British Medical Bulletin, 2016, 1–20
doi: 10.1093/bmb/ldv054

Invited Review

Hormones and tendinopathies: the current evidence

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Accepted 30 October 2015

Abstract

Background: Tendinopathies negatively affect the quality of life of millions of people, but we still do not know the factors involved in the development of tendon conditions.

Sources of data: Published articles in English in PubMed and Google Scholar up to June 2015 about hormonal influence on tendinopathies onset. One hundred and two papers were included following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Areas of agreement: *In vitro and in vivo*, tenocytes showed changes in their morphology and in their functional properties according to hormonal imbalances.

Areas of controversy: Genetic pattern, sex, age and comorbidities can influence the hormonal effect on tendons.

Growing points: The increasing prevalence of metabolic disorders prompts to investigate the possible connection between metabolic problems and musculoskeletal diseases.

Areas timely for developing research: The influence of hormones on tendon structure and metabolism needs to be further investigated. If found to be significant, multidisciplinary preventive and therapeutic strategies should then be developed.

Key words: hormones, tendon problems, tendinopathy, hormonal imbalance, diabetes

Background

Tendinopathies negatively impact the quality of life of millions of people. Despite their increasing diffusion and scientific research on this topic, we still do not understand the factors involved in the development of tendon conditions. In humans, the natural history of tendinopathy is difficult to define, as, by the time patients become symptomatic; from a biological and histopathological view point, the condition is already long standing.[1] Several animal models have been developed, but none replicates in full the behavior and features of human tendinopathy.[2]

Several mechanisms have been identified in the pathogenesis of tendinopathy.[3]

A rapid change or a sudden increase of the loading forces acting on the tendons can cause repeated microtraumas[4,5] and, in the long run, can lead to tendinopathy. Also, disuse of tendons can lead to intratendinous changes compatible with a histopathological diagnosis of tendinopathy in the same way as overuse.[6] We still do not understand why similar levels of tendon strain result in tendinopathy in some individuals but not in others. We know that the genetic background of the affected individuals can affect their susceptibility to tendon injury,[7] and a genetic component has been implicated in tendinopathy of the Achilles[8,9] and rotator cuff tendons.[10–12]

Inherited genes or gene variants make some individuals more susceptible to these conditions, but the increasing prevalence of metabolic disorders in the past few years prompts investigation of the possible connection between metabolic problems and musculoskeletal disease.[11,13] Tendons are formed by mesenchymal-derived fibroblast-like cells (tenocytes) surrounded by a complex network of extracellular matrix (ECM) formed by collagenous components, mainly by collagen type I (CICP; >95%) and other types of collagens (type III and V), proteoglycans (PG), fibronectin (FBN) and elastin.[1,14] Tenocytes play a major role in the synthesis of all these components, especially collagen fibers, that drive biomechanical properties of the tendon structure.[15] Moreover, tenocytes play an important role in regenerative response after traumatic injury or spontaneous degeneration.[16] All these cellular and extracellular components are targeted by circulating factors such as growth factors, cytokines and hormones. Humans and animals develop under the physiological control of hormones; different soft tissues and bone diseases are associated with hormone imbalance because of the alteration of biological pathways and the loss of cellular homeostasis control.[17] In addition, some biomechanical properties of the musculoskeletal system seem to be affected by hormonal diseases.[13] Recently, many studies tried to explain this association; today, it is not clear how circulating hormones can act on tendons and which is the link between hormonal and metabolic diseases and the development of tendinopathy.

To our knowledge, no systematic review of such studies has been conducted to date. We therefore set out to ascertain whether there is published evidence on whether and how hormones modify tendons and their metabolism.

Methods

The review and its procedures were organized, conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] Our PRISMA checklist is presented in an online supplement (Fig. 1). We wished to try and ascertain whether:

(a) hormones modify the structure of tendons
(b) endogenous hormones exert an influence on the development of tendinopathies
(c) metabolic disorders exert adverse effects tendons

