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Introduction

Diabetic patients show higher prevalence of rheumatic diseases as compared to general population due to the fact that Diabetes Mellitus (DM) affects all components of musculoskeletal system: muscles, bones and connective tissue [1, 2].

Different musculoskeletal disorders that involve hands and shoulders are described, including palmar flexor tenosynovitis, Dupuytren's contracture, carpal tunnel syndrome, Charcot arthropathy, reflex sympathetic dystrophy and shoulder's adhesive capsulitis. They can be painful and cause functional weakness (Figs. 7.1 and 7.2) [3, 4].

In the hand, DM produces the so-called "diabetic hand syndrome", being Limited joint mobility (LJM) the most frequent manifestation [5]. It is rather underexposed and underdiagnosed compared with other well-known manifestations of the disease. It's association with neuropathy and microvascular complications, should alert the physician about higher risk for the development of "Diabetic foot Syndrome" among other pathologies that can influence patients' health-related quality of life quite dramatically [6]. Prevalence of LJM increases with duration of DM, poor glycemic control, non-enzymatic glycation (NEG) and accumulation of advanced glycation end products (AGEs), increasing age and also in smokers [7, 8].

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Fig 7.1 Dupuytren's contracture



Fig. 7.2 Dupuytren's contracture



The thick skin syndrome includes four cutaneous manifestations: Finger pebbles (FP); Waxy skin (WS); Limited joint mobility (LJM); and Diabetic scleredema (DS) (Table 7.1) [9].

Finger Pebbles

Also known as Huntley's papules, FP consist of multiple tiny papules grouped on the extensor surface and lateral aspect of the fingers, on the knuckles of the metacarpophalangeal and interphalangeal joints, more frequently in the distal ones, and in the periungual region (Figs. 7.3, 7.4 and 7.5) [10, 11].

According to the literature, it is a very common finding that reaches up to 60–70% of diabetic patients, but in our experience, we do not find it so often. Moreover, it can happen in 20% of non-diabetic people, especially, manual workers. It is asymptomatic, and treatment is not required.

Table 7.1 Thick skin syndrome

	Finger pebbles	Waxy skin and limited joint mobility	Diabetic scleredema
Incidence	60%	30%	2.5%
Age	Infants/youth and adults	2 variants: child and youth and the most frequent adults	>40 years
Gender	Equal in both	Equal in both	4:1 male/female
Relationship with diabetes	80% in diabetic patients, 20% in non-diabetics	T1DM and T2DM	More in obese, long-standing and poorly controlled T2DM
Importance	Visual marker of skin thickening in DM	High risk of microvascular complications	Related to insulin resistance, retinopathy, HT, ischemic disease

DM diabetes mellitus, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *HT* arterial hypertension

Fig. 7.3 Tiny papules, mostly located on the interphalangeal joint and periungual region



Fig. 7.4 Huntley's papules



Fig. 7.5 Finger pebbles

When it appears in diabetic patients, it is considered a visual marker of the thickening of the dorsum of the hands. It is associated with either type 1 DM (T1DM) or type 2 DM (T2DM) of both genders equally; although in Huntley's original description—later supported by other authors—it is more frequent in adults with T2DM. It has been suggested that the thickening is not only related to NEG of collagen fibers, but also to epidermal growth factors such as insulin-like growth factor (IGF-1) [12]. Finger pebbles are an early dermatologic sign of sclerodermiform alterations in hands [13].

The histologic features of FP are epidermal hyperplasia with a “church tower” aspect where orthokeratotic hyperkeratosis and regular acanthosis are evident; at the dermis level, we observe changes in the collagen fibers that are arranged vertically, papillomatosis and areas of angiogenesis along with insignificant perivascular infiltrates [14].

Saraiya et al. described an association between FP, acanthosis nigricans (AN) and cutaneous acrochordons in obese T2DM patients with insulin resistance (IR) and high levels of IGF-1 [15, 16]. FP are also associated to severe obesity in the context of IR without underlying DM, as in the reported case by Granel et al., whose patient suffers from Pickwick Syndrome (severe obesity, drowsiness, excessive appetite, hypoventilation, and sleep apnea) [17].

Waxy Skin

It is characterized by cutaneous changes over the dorsum of the hands and forearm due to the accumulation of dermal collagen of the skin. Under physical examination the skin is shiny and tight, difficult to fold, similar to scleroderma but with its own features, both in optical and electron microscopy. Clinical manifestations such as ulcers and Raynaud's phenomenon, capillaroscopic Scleroderma pattern, specific autoantibodies and other laboratory data are helpful in the differential diagnosis between both entities (Table 7.2) (Figs. 7.6 and 7.7) [18].

