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MUSCULOSKELETAL DISORDER IN LONG STANDING TYPE 2 DIABETES MELLITUS AND ROLE OF INFLAMMATORY CYTOKINES

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Abstract

Diabetes mellitus is multi system disease characterized by persistent hyperglycemia that has both acute and chronic biochemical and anatomical squeal, may cause irreversible damage to many organs and organ systems. This disease affects connective tissues in many ways and causes different alterations in periarticular & musculoskeletal system.‘‘Musculoskeletal disorders’’ include a wide range of inflammatory and degenerative conditions affecting the muscles, tendons, ligaments, joints, peripheral nerves, and supporting blood vessels. These include clinical syndromes such as tendon inflammations and related conditions (tenosynovitis, cheiroarthopathy, dupuytren contracture, frozen shoulder etc.), nerve compression disorders (carpal tunnel syndrome), and osteoarthritis. Some of these complications have a known direct association with diabetes, whereas others have a suggested but unproven association. This article will review the musculoskeletal manifestations commonly seen in patients with type 2 diabetes and clarify the role of hyperglycemia and inflammatory cytokines in the development of musculoskeletal disorders in type 2 diabetes.

Key words: Type 2 diabetes mellitus; cheiroarthopathy; Dupuytren’s disease; shoulder capsulitis; flexor tenosynovitis; carpal canal syndrome; osteoarthritis; inflammatory markers

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Introduction:

Musculoskeletal disorders (MSDs) are ailments that affect the muscles and bones. People with diabetes are more prone to MSDs because evidence shows that hyperglycemia accelerates nonenzymatic glycosylation and abnormal collagen deposition in connective tissues leading to diffused fibro-orthrosis[1,2]. MSDs are associated with inflammatory and degenerative conditions affecting the muscles, tendons, ligaments, joints, peripheral nerves and supporting blood vessels. Most commonly involved body regions are the low back, neck, shoulder, forearm and hands[3]. Low grade inflammation and circulating cytokines affecting glucose metabolism in skeletal muscles are associated with type 2 diabetes mellitus (T2DM)[4-6]. T2DM is therefore also considered as a chronic inflammatory disease[7]. Proinflammatory cytokines activates signaling cascade including nuclear factor of κB (NFκB) and c-Jun NH_2-Terminal kinase (JNK) which inhibit insulin signaling by phosphorylation of insulin receptor substrate-1(IRS-1) and IRS-2, thereby inhibiting insulin signaling and stimulation of expression of SOCS (suppressor of cytokines signaling) proteins, which bind IRS-1 and IRS-2 and mediate their degradation[8]. Low grade

inflammation is a part of widespread activation of the innate immune system, which plays a crucial role in the pathophysiology of type 2 diabetes mellitus and associated complication such as musculoskeletal disorders [9]. In support of this increased serum level of IL-6 and TNF-α are associated with increased risk of MSDs in T2DM[10,11]. MSDs are common source of disability and increased prevalence is recognized in patients with type 2 diabetes mellitus. MSDs affect whole body but it is known to predominantly affect the upper limbs especially the hand and shoulder. The relationship with other complications of diabetes, glycaemic control and role of inflammatory markers is uncertain. The MSDs of diabetes are frequently neglected in the clinical consultation.

Musculoskeletal disorders in T2DM patients:

Musculoskeletal disorders in type 2 diabetes mellitus patients are well described disorders. The population suffering from T2DM in India, which is considered to be the diabetes capital of the world, is expected to rise to 70.0 million by 2025 if urgent preventive steps are not taken[12]. India is one of the most developing countries which have seen rapid urbanization and industrialization over the past decade. This has lead to unhealthy lifestyle changes, adversely affecting metabolic functions. The prevalence of MSDs in patients with T2DM has been found to be more than non diabetics[13].There are a wide variety of diabetic musculoskeletal complications involving bones, joints and periarticular soft tissues[14]. The upper extremity complications, known as 'diabetic hand and shoulder', include more specific diabetic-related conditions such as limited joint mobility (LJM) or cheiroarthopathy, trigger finger or flexor tenosynovitis, dupuytren's disease (DD) or dupuytren's contracture (DC), carpal tunnel syndrome (CTS) and frozen shoulder or shoulder capsulitis (CS)[15,16]. The lower extremity complications include Charcot's arthropathy, diabetic foot and osteoarthritis. Although their incidence is decreased, these complications are more serious than diabetic hand complications[17]. In T2DM patients, MSDs are now of increasing importance owing to the increasing incidence of DM and the longer life expectancy of the diabetics[18].

