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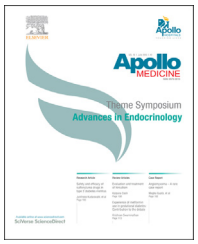

Review Article

# Rheumatic manifestations in diabetes mellitus patients

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ABSTRACT

The incidence of diabetes is increasing in most countries of the world and is a major public health problem. Diabetology and rheumatology are two medical specialties that have much in common, including the immuno-pathogenesis (Auto-immune for example) and share many features. Diabetes affects the connective tissues in many ways and causes alterations in the peri-articular and the musculo-skeletal systems. Patho-genetic mechanisms for some of these conditions have not been studied and understood completely. Some of them are considered intrinsic complications of diabetes; while in others, diabetes seems to be a mere predisposition. In most cases, these manifestations are associated with functional disability and pain, affecting the quality of life of the diabetic patient. The management of such clinical conditions requires multidisciplinary team effort to diagnose them, since early diagnosis leads to a better outcome. This article reviews some clinical, diagnostic, therapeutic and epidemiological aspects of these conditions.



## 1. Introduction

Diabetes mellitus (DM) is a chronic metabolic condition characterized by persistent hyperglycemia with resultant morbidity and mortality related primarily to its associated micro vascular and macro-vascular complications, which share the phenotype of hyperglycemia.[1] Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple-organ systems. The two broad categories of DM are designated as type 1 and type 2. Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogenous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.[1]

Rheumatic manifestations of DM are the commonest of all described endocrine rheumatic manifestations. These manifestations have generally been under-recognized and poorly treated, compared to the other complications, such as neuropathy, nephropathy and retinopathy. These manifestations, involve not only the joints, but also the soft tissues and the bones. In 2004, the National Health Interview Survey in US determined that 58% of diabetic patients will develop functional disability.[2] The percentage of diabetic patients with functional disability will increase as the number of diabetic patients increases. Recent data reveals that the prevalence of rheumatic manifestations in the hands and shoulders in patients with type 1 or type 2 diabetes is 30%.[3] These manifestations are closely linked to age,[4] prolonged disease duration,[5,6] and vascular complications like retinopathy.[7]

In contrast to various vascular complications of diabetes mellitus (DM) that are life threatening, rheumatic manifestations lead to considerable morbidity. The micro vascular and macro-vascular complications of DM have been studied extensively, as opposed to the rheumatic complications which

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have been hitherto neglected. The data regarding the rheumatic and musculoskeletal manifestations are primarily based on observational studies. Many authors have made an attempt to classify rheumatic manifestations of DM in various ways.[3,8,9]

The only proven association that has been reported to occur exclusively among DM patients is diabetic muscle infarction (DMI). The other rheumatic manifestations of DM are also commonly found in various other diseases and are not unique to DM. These manifestations are as follows: Syndromes of limited joint mobility – limited joint mobility, diabetic hand syndrome (diabetic cheiroarthropathy/stiff hand syndrome), adhesive capsulitis (frozen shoulder), trigger finger (flexor tenosynovitis), dupuytren's contractures, calcific periarthritis, osteoarthritis; diffuse idiopathic skeletal hyperostosis (DISH); neuropathic arthropathy (Charcot joints, diabetic osteoarthropathy), carpal tunnel syndrome, gout, diabetic amyotrophy, reflex sympathetic dystrophy.[10]

The table below denotes the potential pathophysiologic relationships that might be linked to these conditions (modified from "Rheumatic manifestations of diabetes mellitus. Dorota Lebiedz-Odrebina, Jonathan Kay. *Rheum Dis Clin N Am.* 36(2010):681–699").

