Review

Occurrence of tendon pathologies in metabolic disorders

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Abstract

This article reviews the pathogenetic role of metabolic disorders, which are of paramount relevance to the progression of tendon damage. In diabetes, the prevalence of rheumatological diseases is high, mainly because of the deleterious effects of advanced glycation end products that deteriorate the biological and mechanical functions of tendons and ligaments. In heterozygous familial hypercholesterolaemia, most patients develop Achilles xanthomatosis, a marker of high risk for cardiovascular disease caused by cholesterol deposition in the tendons. Tendon degeneration has also been observed in non-familial hypercholesterolaemia. Monosodium urate crystal deposition in soft tissues is a hallmark of chronic gouty arthritis. In this group of diseases, the mobilization of cholesterol and uric acid crystals is presumably followed by low-grade inflammation, which is responsible for tendon degeneration. Adiposity may contribute to tendon disorders via two different mechanisms: increased weight on the load-bearing tendons and systemic dysmetabolic factors that trigger subclinical persistent inflammation. Finally, tendon abnormalities have been observed in some rare congenital metabolism disorders such as alkaptonuria.

Key words: tendinopathy, diabetes mellitus, hypercholesterolaemia, hyperuricaemia, obesity.

Introduction

Progress in research has increased our understanding of tendon physiology and the pathogenetic pathways of chronic tendinopathies. Trans-membrane proteins called integrins connect the extracellular collagen fibrils to the cytoskeleton of tenocytes. Under normal exercise conditions, fibril stretching activates subcellular biology, releasing growth factors and triggering the subsequent synthesis of extracellular matrix components, predominantly proteoglycans and collagen neo-fibrils [1]. Homeostasis is maintained by the simultaneous production of appropriate metalloproteinases (MMPs), which counteracts the anabolic effects of growth factors [2]. When fibril stretching is increased but remains within the physiological window, synthesis prevails over degradation and tendon hypertrophy occurs. However, when repeated loading deviates from normal limits by differences in magnitude, frequency, duration and/or direction, overuse injury may develop. An aberration in proteoglycan metabolism is likely to drive the pathogenesis of tendon damage, as excess proteoglycan production leads to water retention and pressure from swelling. The biochemical adaptation to these changes involves the production of pro-inflammatory agents such as IL-1β, TNF-α and prostaglandins (PG). Some of the detrimental effects of these pro-inflammatory cytokines include enhanced production of MMPs that cause matrix destruction.

The following pathogenetic cascade is very complex and involves tenocyte apoptosis, hypoxia, neovessel proliferation, smoldering disorganized fibrillogenesis, collagen fibre disruption and hyaline and mucoid degeneration, usually with an absence of inflammation in the advanced stages [1–4].

Of note, the progression of the disease is characterized by substantial individual differences. Indeed, tendon integrity is disrupted at comparably high loads only in some individuals, and in a small subset of individuals, exposed to such environmental chemicals as fluoroquinolone antibiotics and statins, tendon integrity disruption can occur even within a normal mechanical load range [5]. Intrinsic and extrinsic factors, including genetics, age, drugs, hormones and blood supply, influence the biological milieu and tendon adaptation to mechanical loading.
In this context, the role of metabolic factors is of paramount importance. Clinical and experimental research shows that diabetes [6], obesity [7] and, to a lesser extent, hypercholesterolaemia [8], hyperuricaemia [9] and some rare congenital metabolism disorders (alkaptonuria, glucose-6-phosphatase deficiency and hypergalactosaemia) [10] are frequently associated with tendon degeneration, thus influencing the mechanical properties of tendons and even impairing the healing process after surgery. The aim of this review is to summarize the present knowledge on this topic and to analyse the mechanisms for the negative effects of these metabolic disorders.

A search of English language articles was performed in PubMed, Web of Knowledge (WOK) and EMBASE using the key search terms tendinopathy or tendon, combined with obesity, diabetes, hypercholesterolaemia, hyperuricaemia, alkaptonuria, glucose-6-phosphatase or hypergalactosaemia, independently. Bibliographies were hand searched to include any applicable studies that were not captured by our search. Articles were eligible if they provided specific information related to the correlation between tendon disease and metabolic disorders.