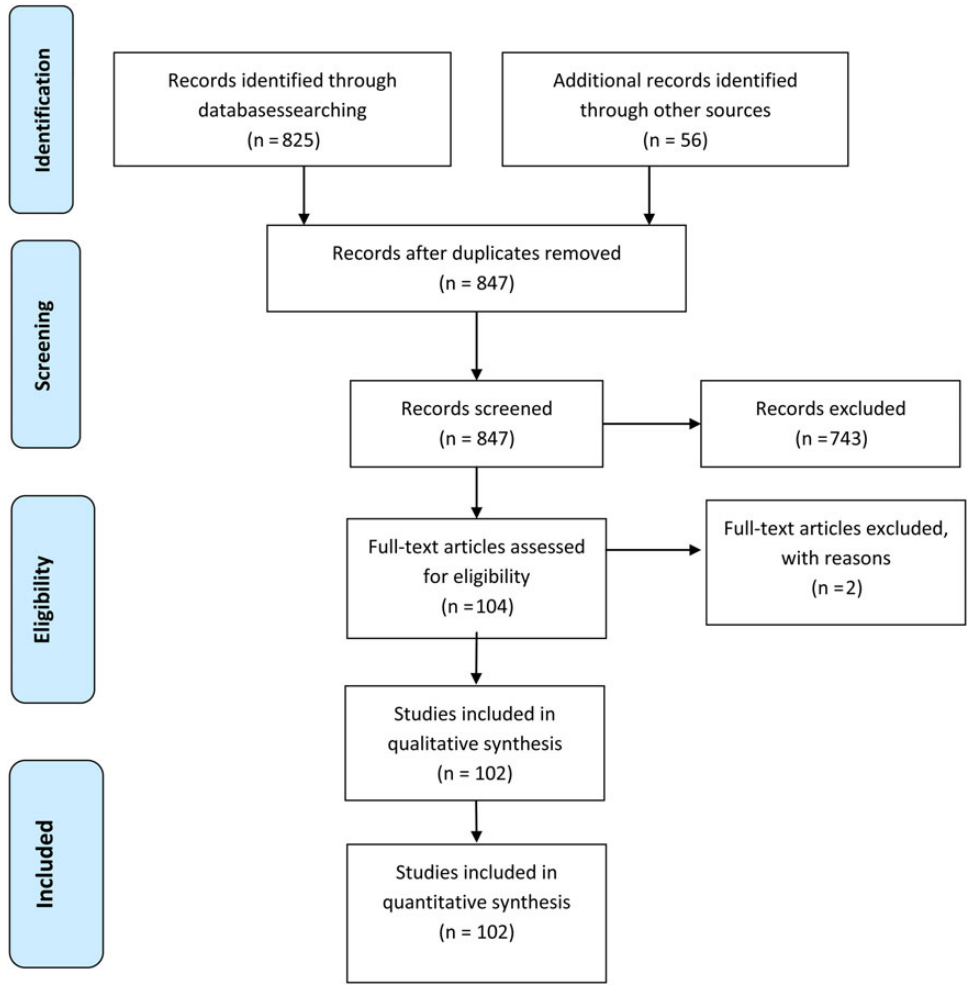

Fig. 1 PRISMA 2009 flow diagram.

Source of studies and search strategy

We performed a systematic search (up to June, 2015) in the PubMed and Google Scholar electronic databases of articles assessing the association between hormones and tendinopathies published in English only. The search strategy covered all the hormones and their association with the development of tendon pathology, including tendinosis, tendinitis and tendinopathy. In addition, considering that insulin deficiency and diabetes produce marked imbalances in several metabolic pathways, we also searched for the association between diabetes and tendon conditions. In the search strategy, we used various combinations of the following key terms and MesH terms: tendinopathies, tendinitis, tendons, hyperthyroidism, hypothyroidism, thyroid, thyroid hormones, diabetes, diabetic pathology, hyperglycemia, glicemia, Cushing, cortisol, estrogen, testosterone, growth hormone (GH) and growth hormone. We only considered for inclusion in the present review published articles that had considered the association between hormones and tendinopathies in animal or human models, *in vitro* or *in vivo*. Case reports, editorials, technical notes and narrative review articles were excluded.

Study selection and eligibility criteria

Two orthopedic residents performed the search and evaluated the articles independently. A researcher experienced in systematic reviews solved cases of

doubt. At the beginning of the procedure, each examiner read the abstracts of all the articles, selected the relevant ones according to inclusion and exclusion criteria previously determined, and then compared the results with the other examiner. After 3 weeks, the same studies were read again to establish the agreement of the researchers on the selection. No disagreement was observed among the investigators.

Data collection

One reviewer extracted the data from the full-text articles to Excel spreadsheet structured tables to analyze the study in a descriptive fashion. The second researcher independently double checked the extraction of primary data from all the articles. Doubts and inconsistencies were followed and solved by discussion. The following information was extracted from articles: type of model (animal or human), methods (*in vivo* or *in vitro*), population, methods and results.

Results

After our initial literature search, a total of 847 potentially relevant citations were identified. After the first inspection of the title and the abstracts, 743 were not included, because they did not investigate the association between hormones and pathogenesis of tendinopathies or because they reported about the use of hormones or hormone derivatives as therapeutic agents for tendon diseases. In addition, some of the excluded studies did not report the presence of a control group. A total of 102 articles were eventually included in the present review. All of them used different models and different protocols, making statistical data analyses impossible. Study selection, retrieval and inclusion and exclusion reasons are showed in the flowchart below (Fig. 1). The number of the reference, the methods and the data collected from the included articles are shown in the tables.

Discussion

Hormones affect tendons from a morphological and functional point of view. *In vitro* and *in vivo* studies, conducted in animals or in humans, have shown that subjects with hormonal imbalances present a reduction of the structural homogeneity of the tendons and an alteration of their ability to withstand mechanical stress. Influences on tendons vary according to the hormone.

Insulin and diabetes

Diabetes mellitus is caused by impairment of insulin action (either through a lack of its production or by an incorrect function of insulin receptors in peripheral cells), resulting in failure to control circulating glucose levels.

The associations between imbalance of the insulin pathway, diabetes and the onset of tendinopathies were investigated through *in vitro* and *in vivo* studies, in animals and in humans.

Animal studies involved rats, rabbits, canine and porcine tendons.

In vitro studies on animal tenocytes clarified the biochemical and histological pattern of tendons of diabetic patients. One of the main assessment is that during diabetes the impact of glycation on the joints is stronger on the tendon rather than the bone.[19] At a humoral level, higher levels of interleukin-1 beta (IL-1-β) and advanced glycated endproducts (AGEs) have been showed in tendons of diabetic patients;[20] AGEs and oxidative stress mediators such as H_2O_2 can directly induce cross-linking of collagen and formation of new covalent stabilizing bonds[21] influencing thermal stability of tendons[22] and ending in modifications of their microstructural organization.[23–27] The effects of AGEs on cells, such as the increased activity of the cross-linking transglutaminase (Tgase) enzymes, can also contribute to the genesis of calcification in diabetic tendons.[28] Tumor necrosis factor alpha (TNF-α) and chronic inflammation increase and high glucose concentration upregulates the expression of metalloproteinases MMP-9 and MMP-13 in tendons[29] which are more susceptible to injury and tears with an impaired tissue healing and remodeling.[30] Alterations in proliferative, angiogenic and inflammatory processes occur in the diabetic state,[31] with a stronger production of nitro derivates and an increased expression of

vascular endothelial growth factor (VEGF).[32] Diabetes determines an impaired tenocytes differentiation[33] with an important dysregulation of inflammatory and growth mediators and proteoglicans production[34] in injured tendons.[35,36]