| Conditions unique to DM | Conditions more frequent in DM | Conditions sharing risk factors of DM and metabolic syndrome |
|---|---|---|
| Diabetic muscle Infarction | Limited joint mobility | Diffuse Idiopathic Skeletal Hyperostosis (DISH) |
| | Neuropathic arthropathy | Gout |
| | Stiff/Diabetic hand syndrome | Osteoarthritis |
| | Dupuytren's contracture | |
| | Stenosing flexor tenosynovitis/Trigger finger | |
| | Frozen shoulder/Shoulder adhesive capsulitis | |
| | Calcific shoulder periarthritis | |
| | Carpal tunnel syndrome | |

## 2. Diabetic muscle infarction (DMI)

DMI is rare complication of DM, Angerwall et al first described it as "Tumoriform focal muscular degeneration" in two diabetic patients way back in 1965.[11] Since then many cases have been reported and more than half of these patients had type 1 DM with a mean duration of 15 years.[12,13] It presents with acute onset of muscle pain and swelling. 80% of cases have thigh muscle involvement, however isolated calf muscle, simultaneous thigh and calf muscle and upper extremity muscle involvement have also been described. A palpable mass has also been reported. Recurrence in the same or different group of muscle has been observed. The mean mortality rate is 10% with DMI within 2 years of the initial diagnosis, wherein mortality were predominantly due to the macro-vascular complications.[14]

The typical clinical presentation and characteristic findings on radiology, suggests the diagnosis of DMI. There is no specific laboratory marker for DMI. Serum creatine kinase (CK) levels were elevated in slightly fewer than half of those patients for whom a level was reported. MRI shows typically isointense swelling on T1 weighted images and diffuse heterogenous hyper intensity on T2 weighted images of the affected muscle with surrounding subfascial and subcutaneous edema. Gadolinium contrast is not essential but if used will show non-enhancing areas surrounded by peripheral enhancement.[15] Muscle biopsy is reserved for patients in whom diagnosis is uncertain, with atypical presentation and for those who do not improve with anti platelet or anti-inflammatory therapy.[16] Typical biopsy findings will reveal muscle fiber necrosis, edema, phagocytosis of necrotic fibers, granulation tissue and collagen deposition.

Patho-physiologically it has been suggested that reperfusion injury after muscle ischemia resulted in muscle infarction, as almost all patients with DMI had microangiopathic complications of DM. Also the theory of endothelial dysfunction in DM and the hypercoagulability resulting from alternation of the coagulation- fibrinolytic system has been proposed.[17] But, due to the rarity of the condition, the association between antiphospholipid antibody syndrome and DMI has not been proven.[18]

Differential diagnosis is made with myositis, venous thrombosis, tumor and diabetic amyotrophy, adverse effect of simvastatin, ruptured Baker's cyst. The recommended management of this condition is symptomatic, with pain relief and short-term immobilization as necessary. This condition tends to resolve in most cases over a period of a few weeks. Optimizing diabetic control is of paramount importance.[19] Medical therapy with antiplatelets and/or anti-inflammatory drugs is recommended, but due to infrequent occurrence of this disease, there has not been any randomized controlled trial.

## 3. Upper limb manifestations

It mainly involves upper limb musculoskeletal structures and it appears to be associated with the duration of diabetes, poor metabolic control and presence of micro vascular complications.[20] Each one of the following is explained as under:

**"Stiff-hand syndrome" or Diabetic cheiroarthropathy** (derived from greek word "cheiros", which means hand) is characterized by hardened and stiff skin of the fingers and palm and painless limitation of mobility of the small joints of the hands. The prevalence is 8%–50% among patients with diabetes, while only 4%–20% among individuals without DM.[21,22] Diabetic cheiroarthropathy is primarily a clinical diagnosis and the imaging findings are nonspecific.[23] There two clinical signs which are indicative of the diagnosis are 1) The prayer sign, in which, the patient is unable to approximate the palmar surface of the fingers when raising the hands as if in prayer and 2) The tabletop sign, in which, when the patient is asked to lay the palms flat on the tabletop, he is unable to touch the palmar surface of the fingers to the table. Limited mobility should be confirmed by demonstration of loss of passive extension of the proximal interphalangeal and metacarpophalangeal joints, which are less than 180° and less