrosis observed in pathologic specimens is accompanied by increased TGF-β, and fibroblast growth factor induces fibrous hyperproliferation and increase in type III collagen. Nocturnal paresthesia may be managed by using a splint to restrict the wrist movement to a neutral position.

Irrespective of diabetes status, CS injections can help offer relaxation. In nonresponsive patients, or in those with severe symptoms of nerve compression surgical intervention under

local anesthesia may be considered [66].

Stiff hand syndrome

Stiff hand syndrome or restricted hand function affects patients with more than 20 years of diabetes. Persistent condition in rare scenario may cause pricking or burning sensation and pain. Probably related to circulatory failure [67], it affects all the fingers simultaneously with skin being rigid on the palmar side. The symptoms may progress to vessel calcifications that can be detected radiologically. To distinguish from reflex sympathetic dystrophy, it is important to evaluate patient history of stroke, myocardial infarction, trauma, arm fracture, and herpes zoster. In such cases, alternatively, physical therapy may be considered for effective management [23].

Flexor tenosynovitis (trigger finger)

The flexor tenosynovitis ("trigger finger"), is a tendinous inflammation of the flexor sheaths that travel through the fibro osseous tunnels. The tunnel delivers mechanical stability to the tendons. Repeated used of fibro-osseous tunellite, may lead to inflammation. As a result, the tunnels become swollen, proximal to the metacarpophalangeal (MCP) joint, leading to nodule formation on the flexor tendons. This thereby restricts the flexing movement of the fingers. Increased incidence is observed in individuals with poorly controlled T1DMs (20%) or those with T2DMs (3.8%) versus 3% in individuals with good glycemic control [61, 62]. Continued use of the affected regions extends the distal spread of the pain from the fingers to even the palm regions causing frequent locked up of flexed fingers. This extended pain to the palm affects the quality of night sleep in patients although the locking gradually resolves.

Diagnosis is based on patient history, presenting complaints, on physical examination. At the MCP joint, the flexor tendon must be palpated to observe for local tenderness or swelling. Painless sensation of opening and closing of hands exclude trigger finger. Symptoms may improve with less frequent use of finger movements. Occasionally, severe scenario of "locked fixed finger" might occur. in which a local anesthetic application may be necessary. These patients frequently have associated microvascular complications [68].

Treatment objective is to subside swelling and inflammation in the channel and improve tendon flexibility Recurrence of tenosynovitis may also be prevented.

In the first few weeks of presentation, immobilization can help revert the condition. Upon relief from acute symptoms, routine management with stretching exercises would effectively prevent recurrence. In a "locked fixed finger" scenario, CS injections could be advantageous. Susceptible individuals operating vibrating instruments must consider using anti-vibration gloves. Supplementing with local CS along with lidocaine has been found to be effective for 1 year. Although this treatment is less effective in individuals with diabetes, it might be considered in scenario where immobilization techniques are ineffective [69].

Joint disorders

Charcot osteoarthropathy (COA; Charcot joint, neuropathic arthropathy)

COA is a progressive, degenerative disease of the foot and ankle joints that could eventually lead to deformities of the joint. COA is common in diabetic patients (1/680 individuals with diabetes). Radiological studies indicated a 10% incidence of arthropathy in the foot and ankle in diabetic neuropathy [70]. In the initial stages, patient might experience swelling and inflammation with erythema in the foot, frequently observed as the "rocker-bottom" appearance in the middle of the foot. More commonly affecting the small joints of the foot, rare manifestations could involve knee, wrist, shoulder, and intervertebral joints. Multiple traumatic injuries may result in micro or macro fractures of the joint. These patients may suffer with dislocations accompanied with loss of joint function, osteomyelitis, and sepsis.

Current understanding of the pathogenesis of the disease is that neuropathy and successive loss of protective pain perception mechanisms contribute to damages to the joints [70-73].

Early diagnosis help prevent progression of the disease and can save the limbs. To prevent the progress of the disease, immobilization of the feet must be continued to reduce inflammation in the acute phase [74] until no further bone damage is detected [75]. During physical movement, relying on orthotic supports helps in reducing weight burden on the foot. For management, bisphosphonates are often used. A single 90 mg pamidronate infusion for a period 6 months followed by a weekly 70 mg alendronate ameliorates the pain and symptoms and rectifies bone markers [76]. Patients with chronic foot ulcer and/or deformities may require surgery.

Gouty arthritis

Gout is an inflammatory arthritis affects the metatarsophalangeal (MTP) joint in the middle of the foot and the wrist. It is characterized by accumulation of monosodium urate crystals in the joints. A robust frequent association between serum urate concentrations, gout, abdominal obesity, metabolic syndrome and diabetes is acknowledged [22, 77]. Frequently recurring episodes are observed in cases of persistent hyperuricemia or disease with chronic tophus or erosive arthritis. For acute treatment, non-steroidal anti-inflammatory drugs (NSAIDs), CS, or colchicine are recommended. In patients experiencing chronic frequent episodes, long-term urate-reducing agents like xanthine oxidase inhibitor allopurinol, febuxostat; uricosuric agents such as probenecid or benzbromaron are considered.

Osteoarthritis (OA)

OA associated with pain, chronic disability and altered joint

function is majorly attributed to the pressure of heavy body weight on the joint cartilage. There is a frequent association between OA, obesity, and T2DM [78, 79]. The underlying pathogenic mechanism is attributable to low-grade inflammation and oxidative stress-mediated response [78]. Since the prevailing studies on diabetes and OA do not correct for the body mass index (BMI), the precise direct correlation between diabetes and OA could not be established.

Rheumatoid arthritis

Diabetic patients with family history of RA should be monitored effectively for the evolution of the disease and the disease progression due to the underlying inflammatory cascade in metabolic syndrome. The inflammatory milieu by itself is a trigger for insulin resistance and hyperinsulinemia. Uncontrolled diabetes adds up to the progression of the disease and should be treated as an additional risk factor for RA patients [80]. On the other hand, the systemic inflammation that prevails in RA patients could trigger developing diabetes in future in those who have had a metabolic syndrome earlier. The inflammatory markers C-reactive protein (CRP) is increased in both RA and DM while the prevalence of DM in inflammatory RA remains high [81]. Morbidity associated with RA restricting mobility and physical activity could further set off obesity, hyperinsulinemia and DM [78]. A new meta- analysis is needed to appreciate the co-occurrence and causal associations although an earlier meta-analysis showed that patients with RA had a higher risk of DM (relative risk, 1.24; 95% confidence interval (CI)) [82]. Inflammatory modulators and other agents used in the management of RA such as methotrexate, TNF-α antagonists show some value in reducing metabolic parameters in RA and DM. However, more analysis into these aspects is necessary to enhance our knowledge [83].

Conclusions

Diabetes and its musculoskeletal complications are less spoken but carry huge morbidity with a profound impact on quality of life of the patient. Diabetic foot amputation is one of the common debilitating catastrophic consequences. Early assessment and strict control of diabetes can prevent other long-term micro and macrovascular complications. These measures can reduce the term of enduring pain and morbidity in susceptible individuals.

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Conflict of Interest

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Author Contributions

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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