At histology, the tendons of diabetic animals showed a loss of tissue viscoelasticity,[37] less fibrocartilage and organized collagen and an increased AGE deposition at the bone–tendon interface.[38] Diabetic collagens fibers are poorly organized[39,40] and larger than normal[41] and show higher degrees of polymerization because of increased intra- and inter-molecular interactions. Moreover, tendinopathic tendons in diabetic patients have less amount of fibroblast proliferation and lymphocyte infiltration.[42]

Only one study conducted on rabbit Achilles tenocytes *in vitro* showed that the glycated tendons have an increased maximum load, stiffness, Young's modulus of elasticity and toughness indicating that glycation increases the matrix stiffness in the tendons.[43] The other studies underline the presence of twisted and curved collagen fibrils in tendons of diabetic patients with significant alterations in the ultrastructure of collagen.[44,45] Also if one of the first study assessed that the maximum strength of the tendons was increased after 10 days and even more after 30 days of diabetes,[46] however recent researches demonstrate that the biomechanics in diabetic patients is altered compared with healthy subjects.[47] In particular, the tendons of diabetic animals are thickened, they have a reduced Young's modulus of elasticity[48,49] and tensile stress and a decreased resistance to the maximum load with a lower peak force for failure.[50,51] Tendon stiffness in diabetic tendons is generally decreased;[52,53] however, a more recent study suggests that the formation of AGEs can lead to an increase in collagen stiffness and a decrease in toughness, contributing to the weakness of tendon structure[54] (Table 1).

A few studies were conducted on human tenocytes *in vitro* and they showed that glycation takes place at different sites within the tendon and the collagenic structure.[55] High levels of extracellular glucose exert a marked effect on the cellular response to oxidative stress[56] and metabolic dysregulation, negatively affecting and damaging ultrastructure and biomechanics of tendons.[57,58] In particular, human tenocytes cultured with glucose show highly disorganized collagen fibrils[59] and a deep alteration by nonenzymatic browning.[60]

Glycated tendons also show an increase in maximum load, stress, strain, Young's modulus of elasticity and toughness because of the remarkable decrease in soluble collagen content and increase in insoluble collagen and pentosidine that causes collagen cross-linking[61] (Table 2).

In *in vivo* human studies, the incidence of tendinopathies, the functional properties of tendons and their healing process have been investigated. Tendinopathies occur more frequently in diabetic subjects compared with healthy controls with a greater risk of tendon ruptures in patients with type 2 diabetes, especially in the rotator cuff of young individuals. Diabetic patients have a greater risk of tendon tears requiring hospitalisation.[62] Reduced shoulder mobility[63] and great pain in diabetic patients[64] are often associated with an increased tendon thickness,[65] especially in biceps and supraspinatus,[66] and high subacromial IL-1β levels[67] because of the ongoing of the inflammatory process. Only one study found no ultrasonoghaphic differences in the ratio of tears of Rotator Cuff Tears between diabetic and nondiabetic patients.[68] Achillles tendon are strongly disarranged during hyperglycemia,[69] it seems especially in men younger than 44 years old.[70] Ultrasounds detect a poor structure in diabetic Achilles tendons:[71] they are thicker and they have an increased volume while, functionally, stretch distribution between muscle and tendon is altered during walking.[72]

In older subjects, tendinopathies are more frequently localized at the calcaneal insertion,[73] at the plantar fascia and Achilles tendon in the presence of reduced flexion-extension of first metatarsophalangeal joint,[74] possibly related to concomitant neuropathy and Charcot's foot,[75] with clinically positive Abadie's sign.[76] Asymptomatic sonographic abnormalities can be identified at these sites.[77,78] On the other hand, there are no significant structural changes in the patellar and quadriceps tendons in diabetic patients.[79]

It is known that diabetes mellitus is associated with tendon calcifications and reduced range of motion. In addition, diabetic patients have a reduced