Pathophysiology of musculoskeletal disorders in T2DM patients:

Although the precise etiology of T2DM associated periarticular disorders remains uncertain, there is evidence that abnormal collagen deposition in the periarticular connective tissues alters the structural matrix and the mechanical properties of these tissues[1]. Some MSDs seem to be a consequence of diabetic complications such as dysautonomia in neuropathic arthropathy and some share pathological mechanisms with microvascular disease. There is little evidence that genetic factors would be etiologically associated with MSDs in T2DM subjects[19]. T2DM is associated with several metabolic disturbances that can leads to MSDs by altering the connective tissues. Hyperglycaemia and other diabetes-associated metabolic disturbances may lead to conditions such as: Nonenzymatic glycosylation of protein resulting in AGE formation and connective tissue stiffening, nerve damage (Neuropathy)**,** vascular damage (blood vessel), hyperuricemia, reduced bone density , low grade chronic inflammation and abnormal levels of insulin and insulin like growth hormone.The insulin-like growth factor and hyperinsulinemia associated with T2DM may contribute to skeletal anomalies[20]. Insulin stimulates collagen synthesis and influences the proteoglycan composition of bone and cartilage, whilst insulin-like growth factors (such as IGF-1) stimulate osteoblast activity[21]. Finally, the role of obesity and physical inactivity must be associated with musculoskeletal conditions and T2DM.

Cheiroarthopathy:

The prevalence of cheiroarthopathy has varied from 25 to 76% in T2DM subjects[22]. Neither sex nor race has any influence on the prevalence of LJM, but its association with the duration of DM and with age, has been well established. Most of the trials have shown no association between cheiroarthopathy and metabolic control of T2DM[23]. Cheiroarthopathy is characterized by thick, tight, waxy skin, mainly on the dorsal aspect of the hands, with flexion deformities of the metacarpophalangeal and interphalangeal joints and patients may exhibit the

'prayer sign' due to contracture of the flexor tendons (fig.1)[24].

Figure 1. The "prayer sign" indicates the presence of diabetic cheiroarthopathy. It is characterized by patients' inability to completely close gaps between opposed palms and fingers when pressing their hands together.

Several possible biochemical abnormalities related to disturbances in glucose metabolism may contribute to cheiroarthopathy. These include increased non-enzymatic glycosylation of collagen protein, increased cross-linking of collagen, consequent resistance to enzymatic degradation, increased hydration of collagen mediated by the aldose reductase pathway and altered collagen synthesis[25]. Increased formation of advanced glycosylation end-products (AGEs) may be one etiological factor for cheiroarthopathy and it could also explain the association between cheiroarthopathy and micro- and macrovascular complications of T2DM by a common underlying pathogenesis. AGEs form principally from the rearrangement of early glycation products (Amadori products), which gradually break down into irreversible AGEs and accumulate in tissues[26]. They have been reported to increase in association with diabetic microvascular complications[27]. The formation of AGEs may damage cells by impairing the function of a wide range of proteins, including modifications of extracellular structural proteins, s\uch as collagen and also intracellular proteins. In addition, AGEs can alter cellular function by binding to the receptor for AGEs or RAGE. This transmembrane receptor is a member of the immunoglobulin superfamily. Binding of AGEs to their receptor produces cellular signaling events which lead to cellular dysfunction (fig 2).