Diabetes

Clinical observations

Several rheumatological conditions complicate the clinical course of diabetes mellitus. For example, Dupuytren’s disease, characterized by thickening, shortening and fibrosis of the palmar fascia, and trigger finger (also called flexor tenosynovitis) have been found in 10–15% of subjects with diabetes versus 1% in non-diabetic controls (matched for age and sex). Similarly, carpal tunnel syndrome and shoulder adhesive capsulitis (frozen shoulder) have been reported in 11–25% and 10–20% of patients with diabetes, respectively. The prevalence of these conditions increases with the duration of both Type I and Type II diabetes and with poor glycaemic control [11–13]. Symptomatic rotator cuff tears (Fig. 1) are more commonly observed both in subjects with overt Type I or Type II diabetes [14, 15] and in those with high, yet normal, plasma glucose levels [16]. In asymptomatic diabetic subjects, an increased thickness of supraspinatus and biceps tendons and a significantly higher prevalence of tears have been found [17]. These observations are of clinical relevance because, as follow-up studies show [18], pain and functional limitation are likely to occur in a large percentage of people with asymptomatic tears at baseline. In addition, after surgical repair, subjects with diabetes show a restricted range of shoulder motion [19] and a higher incidence of retears [20]. These adverse outcomes can be related to the intrinsically poor quality of the tissue that is being repaired.

In the lower limbs, increased thickness and structural abnormalities of the plantar fascia and Achilles tendon have been observed in both Type I and Type II diabetes mellitus using sonography or magnetic resonance imaging [21–24]. These changes are more severe in patients with neuropathic complications and previous foot ulcers but can also be found in subjects without diabetic complications [25, 26]. Accordingly, reduced ankle joint range of motion, which may restrain the forward progression of the tibia on the fixed foot during the stance phase of walking, has been documented in patients with diabetes [27, 28]. This in turn results in prolonged and excessive weight-bearing stress under the metatarsal heads during the foot-floor interaction, which is thought to contribute to the development of foot ulcers in individuals with diabetes mellitus [28–30]. Imaging techniques, such as magnetic resonance imaging and the more widely used sonography, show that disorganized echotexture, focal hypoechoic areas and increased thickness of the tendons and ligaments are common in diabetic patients [21–24].

Histopathology

According to clinical observations, histopathology shows that joint capsules, ligaments and tendons lose their normal glistening white appearance. In the more affected portions, these structures become grey and amorphous, with poorly marked areas where diffuse, fusiform or nodular thickening may be observed. Electron microscopic investigation shows that collagen fibrils appear twisted, curved, overlapping and otherwise highly disorganised. There is an increased packing density of collagen fibrils, with a decreased number of fibroblasts and tenocytes per unit of surface area. The reduction of elastic fibres is consistent. Finally, the number of capillaries per unit of surface area, and therefore the arterial blood flow, is reduced, particularly in elderly subjects [31].

Pathogenesis

According to an accepted hypothesis, tendon damage in diabetes is caused by an excess of advanced glycation end products (AGEs; Fig. 2). AGEs form at a constant but slow rate and accumulate with time in the normal body. However, their formation is markedly accelerated in diabetes because of the increased availability of glucose.
A key characteristic of reactive AGEs is their ability to form a covalent cross-link within collagen fibres, altering their structure and functionality [13].

Essentially, collagen cross-links can generate via two different pathways: (i) the enzymatically driven, hydroxylysine-derived aldehyde pathway and (ii) the non-enzymatic glycation or oxidation-induced AGE cross-link [32–34]. As opposed to the beneficial effects on collagen strength bestowed by enzymatic cross-links, AGE cross-linking is generally thought to cause deterioration of the biological and mechanical function of tendons and ligaments [35]. In fact, once formed, AGEs can be degraded only when the protein they are linked to is itself degraded. Therefore the most extensive accumulation of AGEs will occur in tissues with low turnover, such as cartilage, bone and tendon.