Table 1 Insulin and diabetes: *in vitro* studies on animals

Number of reference	Model	Results
19	Achilles tendons from rabbits, and femur and tibia from rats were subjected to *in vitro* glycation	The impact of glycation was significant on the tendon but not on the bone
20	Diabetic rats analyzed for tendon and aortic collagen	The amount of AGE in tendon collagen of diabetic rats significantly increases
21	Rabbit forelimb tendons incubated with glucose	Significant increases in glycosylated tendons compared with controls, indicating the formation of new covalent stabilizing bonds
22	Tenocytes from rat tail tendons cultured *in vitro*	H_2O_2 formation influences thermal stability of tendons
23	Shoulder tendons of healthy control and hyperglycemic rats 8 weeks after induction of hyperglicemia	Diabetes increases chronic inflammation, TNF-a, IL1-β and AGEs in the tendons
24	Rat tail tendons incubated	Soluble ages can directly induce cross-linking of collagen
25	Rat tail tendons incubated in glucose *in vitro* and tendons implanted *in vivo* into diabetic rat peritoneal cavity	There is a role of H_2O_2 in cross-linking in diabetes
26	Rat tail tendon collagen for collagen cross-linking evaluation	Increased formation of glycoxidation products and cross-liking of collagen by glucose *in vitro*
27	Tail tendons from streptozocin-diabetic rats	Cross-links are in an unknown, nonreducible form in tendos from diabetic animals
28	Primary porcine tenocytes exposed to *N*-carboxymethyl-lysine (CML)-modified type I collagen in high or normal glucose media	Excess calcification and biomechanical pathology were seen in tendons of diabetic patients
29	Tendon cells from diabetic rat Achilles tendons	High glucose concentration upregulates the expression of MMP-9 and MMP-13 in tenocytes
30	Right Achilles tendon transected in male diabetic rats	During diabetes, tendon healing is impaired mainly due to altered expression of collagen and MMPs
31	Nondiabetic and diabetic rats injected with collagenase	Alterations in inflammatory, angiogenic and proliferative processes occurred in the diabetic state
32	Achilles tendons removed from healthy diabetic rats induced to Diabetes Mellitus I	Higher density of type 1 collagen, higher levels of nitrite/nitrate and increased expression of VEGF in tendons of diabetic patients
33	Tendon stem/progenitor cells from patellar tendons in diabetic rat model	Impaired tenogenic differentiation potential of these cells in diabetic rats
34	Adult porcine patellar tendons were incubated with high or normal glucose levels for 2 weeks	Proteoglican levels were significantly decreased in tendons exposed to high glucose
35	Male diabetic and age- and sex-matched control rats	Type-2 diabetes determines dysregulation of inflammatory and growth mediators in injured tendons
36	Achilles tendons of diabetes mellitus induced in rats by injections of streptozocin (STZ)	Increased TGF-β1 gene expression in healthy and diabetic rats

Table continues

Table 1 Continued

Number of reference	Model	Results
37	Rat tail tendon mode	In tendons of diabetic patients, there is a loss of tissue viscoelasticity driven by matrix-level loss of fiber–fiber sliding
38	Male rats with unilateral detachment of the supraspinatus tendon followed by immediate anatomic repair with transosseous fixation	Diabetic animals have significantly less fibrocartilage and organized collagen, and increased AGE deposition at the tendon–bone interface
39	Tendon fibrils from the tails of 8-month-old diabetic and diabetes resistant	Diabetes induces ultrastructural changes in collagen fibrils
40	*In vitro* procollagen metabolism was studied in Achilles tendons of nondiabetic (control) and diabetic rats	Diabetes reduces collagen accretion in connective tissues in part due to increased intracellular degradation of procollagen
41	Acid soluble rat tail tendon collagen from streptozotocin or alloxan diabetes-induced rats	Diabetic collagens are larger than normal and are capable of higher degrees of polymerization
42	Achilles tendon of rats weighing 300–350 g diabetes induced by STZ	Diabetic animals had a lower peak force for failure in each of the second, fourth and sixth week, less amount of fibroblast proliferation and lymphocyte infiltration
43	Glicated rabbit Achilles tendon	Moderately significant increases in maximum load, energy to yield and toughness of glycated tendons at 4 weeks
44	Tail tendons from streptozocin-diabetic rats	Increase in acid-insoluble collagen (AIC) in tendons of diabetic patients
45	Alloxan diabetes in Swiss mice induced	Alloxan diabetes and metabolites formed in the tissues might accelerate aging of collagen
46	Tail tendons from streptozotocin-diabetic rats, with and without insulin treatment	The maximum strength of the tendons were increased after 10 days of diabetes and even more after 30 days
47	Patellar tendon in diabetes-induced rats	Poorly controlled diabetes negatively affects the mechanical properties of the patellar tendon
48	Achilles tendon in rats type 1 diabetes induced	Diabetes decreases Young's modulus of elasticity and stress tensile load in tendons
49	Achilles tendon of adults diabetes-induced rats and control group	Diabetes significantly decreases the elastic modulus (mpa) of tendons
50	Achilles tendons of 16-week-old diabetic and control male mice	Diabetes significant increases tendon diameter and decreases maximum load, tensile stress, stiffness and elastic modulus
51	Tendon healing assessed in male mice at 5 weeks of age placed on a high-fat or low-fat diet for 12 weeks	High fat mice showed a decreased maximum force in uninjured tendons and insulin receptors were mostly expressed at injury site
52	Achilles, supraspinatus and patellar tendon in db/db mouse model of type II diabetes	Diabetes decreases cross-sectional area and stiffness in all three tendons
53	Canine patella-patellar tendon-tibia complex from a group of juvenile diabetic animals that received insulin therapy	The stiffness of the diabetic preparations is ~13% greater than controls
54	Female diabetic rats	Increased stiffness and strength and decreased toughness at the fiber level in diabetic rats

Table 2 Insulin and diabetes: *In vitro* studies in humans

Number of reference	Model	Results
55	Glycation sites in the axial unit cell of diabetic tendon collagen	Glycation takes place at different rates within the collagen axial unit cell
56	Human tenocytes cultured in either high or low glucose	Extracellular glucose impairs the cellular response to oxidative stress
57	Biomechanical parameters and histopathological findings in Achilles tendon samples from diabetic and nondiabetic patients	Tendons of nondiabetic patients exhibited a superior biomechanical profile. Tendons of diabetic patients had mild impairment of collagen organization and focal collagen degeneration
58	Human extensor tendons	Diabetes induces significant alterations in the ultrastructure of collagen
59	Tendons of diabetic and nondiabetic individuals	Highly disorganized fibrils in tendons of diabetic patients
60	Incubation of tendon fibers	Diabetes is associated with collagen altered by nonenzymatic browning
61	Achilles tendons incubated in phosphate-buffered saline containing ribose	Glycated tendons showed increased maximum load, stress, strain, Young's modulus of elasticity and toughness

functional outcome after rotator cuff surgical repair.[80–82] This is why in case of surgery for rotator cuff repair in diabetic patients, capsular release seems to be beneficial especially for external rotation and final postoperative function.[83]

This is important, because microstructural alterations in tendons impair their functionality and delay the healing of the tears.[84] This should be considered in surgical planning and rehabilitation strategy after surgery. For these reasons, Minimally-invasive procedures and percutaneus repair seem to be more appropriate and viable option for diabetic patients[85] (Table 3).

