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Review Article

Rheumatic and Musculoskeletal Complications of Type 1 Diabetes Mellitus

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Received: June 16, 2025; **Published:** July 29, 2025

Abstract

Type 1 diabetes mellitus (T1DM) affects millions of people and is of significant public health concern. Unlike type 2 diabetes, T1DM is an organ specific autoimmune disease affecting mainly children and young adults, although it can occur at any age. Such affected patients require lifelong insulin therapy and careful meticulous management to prevent acute and chronic complications.

The incidence and prevalence rates of T1DM are increasing in most high-income countries except in females in Finland [7]. Worldwide increases in childhood T1DM were observed by Chen., *et al*. from 1965 to 2012 [4]. This increase in disease burden makes T1DM an important health challenge that needs utmost global attention focussing on prevention, management and care to reduce morbidity and mortality.

In T1DM, an irreversible autoimmune destruction of the pancreatic β cells results in loss insulin production. As a consequence, the ability of the body to control blood glucose is impaired, with resultant elevated blood glucose levels. Human Leukocyte antigen (HLA) association in type 1 diabetes mellitus has been documented, as has been reported in other autoimmune diseases (AID) which are organ-specific [6]. When T1DM is diagnosed, the pathophysiological processes have destroyed most of the pancreatic β cells. High blood glucose levels that ensue due to pancreatic insufficiency ultimately cause a wide array of organ-specific complications which impact significantly on a patient's quality of life. These include cardiovascular, neurological, gastrointestinal, immunological and rheumatic and musculoskeletal system (RMD) complications, to mention a few.

In this review, we focus on the rheumatic and musculoskeletal complications of T1DM. These complications include diabetic cheiroarthropathy, adhesive capsulitis (AC), carpal tunnel syndrome (CTS), diabetic osteoarthropathy, diffuse idiopathic skeletal hyperostosis (DISH) *inter alia*. T1DM has been demonstrated in multiple studies to have a significant association with rheumatic conditions such as Juvenile Idiopathic Arthritis (JIA), Osteoporosis, Sjogren's syndrome, Osteoarthritis and, not surprisingly, other autoimmune diseases such as hypothyroidism.

Keywords: *T1DM; Type 1 Diabetes Mellitus; Rheumatic and Musculoskeletal Disorder (RMD); Osteoporosis; JIA; Diabetic Cheiroarthropathy; Osteoarthritis; Hypothyroidism; DISH; Children; Adolescent; Charcot's Joint*

Introduction

Diabetic cheiroarthropathy, also known as 'diabetic hand' or 'diabetic stiff hand syndrome', is characterised by limited joint mobility, and thickened skin, mostly occurring in the hands. Long-standing, uncontrolled hyperglycemia is the major cause of this complication due to the accumulation of advanced glycation end products (AGEs), which are pro-inflammatory and impair the production and structure of collagen and other connective tissues.

Adhesive capsulitis, which is also called 'frozen shoulder', is a condition affecting the shoulder joint and involves pain and stiffness with resultant restricted shoulder joint mobility. This condition is challenging to manage as it is refractory to most treatments.

In CTS the underlying pathology is compression or entrapment of the median nerve leading to pain, numbness, and tingling sensations in the hands and fingers. It is a complication of high glucose levels due to the changes in connective tissues and nerve damage posed by DM. CTS is worse with activity and at night time [1].

Diabetic osteoarthropathy, also known as 'Charcot's joints', is a major complication whereby progressive bone and joint destruction primarily affects the ankles and feet. Due to poor blood supply to the lower extremities and neuropathy, severe deformity and disability are imminent in this condition.

Diffuse idiopathic skeletal hyperostosis (DISH) is mostly a spinal condition, which is due to calcification and hardening of tendons and ligaments causing pain and stiffness.

Pathophysiology

The underlying pathophysiologic mechanisms of T1DM linked RMD complications include:

1. Chronic hyperglycemia leading to the build-up of AGEs,
2. Oxidative stress,
3. Metabolic derangements and their sequelae, and
4. Inflammation.