Other major features of AGEs relate to their interactions with a variety of cell-surface AGE-binding receptors (i.e. AGE-R1, AGE-R2, AGE-R3 and RAGE) [36]. Ligand engagement of AGE-binding receptors activates several critical molecular pathways and triggers a number of effects, including pro-oxidant events, via generation of reactive oxygen species, and further pro-inflammatory events via NF-κβ signalling [37]. This in turn accelerates AGE cross-linking in collagen fibres and leads to sustained upregulation of pro-inflammatory mediators and to a dysfunctional cell phenotype [38, 39].

Further AGE negative effects include (i) the modification of short-lived proteins, such as the basic fibroblast growth factors, which is followed by markedly decreased mitogenic activity; (ii) intracellular AGE formation, which leads to the quenching of nitric oxide and impaired growth factor signalling and (iii) enhanced apoptosis via oxidative stress, increased caspase activities and/or extrinsic signalling through pro-apoptotic cytokines [40, 41].

Tendon damage ensues from these complex pathways. In addition to degeneration, tendon and ligament thickness increases as expression of the abnormal storage and the architectural distortion of collagen layers [42, 43]. From the biomechanical point of view, several studies have demonstrated that collagen toughness and stiffness and the elastic modulus are strongly influenced by AGE cross-link formation [44, 45].

In addition to the AGE-mediated pathogenetic mechanism, hyperglycaemia in itself may lead to alterations in the redox environment, specifically in the polyol pathway, resulting in increased intracellular water and cellular oedema. Microvascular disease may lead to tissue

**Fig. 2** Common pathogenetic pathways of tendon damage in metabolic disorders.

Diabetes and obesity are the best-known factors of tendon degeneration. Hypercholesterolaemia and hyperuricaemia are frequently associated. The ensuing collagen cross-linking, tenocyte apoptosis and release of inflammatory cytokines lead progressively to tendon damage.
hypoxia with overproduction of oxygen free radicals, creating a permissive apoptotic environment [46].

It is not surprising that these metabolic abnormalities may be present in the early clinical stages of Type II diabetes [24]. Indeed, while Type I diabetes is diagnosed at an early stage because of a relatively acute clinical onset characterized by extreme elevations in glucose concentrations, Type II diabetes is usually diagnosed later, when many patients already exhibit chronic complications. Certainly these subjects could have glucose intolerance or mild Type II diabetes mellitus for a significant length of time before diabetes is clinically diagnosed.

The ultrasonographic finding of reduced neovascularization inside the degenerated tendons [47] is consistent with several observations that show decreased vascular endothelial growth factor levels and reduced angiogenesis in different experimental and clinical diabetic conditions [48–50]. This finding adds to our knowledge about the pathogenesis of diabetic tendinopathy. The downregulation of this factor can limit vessel and nerve ingrowth and can also affect neurogenesis, reducing neural progenitor cell recruitment, axonal outgrowth, neuronal survival and the proliferation of Schwann cells [51]. The association between reduced nerve proliferation inside tendons and sensitive neuropathy reduces pain perception. Consequently, diabetic patients, who lack distress signals, may excessively exercise their tendons, making them prone to overuse damage.

Hypercholesterolaemia

Clinical observations and histopathology

Heterozygous familial hypercholesterolaemia (HeFH) is caused by a defect in the catabolism of low-density lipoprotein (LDL), usually resulting from the inheritance of a mutant LDL receptor gene. Untreated HeFH is associated with a high mortality and morbidity from coronary heart disease, but when intensive treatment occurs early, life expectancy can be substantially improved.

Most patients with HeFH develop tendon xanthoma, mainly in the Achilles tendon (Fig. 3), which becomes increasingly common from the third decade onwards. The early detection of xanthoma is thus exceptionally important. Unfortunately, in several cases the clinical diagnosis is difficult because the nodules are too small to be detected or because the pain is ascribed to an unspecific tenosynovitis. In this regard, Beeharry et al. [52] have shown that episodes of Achilles tendon pain lasting more than 3 days are very common in patients with HeFH, even in the absence of apparent xanthomatosis. Therefore these authors suggest that serum cholesterol measurement in young patients presenting with a painful Achilles tendon is mandatory because it could allow the early diagnosis of HeFH.