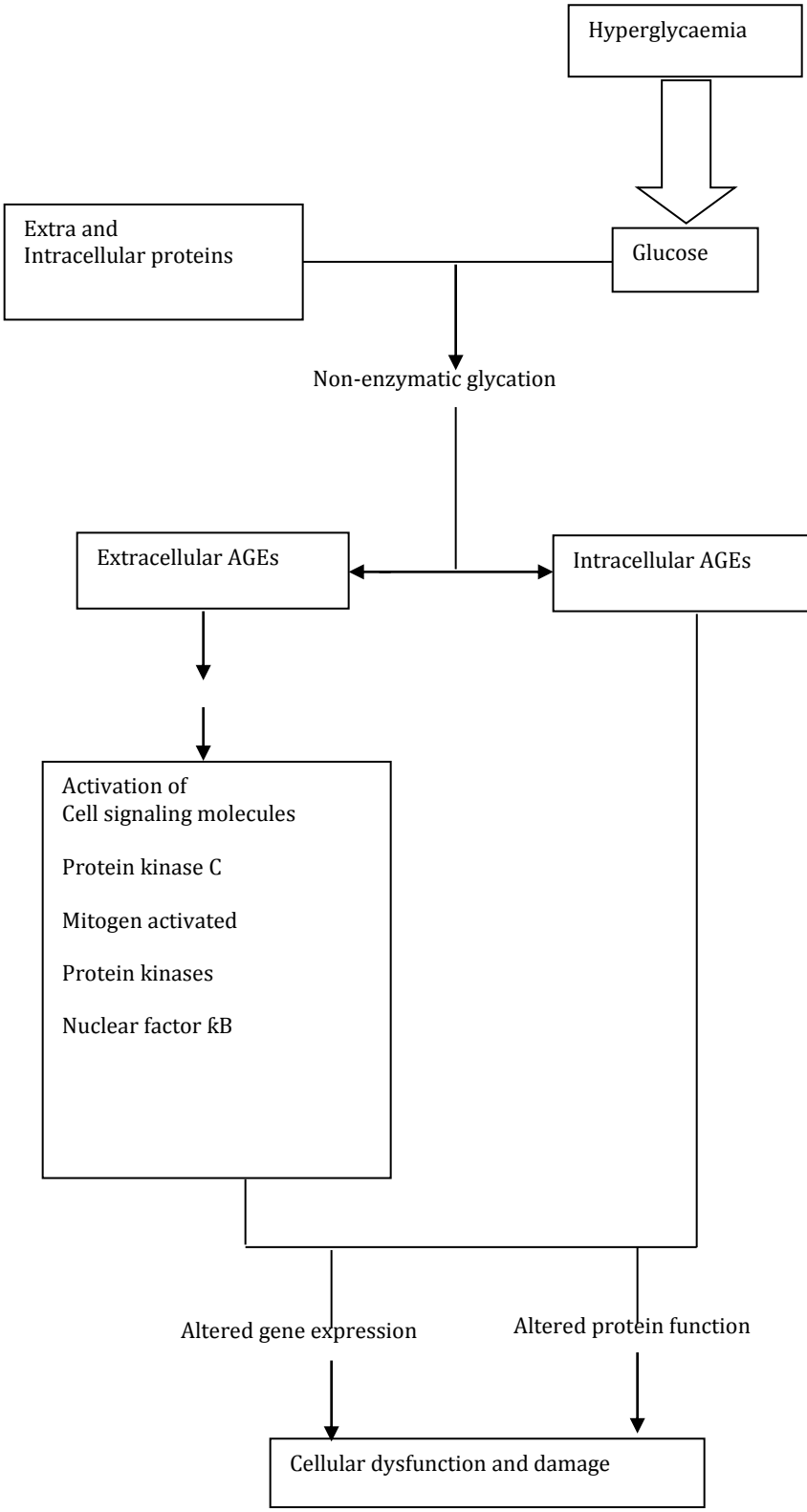

Figure 2: ***Advanced glycation end product (AGE) pathway theory***

Experimental studies have also shown that defects in the vasodilatory response to nitric oxide correlate with the level of accumulated AGEs and that these defects are prevented by inhibition of AGE formation. AGEs have also been shown to decrease vascular elasticity[28].