Thyroid hormones

Thyroid hormones (Ths) affect the structural setting of the tendons, as demonstrated in *in vitro* studies on rats, chicks and pigs, and both *in vitro* and *in vivo* studies in humans.

Immunocytochemical techniques and microscopic analysis on animal tenocytes and fibrochondrocytes from fibrocartilaginous entheses[86] showed that injured tendons that progress toward healing show a gradual decrease in the number of triiodothyronine (T3) receptors of collagen-forming fibroblasts, and their ability to synthetize collagen decreases. The T3-mediated upregulation of collagen is reflected in a change of the cross-linking pattern, with a resulting improvement of collagen quality[87] (Table 4).

In vitro studies investigated cultured human tenocytes and analysed the action of T3 and thyroxine (T4) on cell proliferation from biopsies from rotator cuff tendons. Ths play an important role in cell growth and proliferation in a dose-dependent manner[88,89] (Table 5).

The ECM is involved in thyroid actions because of a surface receptor for Ths that has been found on a structural protein of the plasmatic membrane of virtually all cells.[90] This integrin aVβ3 interacts with different ECM proteins such as vitronectin, FBN and osteopontin activating transcriptional pathways and inducing cellular responses such as angiogenesis and proliferation. Angiogenesis seems to be a process closely related to VEGFs and basic fibroblast growth factors (bFGF) activation,[91] which contribute to the formation of vascular structures.[92] Incomplete vascularization with tissue hypoxia, reactive oxygen species involvement and apoptosis seem to be connected with rotator cuff tendinopathies.[93]

In vivo studies underlined that hypothyroidism leads to hypoxia and apoptosis, contributing to

Table 3 Insulin and diabetes: *in vivo* study in humans

Number of reference	Model	Results
62	Patients from the longitudinal observational Fremantle Diabetes Study, and age- and sex-matched control subjects without diabetes	Here is a greater risk of tendon rupture requiring hospitalization in people with type 2 diabetes
63	Shoulder motion and tendon thickness in diabetic and control individuals	Increased biceps and supraspinatus thickness and decreased shoulder joint mobility and upper extremity function in diabetic subjects
64	Subjects aged 30 or older participating in a national Finnish Health Survey during 2000–01 with shoulder pain and chronic tendinitis	Metabolic syndrome, type 2 diabetes mellitus and carotid intima-media thickness were associated with shoulder pain in men
65	Ultrasound examination was performed on both shoulders in diabetic and control patients	Tendons thickness was greater in diabetics than in controls.
66	Ultrasonography (USG) technique for biceps and supraspinatus tendons in diabetic and control patients	Increased biceps and supraspinatus tendon thickness in diabetic patients that was aggravated with aging in diabetic patients
67	Diabetic and nondiabetic patients with rotator cuff tearing	Diabetic patients with rotator cuff tearing have increased subacromial IL-1β levels, SROMD and VAS scores and lower constant scores
68	Diabetic and nondiabetic subjects who had chronic shoulder pain	No difference in the ratio of tears of Rotator Cuff Tears was found on US examinations between two groups. He adjusted OR for CT in diabetic patients became insignificant after controlling for the other variables
69	Ultrasound examination of the Achilles tendon in diabetic individuals	Disorganized tendon fibers and calcification within the Achilles tendon in diabetic patients
70	Patients with a diagnosis of Achilles tendinopathy	Diabetes mellitus and Achilles tendinopathy were found to have a statistical association only for men younger than 44 years old
71	Ultrasonographic images of the tendon in type 2 diabetes patients, type 1 diabetes patients and controls	Type 2, and possibly type 1, diabetes patients showed poorer ultrasonographic Achilles tendon structure
72	Estimation of tendon length changes in medial gastrocnemius, soleus and tibialis anterior muscles in nonneuropathic diabetic patients and controls	Achilles tendon length changes were attenuated in diabetes patients compared with controls and were inversely correlated with diabetes duration as was ankle range of motion
73	Calcaneal insertion disorders in noninsulin-dependent diabetes in comparison to sex- and age-matched controls	Calcaneal insertion disorders were found to be more common among the diabetic subjects
74	Thickness of Achilles tendon and plantar fascia was measured by ultrasound in diabetic patients, with or without neuropathy and healthy volunteers	Flexion-extension of the first metatarsophalangeal joint was significantly smaller in diabetics
75	Achilles tendons from patients with Charcot's and non-Charcot's foot controls	Significant difference in ultimate tensile strength and elasticity between tendons of patients with Charcot's foot and those of non-Charcot's controls
76	Patients suffering from diabetes, with at least one Achilles tendon positive to Abadie's sign	Abadie's sign was a useful tool for assisting in the diagnosis of asymptomatic Achilles intratendinous changes