Sonography is very useful for detecting tendon abnormalities (Grade 1: minor sonostructural changes; Grade 2: diffuse heterogeneous echo pattern; Grade 3: focal hypoechoic lesions). Sonography can visualize xanthoma located deep within the tendon that cannot be detected by palpation. Tsouli et al. [53], in a large case-control study, found a Grade 2 Achilles tendon echostructure in 30 of 80 patients and a Grade 3 in 8 of 80 patients. The thickness of the tendon was increased in patients with HeFH compared with controls in proportion to the echostructural abnormalities. Only patients with minor sonographic changes showed significant reductions in Achilles tendon thickness after statin treatment (from 4.9 ± 0.55 mm to 4.5 ± 0.43 mm, P < 0.01), whereas patients with Grade 2 and Grade 3 abnormal echostructures remained unchanged, and no significant reduction was observed [53]. Exacerbations of Achilles tendinopathy can occur when statin treatment is started and is attributable to the rapid lowering of cholesterol [53]. The condition would seem to be akin to the exacerbations of gout that occur when allopurinol treatment begins and the serum uric acid level decreases rapidly. The mobilization of cholesterol, like that of uric acid crystals, presumably provokes an inflammatory cell reaction [52, 54].

Histologically, cholesterol deposition is observed both extracellularly and inside histiocytes and other foam cells, which show numerous intracytoplasmic lipid vacuoles, lysosomes and myelin figures. An inflammatory cell infiltrate and a fibrous reaction may be associated.

The deleterious effects of non-familial hypercholesterolaemia on tendons have been debated. Some studies have shown that in patients with Achilles tendon rupture, the concentration of serum lipids is higher than in controls [8] and that the esterified fraction of cholesterol is elevated in biopsies from degenerated Achilles tendons [55]. However, in a study comparing the sonographic characteristics of Achilles tendon in subjects with familial hypercholesterolaemia with those of patients with non-familial hypercholesterolaemia, abnormal patterns were noted only in subjects with familial hypercholesterolaemia [56]. Similarly, conflicting results have been reported for rotator cuff tendons. According to Abboud et al. [57], total cholesterol, triglycerides and LDL cholesterol concentrations
are higher in patients with rotator cuff tendon tears, and their high-density lipoprotein cholesterol is lower than that of the control group. However, these results are challenged by the findings of Longo et al. [58] who found no differences in the lipid profiles of subjects who underwent surgery for rotator cuff tears or meniscectomy.

Pathogenesis

The pathogenetic mechanisms leading to the formation of xanthoma have been elucidated. LDL derived from the circulation accumulate into tendons and become oxidized. Oxidized LDL (oxLDL) contains various oxidatively modified phospholipids and cholesterols, isoprostanes, oxidized arachidonoyl residues, lysolipids and lysophosphatidic acid [59]. As might be expected from this, the effect of oxLDL on inflammatory cells is complex, dependent on the concentration of the particles and the extent and mode of oxidation [60]. It is worth mentioning that specific oxidative-truncated phospholipids rapidly enter nucleated cells, travel to the mitochondria and initiate the mitochondrial dependent pathway to apoptotic cell death [59].

Artieda et al. [61] have shown that macrophages from HeFH patients with tendon xanthoma have a high predisposition to form foam cells after oxLDL overload than those from HeFH patients without xanthoma. Moreover, macrophages from HeFH patients exhibit a differential gene expression profile characterized by increased plasma tryptase, TNF-α, IL-8 and IL-6 expression [61]. In a familial form of massive tendon xanthomatosis, Matsuura et al. [62] showed decreased high-density lipoprotein-mediated cholesterol efflux associated with genetic variation in the reverse cholesterol transport and LDL oxidation pathways [63]. Interestingly, xanthomatosis and atherosclerosis share these genetic abnormalities and therefore may result from the same pathophysiological mechanisms. This explains why tendon xanthoma is a marker of high risk for cardiovascular disease.