Dupuytren's contracture (DC):

Dupuytren's contracture belongs to the group of fibromatoses, affects focal flexor contracture and palmar fascia of the hand (fig 3).

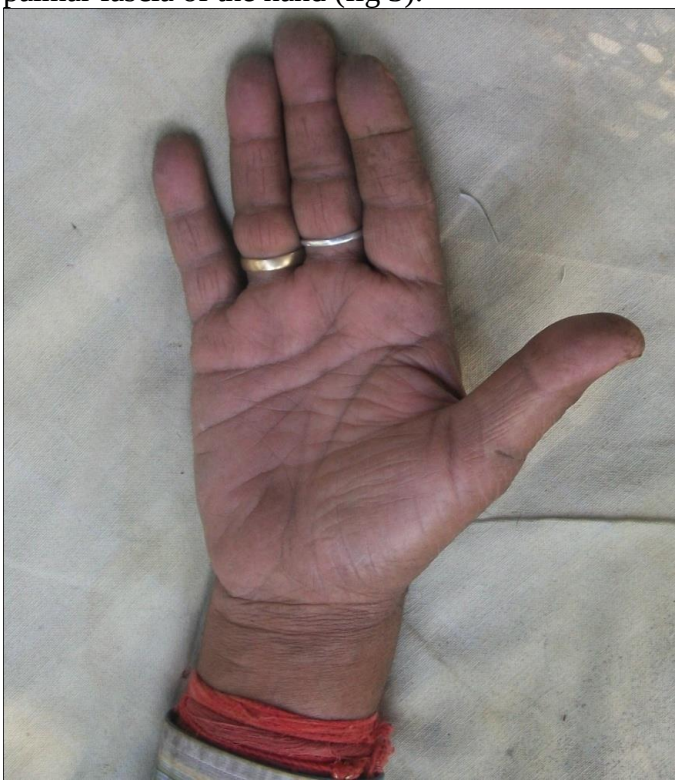

Figure 3. *Dupuytren's contracture*

DC is related to the plantar fibromatosis, penile fibromatosis and fibromatosis of the dorsum of the proximal interphalangeal joints called knuckle pads[29]. Typically, it is characterized by cords and nodules in the palm of the hand, the pathologic counterpart to the tendon and pretendinous bands. At the beginning of the disease nodule-formation in the palm of the hand is common. Later nodules may form near the metacarpophalangeal joint or next to the PIP joint of the thumb and digits. Depending on the progress of the individual disease contractures might form along normal fascia structures[30,31]. During the physical examination, physicians should note the site of the nodule and the presence of contractures, bands, skin pitting, tenderness and dimpling[32]. Bilateral involvement is common, although one hand is usually more severely involved than the other. The fingers most commonly involved (in decreasing order) are the fourth, fifth, third and second. Soft tissue tumors of the palm and digits may be confused with DC[33]. DC affects mainly patients older than 50 years[34]. This leads to an expected increase of incidence along with the steadily growing life expectancy[35]. Histologically, the cords of DC consist of a dense collagenous matrix containing fibroblasts, arranged along the longitudinal lines of stress. Nodules, which occur within the cords, contain myofibroblasts in bundles of collagen[36]. Initially, there is a proliferative stage characterized by an increase in myofibroblasts. The subsequent involutional stage involves alignment of these cells along the longitudinal lines of tension. The microvessels within this tissue are considerably narrowed. The abnormal tissue contains increased glycosaminoglycans, collagen and chondroitin sulfate, with an increase in the ratio of type III to type I collagen. It has been suggested that DC is a result of local hypoxia and chronic ischemia. The xanthine oxidase pathway is believed to have played a central role, while the palmar fat of those with DC has shown a lipid composition compatible with that of mild hypoxia. High levels of free radicals have been found, which can induce fibroblast proliferation in vitro[37]. A genetic predisposition for DC has been suggested. Transforming growth factor-β1 (TGF-β1) is a major or key fibrogenic cytokine that is able to stimulate fibroblast proliferation and extracellular matrix deposition and has been implicated in the pathogenesis of DC[38].