Table continues

Table 3 Continued

Number of reference	Model	Results
77	Plantar fascia and Achilles tendon thickness was measured by means of sonography in recent-onset type II diabetic subjects	Plantar fascia and Achilles tendon thickness are increased in the early stages of type II diabetes
78	Ultrasound scans of Achilles tendon in diabetic patients	Asymptomatic sonographic abnormalities (ASA) were more frequently localized at the enthesis in the diabetic group
79	Diabetic and nondiabetic patients with primary osteoarthritis of the right knee	No significant structural changes in the patellar and quadriceps tendons in diabetic patients in mid-term
80	Arthroscopic outcome, as Constant-Murley score in diabetic and nondiabetic patients	This was significantly greater in nondiabetic patients than in diabetics
81	Open repair of full thickness rotator cuff tears in 30 diabetic patients	Lower improvement in motion and function in diabetic patients
82	Patients who underwent rotator cuff repair	Diabetes mellitus is associated with range of motion loss
83	Diabetic or control patients who underwent arthroscopic repair of a small- to large-sized full thickness rotator cuff tear	In patients with diabetes mellitus, capsular release for rotator cuff repair seems to be beneficial, especially for external rotation and final postoperative function
84	Ultrasound features of tendinopathy in diabetic and nondiabetic >55 aged patients	In subjects with diabetes, tendinopathic features are significantly higher than healthy controls
85	Subjects operated of percutaneous repair of an acute Achilles tendon rupture	Percutaneous repair of the AT is a viable option for diabetic patients

Table 4 Thyroid hormones: *in vitro* studies in animals

Number of reference	Model	Results
86	Fibrochondrocytes from fibrocartilaginous entheses of miniature pig's Achilles tendon	Dynamic mechanical strain modulates thyroid receptors expressions that play an important role in fibrochondrocyte differentiation
87	Cell nucleus and heteroeuchromatin transition zone in 25 chicks	There is a gradual decrease in the number of T3 receptors of collagen-forming fibroblasts as the tendons healed and their capacity to synthetize collagen diminished

Table 5 Thyroid hormones: *in vitro* studies in humans

Number of reference	Model	Results
88	Three group of patients: healthy, rotator cuff teared affected by thyroid disease; rotator cuff teared not affected	Thyroid hormones enhance, *in vitro*, tenocyte growth and counteract apoptosis in healthy tenocytes
89	Primary tenocyte-like cells cultivated for 1, 7 and 14 days in the presence of T3 or T4 individually or in combination with ascorbic acid (AA)	Ths (T3 or T4) in synergism with AA increase significantly the total collagen production after 14 days

musculoskeletal problems in humans.[94] These two conditions are greatest in mild impingement and in partial, small, medium and large rotator cuff tears with macroscopic deterioration of the tendons.[95] The pattern of worsening hypoxia-induced apoptosis supports a continuous failure of the rotator cuff;[96] this is why it is important to determine the actual size of these effects on the functional recovery in tendon injuries. Disorders of thyroid metabolism are a most interesting aspect of calcific tendinopathy.[97] One of the most reliable theories on the genesis of calcific tendinopathies concerns the hypothyroidism-related reduction of oxygenation in the rotator cuff tendons with a consequent metaplasia that leads to calcium deposition[98] (Table 6).

Estrogens

Animal studies focused on rabbits, rats and monkeys divided into normal and ovariectomized groups investigated *in vitro* the role of estrogen on ECM composition. Protein analysis showed that estrogen and progesterone upregulate gene expression for the proteoglycans aggrecan, biglycan, decorin and versican in tendons.[99] In addition, estrogen deficiency negatively affects tendon metabolism and healing,[100,101] reducing proliferation rate, increasing apoptosis[102] and altering tendons composition in terms of collagen I, aggrecan and elastin. Only one study found no evidence of sex-based differences on the mechanical properties of tendons.[103]

Few studies demonstrated the role of estrogen on tendons and ligament response to excessive loading, biomechanical properties and resistance to injuries[104,105] (Table 7).

One *in vitro* study conducted on tenocyte of the posterior tibial and flexor digitorum longus tendons demonstrated that these tendons express the estrogen receptors α and β[106] (Table 8). Normal and dysfunctional tendons of both male and female patients expressed both these receptors, and the crucial sites of estrogen action may be tendon fibrils[107] which are the basic strength unit of the tendon. As such, their status influences the biomechanical properties of tendons.[108]

In vivo studies on humans were conducted to evaluate changes in the functional performance of the tendons of female athletes according to hormonal fluctuations typical of the menstrual cycle. Dynamometry, ultrasonography, electromyography and biochemical assessment were used to investigate tendons.[109] Some researches show that estrogens do not modify the stiffness of tendons, an effect that may be modulated by physical training.[110] Estrogens are associated with a higher relative number of smaller fibrils[111] and with a decrease in tendons diameter.[112] In women, tendons have a lower rate of new connective tissue formation, respond less to mechanical loading and have a lower mechanical strength.[113] This may be modified by physical training, even though we know that tendons capability to adapt to loading is attenuated in women. This effect could be due to continuous hormonal changes that negatively influence tendon activities during training by inhibiting fibroblast proliferative rate. In addition, there are no significant differences in tendon mechanical properties

Table 6 Thyroid hormones: *in vivo* study in humans

Number of reference	Model	Results
94	Patients with severe hypothyroidism and rheumatic signs and symptoms were studied before or within 4 days of receiving thyroid replacement therapy	Hypothyroidism, a treatable disease, could be identified as a cause of musculoskeletal problems
97	Retrospective, observational cohort study of 441 patients who underwent arthroscopic and mini-open repair for nontraumatic degenerative rotator cuff tears	Thyroid disease is highly frequent (until 63% for 60 < 80 years) in females group independent of the age
98	Retrospective, observational cohort study of consecutive patients with calcific tendinitis of the shoulder	Disorders of thyroid and estrogen metabolism may contribute to calcific tendinitis etiology