The mechanism by which non-familial hypercholesterolaemia subjects develop damaged tendon tissues is unknown. It has been hypothesized that microscopic cholesterol deposition inside the tendons, undetectable with the usual imaging techniques, could initiate and maintain a low-grade, persistent inflammation; this, in turn, may be responsible for chronic tendon degeneration and biomechanical changes, as shown by experimental studies of the patellar and rotator cuff tendons of hypercholesterolaemic knockout mice [64].

Hyperuricaemia

Clinical observations and histopathology

Monosodium urate monohydrate (MSU) crystal deposits (called tophi from the Latin word tofus, porous stone) in joints (cartilage, synovial membranes and tendons) and in other soft tissues are hallmarks of chronic gouty arthritis. In inter-critical periods, they appear as indolent nodules, which are difficult to differentiate from rheumatoid nodules and other types of subcutaneous nodules. Gout is diagnosed with certainty upon the finding of MSU crystals. Evaluated via polarized light microscopy, these crystals are typically needle-shaped and negatively birefringent, whereas calcium pyrophosphate dehydrate crystals (pseudogout) are weakly positively birefringent and more rectangular than MSU crystals. Specific diagnostic sonographic features include a hyperechoic, irregular band over the superficial margin of the articular cartilage described as a double contour sign; hypoechoic to hyperechoic, inhomogeneous material surrounded by a small anechoic rim represents tophaceous material [65]. An increase of blood flow surrounding MSU deposits using power Doppler has been described as an indicator of inflammatory activity [66]. The histopathological equivalent of the anechoic rim is the tophus wall, formed by macrophages, lymphocytes and large foreign body giant cells.

Gouty arthritis is predominantly a disease of the lower extremities. The toe is the most common site of initial involvement, followed in order of frequency by the ankles, heel, knee, wrists, fingers and elbows. Gouty bursitis also occurs, and the pre-patellar and olecranon bursae are the most commonly involved sites.

Interestingly, urate deposits in tendons and the synovium and the prevalence of patellar and Achilles enthesopathy (15% vs 1.9%; \( P = 0.0007 \)) occur more frequently in subjects with asymptomatic hyperuricaemia than in asymptomatic, normouricaemic individuals [9, 67].

Pathogenesis

The mechanisms of MSU deposition have been elucidated. In vitro studies show that when serum uric acid levels reach approximately 7 mg/dl, MSU crystals begin to precipitate. However, the in vivo threshold of precipitation depends on several biological factors. Traumas, mechanical stress and lower temperature favour MSU precipitation and explain the frequent localization of tophi in the first metatarsal–phalangeal joint and the helix of the ear. Poor blood supply also plays a role, as shown by the preferential deposition in tissue with little or absent vascularization (tendon, ligaments and cartilage). Other factors that can contribute to the decreased solubility of sodium urate and crystallization are alterations in the extracellular matrix, which lead to an increase in non-aggregated proteoglycans, chondroitin sulfate, insoluble collagen fibrils and other molecules in the affected joint [54].

Chronic cumulative urate crystal deposition leads to tophi formation. Tophi are usually walled off, but microtrauma-related changes in the size and packing of the crystal may loosen tophi from the organic matrix. This activity leads to crystal shedding and facilitates crystal interaction with residential inflammatory cells, leading to an acute gouty flare. A variety of inflammatory mediators, such as IL-1β, chemokines and PGs, are released. A number of factors have been identified to explain the self-resolution of the acute attack: crystal dissolution or coating with proteins, neutrophil apoptosis, the inactivation of inflammatory mediators and the release of
anti-inflammatory mediators. As for cholesterol, it is highly probable that microscopic deposition of MSU crystals can occur in tendons, followed by low-grade persistent inflammation that causes chronic tendon degeneration [67].

**Obesity**

**Clinical observations**

Adiposity is a well-known risk factor for tendinopathies [7]. Load-bearing tendons, such as the Achilles and patellar tendons, are more frequently affected, and plantar fasciitis is commonly observed [28, 68–70]. Recently adiposity has also been recognized as a risk factor for tendinopathy in non-load-bearing tendons. A positive correlation has been found between increasing adiposity and rotator cuff tendinopathy [71], and obesity has also been shown to have a negative impact on the functional outcomes after arthroscopic rotator cuff repair surgery [72].