Table 7.2 Clues for the diagnosis of sclerodermiform changes in DM versus scleroderma

	DM	Scleroderma
Age	10–20 years	40–50 years
Gender	Equal	3:1 female/male
Diabetes	Type 1 and 2	There may be an abnormal glucose tolerance
Pain	No	Yes
Raynaud	No	Yes
Digital ulcers	No	Yes
Telangiectasia	No	Yes
Pigmentation	No	Yes
Capillaroscopy	Capillaries loss	SD pattern
Histology	Dermal collagen is thickened and hyalinized, spaces and clefts between fibers. Fat around eccrine sweat glands is preserved. No inflammatory reaction	Epidermal atrophy Homogenization of the dermis with loss of spaces between collagen bundles. Replacement of the periglandular fat by collagen

Fig. 7.6 Waxy skin. The skin is shiny and tight, difficult to fold**Fig. 7.7** Waxy skin at the phalanges. Limited joint mobility in an early stage. Normal aged and wrinkled skin of the patient at the back of the hand is observed

Waxy skin is more frequent in diabetic patients with LJM, in particular with those with moderate or severe involvement, than in diabetic individuals without that manifestation, which in turn, have thicker skin compared to non-diabetics. Histopathologically, dermoepidermal thickening with accumulation of collagen and loss of cutaneous appendages are characteristic features.

Limited Joint Mobility

LJM is caused by the thickening and stiffness of the periarticular connective tissue. It involves mainly the small joints of the hands and results in a severe finger contracture and the inability to extend the metacarpophalangeal and proximal and distal interphalangeal joints starting with the fifth and fourth fingers and expanding radially. It is painless and generally goes unnoticed until the deformity becomes so severe that it interferes with daily life with less grip strength and a notable difficulty to close the fingers into a fist and make fine movements (Figs. 7.8, 7.9, 7.10, 7.11, 7.12, 7.13, 7.14, 7.15, 7.16 and 7.17).



Fig. 7.8 Limited joint mobility of the fifth finger of both hands. Prayer sign

Fig. 7.9 Limited joint mobility. Severe degree. Prayer sign



Fig. 7.10 Limited joint mobility. Severe degree

Fig. 7.11 Limited joint mobility of the fifth fingers of both hands



Fig. 7.12 Limited joint mobility of the fifth fingers of both hands



Fig. 7.13 Limited joint mobility of the fourth and fifth fingers of both hands



Fig. 7.14 Limited joint mobility. Prayer sign



Fig. 7.15 Limited joint mobility. Severe degree



It is also known as cheiroarthropathy or “diabetic stiff hand syndrome” and has a prevalence of 30–40% of T1DM patients (8–50% of diabetic individuals); although it is also present in T2DM, both male and female equally.

Apart from the hands, other joints can be affected like wrists, elbows, knees, ankles, shoulders, the cervical and thoracolumbar spine, and other organs (lungs) [19]. Its original description on the 70s belongs to Rosebloom et al., where they reported three cases with long-lasting T1DM and LJM of the hands, wrists, elbows and ankles and in two of them along spinal column with other clinical features. X-rays did not show any joint disorders, which confirmed that the thickening was due to the thickening and stiffness of the periarticular tissue [20].

The main risk factor for the appearance of this disease is the DM duration [21]. There is a relationship between joint stiffness and increased NEG of periarticular collagen, cartilage and tendon, based on the proof that each increased unit of HbA1c from the beginning of the disease, corresponded to 46% of increase risk of developing LJM.

It is essential to emphasize that the presence of LJM in diabetic patients is an important marker of subsequent microvascular disease and can constitute a useful clinical tool for the identification of a subset of patients at high risk for developing early complications.

Fig. 7.16 Limited joint mobility. Severe degree



Some authors refer that LJM is an independent factor for the development of microvascular complications and increases the risk 3–5 times in these patients. A recent analysis found that in the presence of LJM, there is an 83% increase in the risk of developing microvascular complications after 16 years of having DM, as opposed to 25% of risk in the absence of LJM. Rosenbloom et al. observed that it is even more frequent in the case of the male gender, possibly due to a poor glycemic control, coronary heart and cerebrovascular disease. In women, it is related to early macrovascular complications [22].

In addition, LJM is associated with several disorders that should be taken into account such as higher risk of accidental falls—which is moderate according to balance assessment (19–20 s), and diabetic foot ulcers, due to an increase of the pressure on the metatarsophalangeal and submetatarsal joints plantar points [23, 24].