RMD literature review in T1DM

A review of literature using the PubMed, Cochrane Library, and Science Direct databases using keywords was sought and only reputable sources were considered and those written in the English language were employed.

A study done by Larkin., *et al*. demonstrated Cheiroarthropathy to be present in most cases of patients with long-standing T1DM (of approximately 3 decades duration) as well as those with uncontrolled blood glucose levels, and of those afflicted, more than one type of Cheiroarthropathy (defined as AC, CTS, Tenosynovitis, Dupuytren's Contracture or a positive prayer sign) was found in half of them whilst the other half exhibited only one form of Cheiroarthropathy [8]. Therefore screening for Cheiroarthropathy in T1DM has been highly recommended [8].

Another study in Sweden showed an eightfold increase in the prevalence of hand disorders, which include limited joint mobility, Trigger finger, Dupuytren's disease, osteoarthritis of the first carpometacarpal joint and carpal tunnel syndrome in T1DM patients as compared to those without diabetes [10]. Furthermore, it was also demonstrated that such patients also had other RMD diabetic complications [10]. DISH was described in 70% of participants with metabolic disorders with dyslipidemia and/or hyperuricemia when compared to those without where only 45% of controls [16].

Interestingly, pregnant, T1DM patients in their second trimester were shown to have a higher incidence rate of low back pain and pelvic pain in comparison to non-diabetics [3].

Musculoskeletal and neurologic complications have been reported in T1DM. Increased fracture risk in T1DM patients has been reported secondary to osteoporosis [11,13]. This increased fracture rate was observed in another [13]. It has been observed that both markers of bone turnover; Pro-collagen 1 N-propeptide (P1NP) and Cross-linked C-telopeptide (CTX) are lower in T1DM and show a positive correlation between neuropathy and tibial cortical bone density [13]. Nerve conduction and velocity were greater the higher the Bone Mineral Density (BMD) in the proximal femur. Furthermore, Sayilekshmy M., *et al.* cited by Tatiane V demonstrated an association between bone turnover and nerve profile density using histophotometry implying a link between bone remodelling and innervation [13]. In addition, negative correlations were noted between cortical porosity of the tibia and radius with nerve conduction amplitude and velocity. This explains in part why severe neuropathy is associated with higher cortical porosity.

Chronic hyperglycemia's involvement in the formation of AGEs has been found to have a profound impact on collagen production and decreased osteoclast differentiation and function [13]. AGE perturbates the catabolic activities in chondrocytes by binding to glycation end products receptors (RAGE) [18]. This binding also induces cellular oxidative stress which triggers the secretion of many pro-inflammatory cytokines such as IL-1β and TNF-α which are involved in osteoporosis and osteoarthritis pathophysiology [18]. Interestingly, increased fracture risk was demonstrated even in patients with well-managed, established T1DM; a low BMD, low bone turnover, increased cortical porosity of the tibia and reduced muscle strength and stiffness have also been reported [13]. Between T1DM and osteoporosis, a cause-and-effect relationship was found in some sites such as the femoral neck and lumbar spine [4].

Diabetic bone disease, as well as diabetic myopathy, are gaining prominence as notable complications of T1DM and the anatomical proximity of these organs/systems and their interdependent functionality, allows for an interplay between high glucose levels, insulin, osteokines and myokines in dysregulating muscle-bone unit functions. Hence, exercise, calcium/vitamin D supplementation and intensive diabetes management have been suggested as preventive and protective measures to fortify musculoskeletal health [16].

Another rare complication in T1DM is a presentation of an acutely painful limb but with no history of trauma, is myonecrosis. A recommendation is that orthopaedic surgeons need to have a high index of suspicion for it and diagnosis is made by T2 weighted MRI and treatment is a non-surgical approach with bed rest and intensive glycemic control. However, it can be recurrent [17].