Further studies have shown that the probability of tendon abnormalities is higher in males with an increased waist circumference (74% in subjects with a waist circumference >83 cm vs 15% in males with a waist circumference <83 cm). In a population-based study, asymptomatic Achilles tendon pathology was associated with central fat distribution in men and peripheral fat distribution in women. It has been hypothesized that in men Achilles tendon pathology is linked to metabolic syndrome, whereas in women oestrogens may prevent the central accumulation of adipose tissue [73]. In another study, Gaida et al. [74] observed that subjects with symptomatic Achilles tendinopathy had higher triglyceride levels ($P = 0.039$), lower HDL cholesterol (HDL-C) ($P = 0.016$), higher triglyceride/HDL-C ratio ($P = 0.036$) and further elevated apolipoprotein B concentration ($P = 0.017$) compared with controls matched for gender, age and body mass index. Typically this pattern of dyslipidaemia is displayed by individuals with insulin resistance and is common in those with metabolic syndrome.

**Pathogenesis**

Prevailing hypotheses of tendon damage in obese subjects are associated with two different mechanisms: the increased yield on the load-bearing tendons and the biochemical alterations attributed to systemic dysmetabolic factors.

Indeed, weight-bearing tendons are exposed to higher loads with increasing adiposity, and the higher loads lead to overuse tendinopathy. Alternatively, the systemic hypothesis is based on studies showing that the association with adiposity is equally strong for the non-load-bearing and load-bearing tendons [74].

Adipose tissue is now recognized as a major endocrine and signalling organ. In obese subjects, adipose tissue releases bioactive peptides and hormones; the adipokinesome includes a full range of proteins such as chemerin, lipocalin 2, serum amyloid A3, leptin and adiponectin [75]. These proteins influence several activities in various mesenchymal cell phenotypes (tenocytes, chondrocytes and osteocytes), which may directly modify tendon structure. In particular, adipokines are able to modulate cytokines, prostanoids and MMP production [76, 77].

The persistently raised serum levels of PGE2, TNF-$\alpha$ and LTB4 observed in obesity and in subjects with impaired insulin sensitivity provide supplementary evidence that a systemic state of chronic, subclinical, low-grade inflammation is present in these conditions and may act as a prolonged disruptor of tendon homeostasis [78–81]. Moreover, the migration of immune cells, such as macrophages and mast cells, into adipose tissue is associated with a decrease in the circulating levels of these cells. As a consequence, the release of pro-fibrotic factors, such as TGF-$\beta$, is reduced, and this may have a detrimental effect on tendon healing, especially if the production of Type I and III collagen is also reduced [81, 82]. In subjects with visceral fat, the cluster of metabolic abnormalities is considered the consequence of insulin resistance [73]. Elevated insulin concentrations fail to stimulate increased glucose uptake into muscle, which leads to fasting hyperglycaemia, impaired glucose tolerance and eventually Type II diabetes mellitus. Therefore AGE formation is increased in obesity.

So, it is evident that obesity and diabetes share common pathogenetic pathways characterized by increased cross-linking between collagen fibrils mediated by AGEs and low-grade inflammation, both of which amplify the deleterious effect of tendon overuse (Fig. 2) [73]. Interestingly, ultrastructural studies demonstrate that genetically obese Zucker rats have a relative prevalence of larger collagen fibrils as a consequence of excessive covalent cross-links. Consequently, the fibril diameter shows unimodal distribution, in contrast with the bimodal pattern observed in regularly exercised lean animals. Because thin fibrils confer greater elasticity to tendons, the relative lack of these fibrils in obese animals could be responsible for increased stiffness and microruptures as a consequence of excessive exercise [83].

**Congenital metabolism disorders**

Tendon abnormalities have also been described in some inherited metabolism disorders.

Alkaptonuria is a rare inborn metabolic disease caused by a deficiency of the enzyme homogentisic acid oxidase, which is involved in the metabolism of homogentisic acid, a metabolic product of the aromatic amino acids phenylalanine and tyrosine. The homogentisic acid accumulates in the fibrillar collagens and binds to them irreversibly, becoming polymerized to form a dark pigment, which confers a characteristic ochre or yellow appearance to connective tissues (ohcronosis). The accumulation of homogentisic acid inhibits collagen cross-linking, leading to a reduction in the structural integrity of collagen, thus increasing the likelihood of spontaneous rupture [84].