Frozen Shoulder: The most disabling of the common musculoskeletal problems is adhesive capsulitis, which is also known as frozen shoulder, shoulder periarthritis or obliterative bursitis[39]. Frozen shoulder is characterized by a painful and stiff shoulder whose glenohumeral motion is globally limited[40], occurring in up to 30 % of patients with diabetes[41]. The thickened joint capsule is closely applied and adherent to the humeral head, resulting in considerable reduction in the volume of the glenohumeral joint (fig 4).

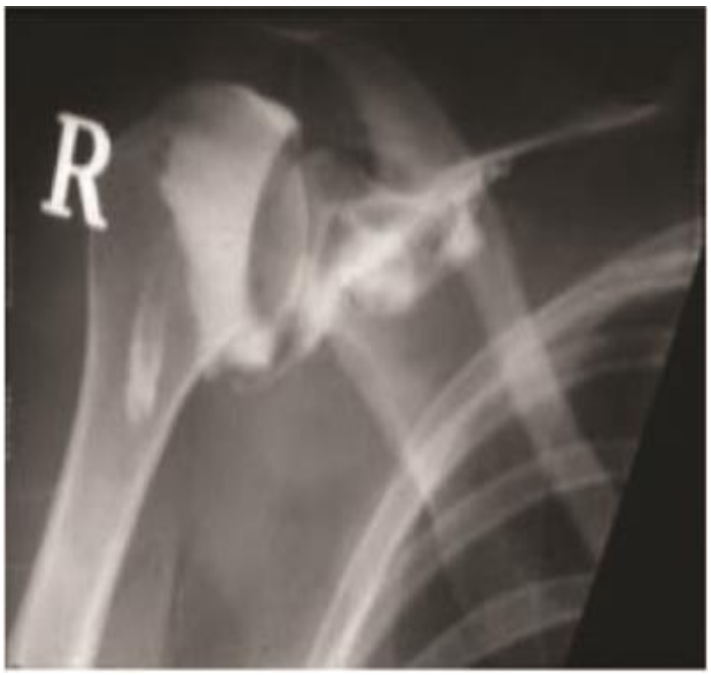

Figure 4: *Shoulder arthrogram showing a contracted and adherent joint capsule in adhesive capsulitis.*

The natural history of the disease is characterized by three distinct phases: painful, adhesive and resolution phases. The condition is also more commonly bilateral in diabetes. Due to increased connective tissue production in the joint capsule thickens and adheres to the humoral head with associated inflammation. The patient may recover after a few years but then relapse at a future time. Increasing age and duration of diabetes are associated with shoulder adhesive capsulitis [41]. Diabetic patients with frozen shoulder are more likely to have other diabetic complications such as limited joint mobility etc[40]. The etiology of SC is not understood. Attempts have been made to relate SC to various circumstances such as inactivity, strain and pre-existing shoulder affection i.e. trauma. Basic pathological changes in SC seem to be the thickening of the joint capsule and its adherence to the head of the humerus, which results in marked reduction in the volume of the glenohumeral joint. The predominant cells involved are fibroblasts and myofibroblasts which lay down a dense matrix of type I and type II collagen within the capsule[42]. Histological and histochemical studies indicate that fibroplasia and capsular contracture are caused by a cytokine driven inflammatory and fibrotic process[43].

Flexor Tenosynovitis: Flexor tenosynovitis (trigger finger) is another frequent diabetic complication of the hands (fig. 5).