The prevalence of autoimmune RMDs has been demonstrated to be higher in T1DM (females higher than males). There is also an increased propensity of other autoimmune diseases (AID) [2]. T1DM characterised as an autoimmune condition in itself, has, not surprisingly, been found to be associated with other autoimmune conditions. The existence of other autoimmune complications is known as Autoimmune Polyglandular Syndrome (APS). Takahashi., *et al*. illustrated an interesting case of a longstanding Ulcerative Colitis case further diagnosed with T1DM and Sjögren's syndrome though euthyroid, was discovered to have antithyroid antibodies illustrating Hashimoto's and has been classified as APS type 3 [14]. AID occurring in a setting of T1DM causes considerable comorbidity and is mostly seen in women, with increasing age and occurs mostly in the white population of note, in one study, the most common AID noted was thyroid disease seconded by autoimmune RMDs [2]. Szablowski., *et al*. expressed that Juvenile idiopathic arthritis (JIA) also has been found to have a significantly higher prevalence in T1DM than in the general population [12].

Discussion

T1DM is an autoimmune condition characteristically reported to be triggered by an interplay of genetic and environmental factors resulting in its development in a particular individual. Environmental factors, however, still need more clarification and specification. The multifarious complications of diabetes are perturbing and therefore ongoing research to elucidate causalities and hence ascertain possible therapeutic modalities that would enable efficient management of this condition is invaluable. Early detection and tight management of T1DM are key to ensuring normal growth and development as well as reducing risk of developing complications in children.

Though RMD are generally non-acute life threatening they do, however, cause significant morbidity in terms of reduction of quality of life as a result of pain and disability. The finding that at least half of afflicted individuals with cheiroarthropathy exhibit more than one form of the disease is concerning and hence early detection is an essential best international clinical practice. The fact that uncontrolled hyperglycaemia is the driving force behind the development and progression of these complications means the ultimate goal is tight glycaemic control through continuous enhancement of therapy and lifestyle modifications. Furthermore, in conditions such as DISH, other metabolic conditions such as hyperuricaemia and hyperlipidaemia come into play and thus, also need to be addressed with active management to mitigate the establishment of such complications.

Priority to bone and muscle health are vital components of T1DM care with regard to RMD complications. Exercise, physical therapy, Vitamin D3 supplementation, avoiding muscle and bone overload and off-loading in some severe instances are some suggested recommendations for maintaining a healthy muscle-bone unit functionality. Effective management of related autoimmune conditions is indispensable.

An important consideration is the aspect of comorbidities in T1DM, witnessed as clusters of autoimmune conditions that have a considerable detrimental effect on an individual's quality of life. These make patient management more challenging and additionally, polypharmacy may aggravate and/or precipitate one condition or more. Rigorous treatment of each condition is however critical for overall good health outcomes.

Looking to the future; the discovery of islet cell antibodies before the development of T1DM is an important finding that can go a long way in developing therapeutic advances to halt the actual progression to frank disease and thus the ensuing complications associated with metabolic derangements as observed. More research is still needed to curb this deleterious multi-system and multi-organ disease whose result is, if uncontrolled, to either compromise the quality of life of an individual or cut short their span of life.

Conclusion

The incidence of T1DM is increasing and therefore there is a need global awareness of the disease by both the public and healthcare professionals. Without a doubt, rheumatic and musculoskeletal complications in T1DM, *inter alia,* cause a significant impact that deserves more attention and consideration to better the management of these patients thus preventing disability and loss of productivity in an individual's life.

The key role of research is of vital importance as a lot of questions still need to be answered and better health outcomes remain the goal of management of these patients to prevent long term complications. Future T1DM research needs to be focused on these key fundamental promising areas:

1. Development of biomarkers for early disease development detection;
2. Cell Immunotherapy strategies aimed at modulating the immune system and preserve beta cell function and prevent progression to end organ failure;
3. Pancreatic β Cell replacement therapy using stem cell therapy and islet cell transplantation.
4. Development of automated artificial Pancreas for simulated physiologic insulin delivery;
5. Genetic defects research to elucidate the exact genetic aberrations in T1DM and identify new therapeutic targets.

Advances in technology and research hold promise for improved outcomes and quality of life for children and young adults with T1DM. enhanced and continued efforts in education, support, and innovation are essential to address the growing burden of this disease globally.

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Volume 14 Issue 8 August 2025