By the fourth or fifth decade, the disease usually progresses from simple alkaptonuria (characterized by dark urine caused by homogentisic acid and without symptoms) to alkaptonuric arthropathy in approximately 30%
of subjects [10]. Achilles and patellar tendons are more frequently affected; they appear yellow or brown, defibril-lated and degenerated, mainly at the site of the tendon’s insertion into bone (enthesis). Ruptures, frequently spontaneous, occur in about 20–30% of cases [85, 86]. Hyperuricaemia is a well-known consequence of glucose-6-phosphatase deficiency, the enzymatic abnormality that characterizes glycogen storage disease. Gouty tenosynovitis is a very rarely occurring manifestation of this congenital disease [87].

Finally, for the sake of thoroughness, it must be noted that increased tendon collagen cross-linking by non-enzymatic galactosylation has been observed in cases of congenital hypergalactosaemia. However, to our knowledge, no clinical tendinopathies have been described in this disease [88].

Conclusions

Ample evidence shows that metabolic disorders have deleterious effects on tendons and favour tendon degeneration. This observation has relevant clinical implications. Subjects with diabetes or who are overweight, particularly young people practicing sport activities, should maintain adequate dietary regimens and pharmacological treatments to achieve a proper body weight and metabolic control. Because physical exercise is an important therapeutic measure, the program of physical activity should be individually prescribed; indeed, an excess of exercise could favour tendon degeneration.

Subjects who participate in sports that selectively overload some tendons (e.g. running) should be monitored more frequently. Orthopaedic surgeons must be aware that when a dysmetabolic condition is present, the healing of fractures is delayed, the osseointegration of autologous bone grafts is sometimes unsatisfactory and post-surgery complications are more frequent. Therefore the treatment of diabetes, obesity, hypercholesterolaemia and hyperuricaemia before and after orthopaedic surgery is mandatory to minimize negative outcomes and to reduce the length of hospital stay.

In subjects referred to orthopaedic observation for tendinopathies or tendon tears, the possibility of undiagnosed hypercholesterolaemia, diabetes or glucose intolerance should be considered. Finally, the treatment of dysmetabolic risk factors could be an additional strategy to slow the progression of asymptomatic tendinopathies.

Rheumatology key messages

- Tendon degeneration is often caused by metabolic disorders (e.g. diabetes, hypercholesterolaemia, hyperuricaemia and obesity).
- Proper control of diabetes, obesity, hypercholes-terolaemia and hyperuricaemia could minimize negative effects on tendons.
- Hypercholesterolaemia, diabetes or glucose intolerance should be considered when treating subjects affected by tendinopathies.

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Clinical vignette

T-cell lymphoma manifesting as a uvular mass

A 54-year-old woman had a 5-year history of RA on regular medication presented with a 3-month history of swelling in her throat and muffled voice. Physical examination revealed a uvular mass (Fig. 1A). CT showed an ill-defined mass in the oropharynx (Fig. 1B) and small enhancing cervical lymph nodes. Oropharyngeal biopsy identified the mass as a malignant T-cell lymphoma. Whole-body PET showed increased fluorodeoxyglucose uptake in the oropharynx and cervical lymph nodes. She achieved partial remission after three courses of cyclophosphamide + hydroxydoxorubicin + oncovin + prednisone (CHOP) chemotherapy but died of sepsis before the fourth course.

Several autoimmune diseases, including SS, SLE, cryoglobulinemia and RA, are associated with an elevated risk of lymphoma development [1]. Peripheral T-cell lymphoma is aggressive with a high relapse rate despite the currently available chemotherapies. More than half of extranodal head and neck lymphomas occur in Waldeyer’s ring, and those expressing T-cell markers arise predominantly in the paranasal sinuses and nasal cavity. Oropharyngeal involvement from peripheral T-cell lymphoma is extremely rare.

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