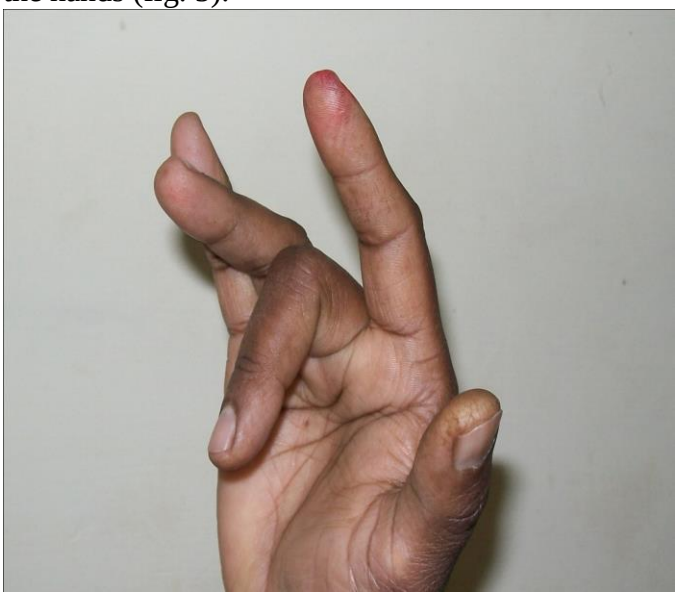

Figure 5. *This patient with flexor tenosynovitis (trigger finger) is trying to straighten out all of his fingers, but the middle finger is locked.*

Flexor tenosynovitis is a condition characterized by painful snapping of the fingers, stiffness and sometimes locking of the fingers in the digit with tenderness[44]. Examination shows a palpable nodule, usually in the area overlying the metacarpophalangeal joint and thickening along the affected flexor tendon sheath on the palmar aspect of the finger and hand[45]. Studies have shown that, trigger finger is more common in female diabetic patients as compared with a nondiabetic population, more often bilateral, multidigit and relatively sparing of the index and small fingers [46]. Trigger finger has been shown to have a prevalence of approximately 20% in multiple studies of diabetic populations, compared with roughly 2% in the general population and the right hand is more prone than the left. As with other hand complications, age and duration of disease are often cited as significant contributing factors[47]. This complication thought to have the same pathogenesis as cheiroarthopathy. The exact reason for the increased risk of inflammation of the synovial sheath in diabetic subjects remains unclear but it is believed that flexor tenosynovitis is caused by fibrous tissue

proliferation in the tendon sheath leading to limitation of the normal movement of the tendon[48].

Role of cytokines in Musculoskeletal disorders:

