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Limited joint mobility syndrome in diabetes mellitus: A minireview

Esther G Gerrits, Gijs W Landman, Leonie Nijenhuis-Rosien, Henk J Bilo

Esther G Gerrits, Department of Internal Medicine, Maastricht University Medical Center, 6229 HX Maastricht, The Netherlands

Gijs W Landman, Leonie Nijenhuis-Rosien, Henk J Bilo, Diabetes Centre, Isala, 8025 AB Zwolle, The Netherlands

Gijs W Landman, Department of Internal Medicine, Gelre Hospital, 7334 DZ Apeldoorn, The Netherlands

Leonie Nijenhuis-Rosien, Innofeet Voetencentrum Nijenhuis, 8013 NA Zwolle, The Netherlands

Henk J Bilo, Department of Internal Medicine, Isala, 8025 AB Zwolle, The Netherlands

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Correspondence to: Esther G Gerrits, MD, PhD, Department of Internal Medicine, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands. esther.gerrits@mumc.nl
Telephone: +31-43-3877005
Fax: +31-43-3875006

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Abstract

Limited joint mobility syndrome (LJMS) or diabetic cheiroarthropathy is a long term complication of diabetes mellitus. The diagnosis of LJMS is based on clinical features: progression of painless stiffness of hands and fingers, fixed flexion contractures of the small hand and foot joints, impairment of fine motion and impaired grip strength in the hands. As the syndrome progresses, it can also affect other joints. It is important to properly diagnose such a complication as LJMS. Moreover, it is important to diagnose LJMS because it is known that the presence of LJMS is associated with micro- and macrovascular complications of diabetes. Due to the lack of curative treatment options, the suggested method to prevent or decelerate the development of LJMS is improving or maintaining good glycemic control. Daily stretching excercises of joints aim to prevent or delay progression of joint stiffness, may reduce the risk of inadvertent falls and will add to maintain quality of life.

Key words: Diabetic cheiroarthropathy; Limited joint mobility; Diabetes mellitus; Joint stiffness; Advanced glycation endproducts

Core tip: "Limited joint mobility syndrome in diabetes mellitus: A minireview" is an article about limited joint mobility syndrome in diabetes mellitus that is an underreported complication, associated with micro and macrovascular complications. From a clinical perspective, a good glycemic control and daily exercising are the main and the base of prevention. Treatment options include symptomatic therapies and surgical correction. Medical treatment targeting the

formation of glycosylated end products accumulating on collagen and other connective tissues are unsuccessful for this complication. This mini-review analyzes all the aspects of a forgotten complication of diabetes mellitus.

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INTRODUCTION

Musculoskeletal disorders such as Achilles tendon pathology, trigger finger, Dupuytren, limited joint mobility syndrome (LJMS), carpal tunnel syndrome, frozen shoulder and plantar fasciitis have been found to occur more often in subjects with diabetes compared to those without diabetes[1-5]. With the increasing number of patients known with diabetes and - consequently - an increase in incidence and prevalence of diabetes related complications along with increasing age of these patient group, it is important to pay attention to the topic of musculoskeletal disorders in order to recognize and diagnose these disorders in clinical practice as early as possible. LJMS is one of the musculoskeletal disorders and is rather underexposed and underdiagnosed compared to the well-known micro- and macrovascular complications of diabetes. Due to their relative relationship to mortality, more attention is paid towards the complications of diabetes such as nephropathy, neuropathy and cardiovascular disease. Less attention is paid to LJMS, although it is associated with neuropathy and other microvascular complications and it can influence patients' health-related quality of life quite dramatically[1,4-9]. In this mini-review, we will exclusively focus on LJMS as a musculoskeletal complication of diabetes. It provides an overview of the pathofysiology, the importance of diagnosing LJMS, the practical implications of the diagnosis and future expectations on this topic.

LJMS

Epidemiology

Stiff hands in long-term diabetes has been described for the first time by Lundbaek[10] in 1957. Less reports have been published about LJMS until 1974, when Rosenbloom *et al*[11] exhibited renewed interest in this syndrome. Joint stiffness and contractures were described as a common feature in children with type 1 diabetes mellitus[11-13]. Currently, we define LJMS as a long term complication of diabetes mellitus, but it can also develop in patients without diabetes. The reported prevalence in diabetes mellitus apparently varies between 8%-58%, depending on the different diabetes patients cohorts and the applied definitions of LJMS[5-9,12,14-16]. The prevalence of LJMS in subjects without DM is difficult to estimate and may vary between 4%-26%[2,4,5,9]. Generally, no clear gender or racial preferences have been found in the development of LJMS in diabetes.

Symptomatology and diagnosis

LJMS of the hands and fingers, also called cheiroarthropathy, is characterized by several clinical features which enhance painless stiffness of hands and fingers, fixed flexion contractures of the small hand joints, impairment of fine motion and impaired grip strength. Ultimately, these features will result in the impairment of joint mobility, especially of the small joints of the hands and may become painful. The "prayer sign" and the "tabletop sign" are clinical tests strongly supporting the diagnosis, which can only be used in the absence of previous hand injury or hand surgery[17]. Under normal conditions, both hands will have contact for the total opposing hand surface parts, when the hands are pressed flat to each other, as making a "prayer sign". If this proves to be impossible, it means there are flexion contractures of the fingers and the sign is considered positive. With the "tabletop sign" one has to put the hands flat on the table with the fore arm in a 90 degree angle. If one hand doesn't make contact with the table at one spot, it means that there are contractures of the small hand joints suggesting the test positive.