Thickening of the plantar fascia and the Achilles tendon, has also been described, more frequently in patients having LJM and peripheral neuropathy and correlated positively with the body mass index (BMI) [25]. Moreover, shoulder and hand's

Fig. 7.17 Limited joint mobility of the fifth and fourth fingers of both hands



LJM may lead to upper extremity impairments compromising the strength and functionality of the upper extremity [26].

The degree of hand involvement has been classified into mild, when the limitation affects one or two proximal interphalangeal joints, one large joint or only metacarpophalangeal bilateral joints. Moderate limitation refers to three or more proximal interphalangeal joints or the joint of one finger and one large bilateral joint. Severe cases are constituted by the deformity of the hand at rest or involvement of the cervical spine. The progression of changes, since the initial detection of a mild limitation to moderate or severe condition varies, starting from 3 month to 4 years, with an average of 2 years. Fifty percent of young patients with DM for more than 5 years develop moderate or severe limitation.

There are simple tests that help in its recognition. One is the “prayer sign”, where it is clearly impossible for the patient to oppose the palms together completely, without leaving a gap between the two; the magnitude will depend on the degree of the patient affectionation. The other is the “table top sign” where the patient is not able to completely extend his/her hand on a table’s surface: this makes the diagnosis of metacarpophalangeal contractures easier (Fig. 7.18) (Table 7.3) [27]. If both tests turn out positive, it is recommended to make a careful examination of each joint.

Fig. 7.18 Limited joint mobility. “table top sign”: the patient is not able to completely extend his/her hand on a flat surface



Table 7.3 Clinical signs for limited joint mobility (LJM)

Prayer sign	Table top sign
Evaluates the ability to oppose hands without leaving a space between them, allowing for the recognition of contractures in the metacarpophalangeal and interphalangeal proximal and distal joints	Determines the ability to completely extend palms on the table’s surface, allowing the recognition of metacarpophalangeal joint contracture

Table 7.4 Degrees of severity of waxy skin and limited joint mobility

Degree 0	No changes
Degree I	Waxy skin, no contractures
Degree II	Contractures in the flexion of both little fingers
Degree III	Bilateral compromise of fingers and wrists
Degree IV	Bilateral compromise of other fingers
Degree V	Bilateral compromise of fingers, wrists and other joints

Brink-Starkman classification

Even though, the prayer sign and the table top sign are widely recognized in literature as diagnostic tools, they are not present in all cases as a rule. For subclinical forms of the disease, goniometry is used which in case of being positive, confirm the association between flexion restriction of small joints of the hands and microvascular complications in patients with DM [28]. In terms of severity assessment, two different classification are used (Tables 7.4 and 7.5) [29].

Cutaneous biopsy is rarely used for the diagnosis of this syndrome. Histopathological findings consist of a normal epidermis and an excess amount of thickened and hyalinized collagen fibers [30].

With regards to the natural evolution, after two decades of its acknowledgement, its incidence has experienced a substantial decrease, probably due to a better metabolic control. In 1998, the same physicians applying the same techniques they used

Table 7.5 Degrees of severity of waxy skin and limited joint mobility

Degree I	Waxy skin
Degree II	Contractures in the flexion of both little fingers
Degree III	Contractures in the flexion of other fingers
Degree IV	Bilateral compromise of wrists
Degree V	Compromise of other joints



Fig. 7.19 Diabetic Scleredema. Thickness, diffuse, and symmetric skin induration of the upper back

in their description compared the initial findings and found that the frequency of LJM had decreased four times along with a dramatic decrease in other manifestations such as short stature. This important reduction in the frequency in kids and teenagers with DM over time was attributed to a better glycaemia and HbA1c monitoring and to new types and release systems of insulin [31, 32].

In the treatment of LJM, metabolic control is mandatory, in addition to physiotherapy and occupational therapy that can be helpful and yield variable results [33].

Diabetic Scleredema

It is a rare disorder that affects generally older than 40 year-old-male diabetic patients, with an approximate incidence of 2.5%. It is characterized by thickness and diffuse, asymptomatic and symmetric skin induration of the posterior neck and upper back, shoulders and arms, which confers an orange-peel appearance. Although less frequent, it may involve other parts of the body like the face, abdomen, thighs, and buttocks. In contrast to scleroderma, hands and feet are spared [34] (Fig. 7.19).