Impaired glucose metabolism, lipid abnormalities, vascular dysfunction and inflammation are key components of the MSDs in T2DM. Emerging data report that inflammatory molecules play an important role in regulating glucose and lipid metabolism, and the excessive activation of inflammatory pathways may represent a fundamental step in the development of MSDs[49-51]. A close relationship between prolonged low grade inflammation and MSDs has recently been established and is supported by: ***1)*** infiltration of inflammatory cells into skeletal muscle, as evidenced by increased macrophages and monocytes etc. in muscle cells[52]; ***2)*** increased inflammatory molecule levels, including TNF-α, IL-6, inducible nitric oxide synthase, fibrinogen, C-reactive protein (CRP) and sialic acid in skeletal muscle are associated with MSDs and incident of T2DM[53]; ***3)*** overexpression of circulating inflammatory cytokines originating from adipose tissue such as TNF-α, IL-6; ***4)*** skeletal muscles are immunogenic organ that produce and release inflammatory cytokines[54]; ***5)*** skeletal muscle possesses many of the components of the innate immune system, including cytokine receptors and toll like receptors (TLRs)[55,56]. Cytokines and other peptides produced by skeletal muscle fibers that exert autocrine, paracrine or endocrine effects have been termed "myokines", these myokines include TNF-α, IL-6, IL-1, IL-8, IL-10, IL-15 and monocyte chemotatic protein (MCP)-1[56].TNF-α is a pleiotropic cytokine that induces various cellular responses such as apoptosis, proliferation and production of inflammatory molecules. TNF-α is the first cytokine recognized to have a direct role in promoting insulin resistance and MSDs[57]. TNF-α exerts its cellular effects via binding to specific receptors, namely TNFR1 and TNFR2 and promotes a complex post receptor signaling events through three major pathways: ***1]*** an apoptotic signaling pathway, ***2]*** activation of JNK and MAPK pathway, and ***3]*** by activation of NF-ƙB pathway. Both TNFR1 and TNFR2 are expressed by skeletal muscle[58,59]. TNF-α decreases tyrosine phosphorylation of IRS-1 and increases IRS-1 serine phosphorylation[60,61]. Thus relative increase in serine to tyrosine phosphorylation may lead to increased ubiquinization/ proteosomal degradation of IRS-1, or decreased ability of IRS-1 to engage the p85 subunit of PI3K leading to decreased insulin metabolic signaling. TNF-α has also reduce signal transduction at the level of PKB (Akt) and insulin-stimulated glucose uptake in skeletal muscle tissue[62]. Furthermore, TNF-α diminishes skeletal muscle IRS tyrosine phosphorylation and Akt activation in a p38 MAP kinase-dependent manner[63]. AMPK also appears to be an important TNF-α signaling target[64]. TNF-α signaling through TNFR1 suppresses AMPK activity via transcriptional upregulation of protein phosphatase 2C. Activation of this phosphatase, in turn, reduces skeletal muscle acetyl CoA carboxylase phosphorylation, suppresses fatty-acid oxidation, and increases intramuscular diacylglycerol accumulation, effects that are associated with hyperglycemia both in vitro and in vivo[62].IL-6 is another important cytokine that regulates immune response and has both proinflammatory and anti-inflammatory effects. IL-6 is produced by various cells, including skeletal muscle[65,66]. Emerging evidence also indicates that IL-6 is involved in glucose metabolism and insulin action. However, the nature of this role remains controversial. IL-6 may exert an insulin-sensitizing effect and enhance insulin-stimulated glucose disposal in skeletal muscle[67-69]. Many studies have shown that severe exercise releases large quantities of IL-6 from muscle that regulates glucose homeostasis during and after exercise[66]. On the other hand, studies have also indicated that IL-6 could exert deleterious effects in insulin action and glucose homeostasis. For example, the circulating level of IL-6 is elevated in various insulin-resistant states, including T2DM. In vivo, acute IL-6 treatment in mice reduces insulin-stimulated skeletal muscle glucose uptake associated with defects in IRS-1/PI 3-kinase activity and increases in fatty acyl-CoA levels in skeletal muscle [70]. IL-6 exerts inhibitory effects on the gene transcription of IRS-1, GLUT-4 and peroxisome proliferator-activated receptor-γ under these conditions[71]. Further, IL-6 induces a rapid

recruitment of IRS-1 to the IL-6 receptor complex in cultured skeletal muscle cells and induces a rapid and transient IRS-1 serine phosphorylation and resultant increased IRS-1 ubiquinization in skeletal muscle tissue[72].Suppressor of cytokines signaling 3 (SOCS3) is another potential and important contributor to the links among inflammation and MSDs[73]. The SOCS family of proteins is thought to participate in negative feedback loops in cytokine signaling. Their expression of SOCS is usually increased by cytokine signaling through activation of nuclear factor ƙB–mediated pathways[74]. In vitro overexpression studies suggest that SOCS3 interacts directly with the insulin receptor, thereby inhibiting IRS-1 tyrosine phosphorylation and finally reduces insulin-stimulated glycogen synthesis in cultured myotubes[75]. Inflammation is therefore associated with reduced insulin sensitivity and MSDs. Insulin resistance in insulin sensitive tissue would increase the availability of substrate for the immune system, whose glucose uptake is not regulated by insulin. However, if this system is constantly activated, long lasting insulin resistance can result in development of MSDs in T2DM[76].

Conclusion:

The complications of type 2 diabetes mellitus are numerous and include involvement of the musculoskeletal system. Several rheumatic conditions are more prevalent or caused by the long term metabolic consequences of diabetes mellitus. When the control of diabetes is poor, higher levels of diabetic complications result. Poor glycaemic control, unhealthy diet, stress and increased level of inflammatory cytokines can lead to worsening of certain rheumatic conditions. These manifestations may go unrecognized or simply be overlooked in daily clinical practice. However, many of these musculoskeletal complications are treatable to varying degrees, with resultant improvements in quality of life and more independence in activities of daily living. It is our recommendation that all patients with diabetes have an appropriate exercise programme, healthy diets overseen by their medical practitioner, as an integral part of their diabetes management in order to reduce the frequency and severity of diabetes related complications.

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