Table 7 Estrogens: *in vitro* studies in animals

Number of reference	Model	Results
99	Tendon complex dissected into six region in ovariectomized (OVH) rabbits and normal control group	Tendons from OVH rabbits had lower gene expressions for the proteoglycans aggrecan, biglycan, decorin and versican
100	Tenocytes isolated from the Achilles tendons of ovariectomized, middle-aged and young rats	Aging and, more significantly, oestrogen deficiency negatively affect tendon metabolism and healing
101	Biomechanical and histological evaluation on Achilles tendon in female rats	Endogenous oestrogen may improve healing of the Achilles tendon in rats
102	Quadriceps muscles, Achilles tendons, menisci and femur cortical bones in rats	Estrogen loss after ovariectomy increases cell apoptosis in tendons
103	Anterior cruciate ligament and patellar tendon in estrogen maintained and OVH monkeys	Endogenous estrogen does not directly affect the mechanical or material properties of the anterior cruciate ligament or the patellar tendon
105	Patellar tendon and lateral collateral ligament in ovariectomized adult female rats with different doses of estrogen, progesterone and testosterone for 3 days	Progesterone and high-dose estrogen upregulate relaxin expression in the patellar tendon and lateral collateral ligament of rat's knee

Table 8 Estrogens: *in vitro* studies in humans

Number of reference	Model	Results
106	Tendon samples harvested from healthy posterior tibial (PTT) and flexor digitorum longus (FDL) tendons	Tenocyte of the PTT and FDL tendons express estrogen receptors erα and erβ. Normal and diseased tendons of both male and female patients expressed both estrogen receptors

between the phases of the menstrual cycle[114,115] (Table 9).

Testosterone

The role of androgen hormones has been investigated widely. *In vitro* studies in rats showed that testosterone downregulates the relaxin/insulin-like family peptide receptor 1 and 2 expression in the patellar tendon and lateral collateral ligament of the knee.[105] The circulating levels of relaxin may affect mesenchimal tissue such as tendons, acting on collagen content, and negatively affect the mechanical properties of connective tissues and tendon stiffness. Studies on metalloproteinases (MMP) underlined that androgens administration reduces MMP expression in tendons, negatively affecting tissue remodeling during different training programs[116] (Table 10).

Testosterone administration can lead to the alterations of biomechanical properties of tendons,[117] reduction of elastic properties,[118] tendon dysfunction and fibrosis, with a higher incidence of spontaneous tendon ruptures.

In vitro studies on cultured male human tenocytes treated with dihydrotestosterone (DHT) showed that increasing concentrations of DHT produced proliferation of these cells and lead to a dedifferentiated phenotype after 48 h of treatment, with an evident negative effect during tendon healing.[119] These findings support a possible association between testosterone abuse and shoulder tendinopathy (Table 11).

Table 9 Estrogens: *in vivo* study in humans

Number of reference	Model	Results
109	Experimental findings on physical training in women	Estrogen may reduce the stiffness of tendons, an effect that may be modified by physical training
110	Achilles tendon strain in women who had been using estrogen for at least 12 months and matched women who were nonestrogen users	Estrogen did not alter the strain behavior of the Achilles tendon
111	Nonusers or habitual users of oral estradiol replacement therapy were women	Estradiol administration was associated with higher collagen synthesis and a higher relative number of smaller fibrils
112	Achilles tendons in active women and controls	Achilles tendon diameter is greater in active postmenopausal women. Hormone replacement therapy appeared to ameliorate this effect in active women
113	Isolated tendon collagen fascicles in women	Tendons in women have a lower rate of new connective tissue formation, respond less to mechanical loading and have a lower mechanical strength
114	*In vivo* patellar tendon properties in normally menstruating women	No significant differences were seen in tendon mechanical properties among the three phases of the menstrual cycle
115	Medial gastrocnemius tendon mechanical properties in healthy females aged 23	No significant difference in the stiffness of the medial gastrocnemius tendon over the course of the menstrual cycle

Table 10 Testosterone: *in vitro* studies in animals

Number of reference	Model	Results
116	Patellar tendon and lateral collateral ligament in ovariectomized adult female rats with different doses of estrogen, progesterone and testosterone for 3 days	Testosterone downregulates relaxin expression in the patellar tendon and lateral collateral ligament of rat's knee
117	Proximal and distal regions of the calcanear tendon (CT) and proximal, intermediate and distal region of superficial (SFT) and deep flexor tendons (DFT) in rats	Androgens decrease both MMP-2 concentration and active form in the three regions of the SFT and on the proximal region of the CT, but not on the DFT

Table 11 Testosterone: *in vitro* studies in humans

Number of reference	Model	Results
120	Cultured human tenocytes from the intact supraspinatus tendon of male subjects	*In vitro*, progressive increasing concentration of testosterone has direct effects on male human tenocytes, increasing cell number after 48 and 72 h of treatment

In vivo, anabolic androgenic steroids (AAS) in combination with jumping exercises enhance calcaneal, superficial and deep flexor tendon remodeling, even though androgen abuse may compromise tendon adaptation with an increased risk of tendon ruptures. In fact, AAS reduce insulin-like growth factor-1 (IGF-1) mRNA levels in some tendons, decreasing collagen synthesis, and compromise tendon healing.[120]

Growth hormone

GH/IGF-1 system is closely linked to collagen synthesis and connective tissue maturation. In rabbits, rats, pigs and horses, only moderate structural changes were observed in tendons with upregulation of GH/IGF-I axis, but disruption of the GH receptor had pronounced effects upon tendon ultrastructure.[121] Electron microscopy and ultrastructural analysis demonstrated that interaction between exercise and GH treatment attenuates the changes in joint structure that result from chronic unloading.[122] Administration of GH in pigs showed that tendons have a temporary response to this hormone in terms of cell division and metabolism.[123] On the other hand, recombinant GH in horses after collagenase induced injury to the superficial digital flexor tendons did not result in significant differences concerning cross-sectional area, tensile stress and stiffness in tendons.[124] A study on short-term explant culture of the deep flexor tendon in rabbits showed that tenocytes increase their ability to repair and to regenerate ECM if they are cultured with recombinant human insulin-like growth factor (rhIGF-I)[125] (Table 12).