Nowadays three types of scleredema are described in literature: Type 1 is the classical form or scleredema adultorum of Buschke that mainly affects women and is typically preceded by an infectious process of upper airways most often due to *Streptococcus* which resolves spontaneously in contrast to Type 3, which is seen in

Table 7.6 Differences between scleredema diabeticorum and classical scleredema

	Scleredema diabeticorum	Classical scleredema
Gender	4:1 male/female	2:1 female/male
Age	Adults	
Previous infection	No	Yes; upper airways due to Streptococcus
Clinics	Insidious onset. Affects skin of the neck and upper back, although it may extend	Sudden onset. Affects skin of neck and upper back, localized in most of the cases
Retinopathy	Yes	No
Associations	Long standing T2DM, poorly controlled, Obese, insulin resistant patients. HT*, myocardial infarction	Rare
Evolution	Persistent	75% resolves spontaneously
Treatment	Generally unresponsive	None

HT* arterial hypertension

long-standing and poor-controlled T2DM, the so-called Scleredema diabeticorum, which differs from the classical or type 1 Scleredema in its predominance in men, it is not preceded by any infectious process and does not resolve spontaneously, besides it is associated with insulin resistant state and obesity (Table 7.6).

In order to make a correct classification and diagnosis, physicians should take a comprehensive clinical history of the patient, laboratory tests with complete blood count, glycaemia, HbA1c levels, etc. and a skin biopsy to confirm the diagnosis [35].

Microscopically, thickened and irregularly distributed collagen fibers, separated by clear spaces in which mucin is deposited, evidenced with Alcian Blue stain, at the reticular dermis can be observed. Sometimes, the increase of the dermis thickness can reach up to four times its normal size. Moreover, subcutaneous fat can be replaced by collagen fibers [36].

Although there is considerable uncertainty about its pathogenesis, one possibility is that hyperglycemia would act as a stimulant for fibroblast proliferation and synthesis of extracellular matrix components. Another hypothesis is that a poor glycemic control may lead to an increase in NEG of the collagen fibers. The accumulation of AGE-modified collagen, which in turn are more resistant to collagenases degradation, is responsible for the skin induration [37–39].

The treatment of SD continues to be a challenge, lacking a gold standard and large placebo controlled trials. Most of the reported cases, achieved variable results. The first therapeutic step is the intensification of the metabolic control, although there is no consensus regarding the correlation between glycemic control and the improvement of SD.

Colchicine has been used in cases of SD, due to its anti-inflammatory properties and to its ability to prevent collagen synthesis [40]. Lin et al. reported a case of an association between SD and eccrine gland loss with the subsequent anhidrosis of the affected area. After 8 month of treatment with allopurinol 100 mg/day a mild relief was noted by the patient but without changes related to the lack of sweating [41].

Fig. 7.20 *Left:* Non-diabetic control patient. Wrinkles after immersion in the water. *Right:* Diabetic patient without wrinkles after immersion in the water



Immunosuppressant drugs like cyclosporine, corticosteroids (CST) and methotrexate (MTX) are other therapeutic options. It is believed that MTX, apart from interfering in the glycation process, can decrease the production of connective tissue or mucin by the fibroblasts and other cells that are involved [42]. Another therapeutic modality could be radiation therapy, psoralen combined with ultraviolet A (PUVA) (accumulative doses of UVA, 120 J/cm²). Shazzad et al. report a case of a patient with SD treated with a combination of PUVA and MTX with a good results [43]. Recently very good response have been reported with UVA1 phototherapy and intravenous immunoglobulin G (IVIG) [44–47].

In our experience, although the small number of patients with SD we have observed, cutaneous lesions didn't improve with a good glycemic control and the therapeutic response to the different modalities described, has been refractory.

As mentioned previously, the diagnosis of thick skin syndrome is basically clinical and there are non-invasive methods of detection like ocular inspection, palpation, the prayer sign and the table top sign. There is another way to check it, which is by detecting cutaneous wrinkles on the finger pads [48]. The patient's hands are submerged in warm water at 42 °C for 30 min. In diabetic patients, no wrinkles on the finger pads are observed, contrary to what happens in the general population (Fig. 7.20). The mechanism by which these wrinkles diminish, is unknown, but it is thought that the cause of the thickening of this part of the skin could be multifactorial and that sympathetic autonomic neuropathy with an increase in the deep tissue turgor, keratin NEG with an increase in the epidermal thickness, and the alteration of the blood flow through the finger pads, participate.

Conclusion

The thick skin syndrome includes several cutaneous manifestations. Many of them are associated with comorbidities, or in association with other syndromes and should be differentiated from other conditions such Scleroderma.

LJM is an often-missed Diabetes marker that in severe cases may interfere with daily life's routine. It's importance lies in the fact that it can be used as a surrogate sign for development of diabetic microvascular complications.

Moreover, it's association with higher risk of accidental falls, diabetic foot ulcers and upper extremity impairments have been reported many times in the literature.

Fortunately, there is an important decrease in its frequency due to a better glycaemia and HbA1c monitoring and the new types and release systems of insulin. Thus, metabolic control in patients with skin thick syndrome is mandatory.

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