Natural course: Besides joints involvement of hands, LJMS can also occur in the small joints of the feet and in the long term progression of disease can also result in impairment of other joints such as the shoulder, hip, ankle, spine and all other joints. Consequently, on the long term, LJMS might increase the risk of falling[18]. A limb threatening situation might occur when the impairment of mobility of toes and feet joints is seen in combination with the presence of neuropathy. The combination can lead to serious plantary pressure points, which translates into a great risk for diabetic foot ulcer[19-21]. When peripheral arterial disease is present, this might even result into an enhanced amputation risk. Conceivably, all these features and complications of LJMS can be accompanied by a significant reduced quality of life.

Differential diagnosis

Sometimes, LJMS is difficult to distinguish from other joint complaints in diabetes patients. Certain musculoskeletal conditions occur more frequently in diabetes patients compared to the general population which include Dupuytren, tenosynovitis and palmar/plantar fasciitis. Complex regional pain syndrome and scleroderma are also part of the differential diagnosis of LJM. The specific clinical features of each different disorder with or without supplementary laboratory and radio- or ultrasonographic evaluation confirm the diagnosis[22-24].

One should keep in mind that any supplementary diagnostic evaluation is quite unspecific, so the diagnosis of limitation of joint mobility mainly relies on the clinical features.

Considering a prevalence of up to 50% and the LJMS accompanied microvascular and limb threatening complications, screening for LJMS in diabetes patients is important, and has to be part of the annual check up or more often when indicated.

PATHOGENESIS

The apparently higher prevalence of LJMS in subjects with diabetes compared to nondiabetic subjects is assuming that there is a correlation between diabetes mellitus and LJMS, but good literature to support this correlation is lacking. As the presence of LJMS is associated with nephropathy, retinopathy and neuropathy, it is not only important to diagnose LJMS *per se*, but also because it can be an early warning signal of the possible presence of one or more of the microvascular complications[1,4-9]. In some cases it might be the first feature of tissue damage in diabetes which should alert physicians to actively screen or search for the presence of microvascular complications as well.

In general, the chances to develop LJMS are associated with age, diabetes duration and degree of glycemic control[1,4-6,9,14]. Theoretically, good glycemic control should diminish the risk of LJMS in an identical fashion as the development of other diabetic complications. Eventually, a combination of factors will contribute to the development and progression of diabetic complications including LJMS.

Besides a variable genetic susceptibility, high oxidative stress levels seem to be one of the factors involved. Intracellular hyperglycemia will cause high levels of oxidative stress and the formation of advanced glycation endproducts (AGEs). These AGEs are damaging glycosylation products, nonezymatically formed under circumstances of hyperglycemic and oxidative stress. In such an unfavourable environment, increased production of reactive oxygen species will be induced that can initiate the inflammatory cascade leading to the production of several cytokines and growth factors causing the hyperglycemia-induced cellular damage[25,26].

Furthermore, besides their damaging effects on the vascular endothelium, these accelerated formated AGEs also form cross-links with long-lived proteins such as skin collagen, tendons and ligaments altering their biological structure and function[27-29]. Collagen has a long half life, which means that collagen degradation will take a long time: for more than ten years. Therefore, the AGE-cross-links to collagen will extensively accumulate in the skin, tendons and ligaments and are considered to play an important role in the development of LJMS.

Genetic susceptibility in combination with other factors such as a hyperglycemic and highly oxidative stress environment will add to the development of LJMS.

THERAPEUTIC OPTIONS

LJMS seems to be an irreversible disorder with no specific curative treatment options. There are no drugs available which directly target LJMS. Only symptomatic therapy, such as analgesics, non-steroidal anti-inflammatory drugs or local corticosteroid injections can be given as a relief and in case of tendinitis or flexor tendon contractures. Surgery is indicated in case of severe contractures. Exercising, which include daily stretching exercises of the palm of the hand and sole of the foot, will also help to prevent or further delay the development of progressive joint stiffness in case of limited joint mobility[30]. In case of limited lower limb joint mobility with or without the presence of neuropathy, professional foot care and rocker bottom shoes are indispensible in order to prevent the developent of diabetic foot ulcers[31].

In general, as LJMS is associated with glycemic control and diabetes duration, just like all other diabetic complications, the best way to prevent LJMS is to strive for good glycemic control from the onset of diabetes diagnosis.

NOVEL STRATEGIES

During the past 20 years, research has been performed to find efficient agents with AGE inhibitory properties without toxicity, meant for safe application in humans. Targeting AGE cross-links with alagebrium (ALT-711) in experimental settings have clearly shown beneficial effects, but in human trials there seems to be a safety concern and alagebrium still has to be proven to be beneficial[32-34]. Aminoguanidine with a preventive effect on the formation and accumulation of AGEs in experimental studies, but not recommended for daily clinical use because of safety concerns and lack of evidence in human[34,35]. Anti-oxidant agents with specific AGE-inhibiting effects (*e.g.*, pyridoxamine, benfotiamine) have shown beneficial effects in animal models, but still have to be proven as an effective therapy in human[34].

With all these unsuccesfull strategies, newly developed targeted drugs are needed in order to prevent or delay the onset of LJMS.

CONCLUSION

LJMS is an underreported complication of diabetes, along and associated with micro- and macrovascular complications, which should be assessed during the annual check up of diabetes care. From a practical perspective, both a good glycemic control and daily excercising are the main and actually only pillars of prevention. Treatment options include symptomatic therapies and surgical correction. Medical treatment targeting the

formation of glycosylated endproducts accumulating on collagen and other connective tissues that are said to be responsible for the development of LJMS, have so far proved to be unsuccesfull. Newly developed targeted drugs are needed in order to prevent or delay the onset of LJMS, to reduce the risk of inadvertent falls and to maintain quality of life of subjects with diabetes.

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