In humans, increased GH availability stimulates collagen synthesis in skeletal muscle and tendon[126,127] without any effect on myofibrillar protein and cartilage synthesis.[128] GH seems to have a matrix-stabilizing effect during inactivity and rehabilitation by stimulating collagen expression in the musculotendinous tissue and increasing the cross-sectional area of tendons.[129] (Table 13). On the contrary, other studies did not record any significant alterations in tendon size or collagen synthesis during GH variations.[130,131]

Cortisol

The only information available on the interaction between cortisol and tendons concerns corticosteroid systemic therapy and injections in the management of symptomatic tendinopathy.[132] There are not data about the influence of cortisol hormone imbalance on tendons.

Animal studies on rat tendons showed that systemic administration of corticosteroids caused reduction of energy to failure and elasticity module and

Table 12 Growth hormone: *in vitro* studies in animals

Number of reference	Model	Results
122	Three groups of mice: giant transgenic mice, dwarf mice and a wild-type control group	Whereas only moderate structural changes were observed with upregulation of GH/IGF-I axis, disruption of the GH receptor had pronounced effects upon tendon ultrastructure
123	Musculotendinous joint (MTJ) of the plantaris muscle in hypophysectomized rats	The interaction between exercise and GH treatments attenuates the changes in MTJ structure that result from chronic unloading
124	Orchidectomized pigs GH treated and controls	Calcanean tendon responds temporally to GH treatment, affecting both cell division and tendon metabolism
125	Superficial digital flexor tendon (SDFT) in horses intramuscular recombinant GH treated	There were no differences in cross-sectional area, maximal load at failure tensile strain, tensile stress or stiffness between tendons from control and treated horse
126	Short-term explant cultures of the deep flexor tendon of the rabbit	Growth factors have the ability to stimulate matrix synthesis and cell proliferation in rabbit flexor tendon

Table 13 Growth hormone: *in vivo* studies in humans

Number of reference	Model	Results
127	Injections of recombinant GH or saline (control) into patellar tendons of healthy elderly men	Local injections of rhgh increase tendon collagen synthesis in humans, either directly or indirectly by increasing local bioactive IGF-I
128	Acromegalic and GH-deficient patients	Higher expression for collagen and IGF-1 in musculotendinous tissue in acromegalic patients relative to GH-deficient patients
129	Healthy young individuals recombinant human GH-administered	Increased GH availability stimulates matrix collagen synthesis in tendon, but without any effect upon myofibrillar protein synthesis
130	Quadriceps and patellar tendon in elderly men randomly assigned to daily injections of recombinant GH	GH seems to have a matrix-stabilizing effect during inactivity and rehabilitation by stimulating collagen expression and increasing tendon CSA and stiffness
131	Articular cartilage thicknesses of shoulder, wrist and knee and sizes of heel tendons in acromegalic patients	No significant change is recorded in right knee cartilage or heel tendon size
132	Collagen and myofibrillar protein in healthy young males	Collagen synthesis in tendon is unaffected by GH receptor blocker supplementation

the increase of strain in tendons, comparing with the control group.[133] Systemic hydrocortisone administration changes significantly mechanical properties of tendons, which may cause their frequent failure.[132] High-volume image-guided injections in human athletes showed that this therapeutic option is effective to improve symptoms, and it reduces neovascularization and decreases maximal tendon thickness at short-term follow-up in chronic resistant Achilles tendinopathy.[134]

Conclusion

There is a relative lack of knowledge about the role of hormones in the pathogenesis of tendinopathy. Most of the studies analyzed reveal an association between the metabolic-hormonal imbalances and tendon degeneration, but this association has not yet been exactly defined.

Studies in animal and cell models show that hormonal imbalances affect the biochemical processes that underlie tendon metabolism. *In vivo* studies are still controversial, because they take into account populations who suffer multiple influences such as age, gender and level of physical activity. Concerning diabetes, it is necessary to distinguish the tendon pathology in diabetic subjects without polyneuropathy compared with patients in whom the neuropathic aspect of the condition is predominant. In these cases, tendon problems should be considered only one facet of the comorbidities associated with the neurological damage.

The role of hormones in tendinopathies is still controversial.

The most significant clinical data concern the association between thyroid hormones disorders and tendon damage, but further studies are needed to better define the action of these hormones and their receptors on tenocytes and composition of the ECM.

The continuous modulation of female sex hormones during the menstrual cycle affects the composition of tendon collagen, because the connective tissues express receptors for both estrogen and progesterone. This leads to a clinically relevant condition in relation to physical training and musculoskeletal performance of female athletes.

Testosterone is also active on tenocytes, but its action is predominantly on the biomechanical properties of tendons, especially strength and stiffness.

Growth hormone impacts tendon morphology, remodeling and genetic expression, underlining its necessity during maturation of tendons.

On the contrary, the study of corticosteroids is still limited to systemic therapy or local injections during tendinopathies.

We hypothesize that hormones could be the unknown actors behind the failed healing response typical of tendinopathies.

The influence of hormones on tendons structure needs to be further investigated to identify the actual influence that hormonal imbalance has in the genesis of tendinopathy. If found to be significant, multidisciplinary preventive and therapeutic strategies should be pursued.

Conflict of interest statement

The authors have no potential conflicts of interest.

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