

Tenocytes do not just lie in a vacuum: the role of lipids, glycemic metabolism and thyroid hormones in tendinopathy and tendon rupture. A narrative review

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Purpose: Tendinopathies and tendon ruptures are a common cause of pain and disabilities. The pathogenesis is considered multifactorial, and currently described as the failed healing response. Traditionally, tendon injuries have been mostly referred to age, overuse or mechanical factors. Recently, some authors have focused their attention on the influence of metabolic diseases and hormones on tendon homeostasis, opening new perspectives. There are even more studies which show how systemic condition and pathologies are able to influence the proliferation of tenocytes, the synthesis of extracellular matrix proteins, and the organization and properties of the extra cellular matrix of the tendons.

Methods: In this article, we reviewed the current knowledge about the influence of lipids, glucose and thyroid hormones on the pathogenesis of tendinopathy.

Results: Beside the traditional extrinsic and mechanical risk factors, this article showed the importance of metabolism and hormones of tendon health, reinforcing the idea of their great influence on the pathogenesis of tendinopathy. Current literature indicates that hypercholesterolemia, obesity, diabetes mellitus and hypothyroidism are all risk factors for tendinopathies and tendon ruptures.

Conclusions: The precise role of each predisposing factor remains incompletely understood, and further epidemiology and laboratory studies should be performed to establish the strength of the association with tendon pathologies and their pathogenetic mechanism.

Keywords: inertial measurement unit; acceleration; max speed; metrics; team sports.

Introduction

Tendinopathy is a chronic condition characterized by pain, focal tendon tenderness, and impaired performance.¹ It is a very common cause of disability, and it is estimated that approximately 30% of consultations for musculoskeletal problems are related to tendon injuries. Tendon injuries can affect people of all ages, impairing the activity of young people during sports, and sedentary adults in their daily activities. For example, Achilles tendinopathy is common cause of pain in runners, and the incidence in top-level runners has been estimated between 7 and 9 %, but 30% of Achilles tendinopathy and ruptures have been reported in older patients with a sedentary lifestyle.¹ Tendon rupture is the final stage of tendinopathy.

Tendon is organized in a strict hierarchical structure.² Their mechanical properties are based on the underlying extracellular matrix (ECM) structure and composition. Tendons are predominantly made up of type I collagen.³ The fibrillar collagen is embedded in a hydrophilic ECM consisting of proteoglycans, glycoproteins and glycosaminoglycans. Tenocytes are specialized fibroblasts embedded in tendon ECM. They are responsible for the synthesis of ECM's proteins and the remodeling of the collagen fibers. The remodeling activity of these cells is important for the maintenance of the tendon homeostasis and function.^{4,5}

The etiology of tendinopathy is currently described as the failed ability of the tendon to heal (the "failed healing response theory"), and it is multifactorial.⁶ Extrinsic risk factors as overuse,

overhead activities, training errors, training surfaces, anatomical predisposition, immobilization, and cigarettes smoke, are well known risk factors. Age, hypovascularization and increased apoptosis have been proposed as intrinsic factors. However, recent studies support genetics and metabolic disorders, as diabetes mellitus, hypothyroidism, and hypercholesterolemia as important factors in the pathogenesis of tendinopathy.⁷ Tenocytes play a key role in the synthesis of the ECM's proteins, and during tendon healing.⁵ All cellular and extracellular components are targeted by circulating factors such as growth factors, cytokines and hormones. Hormones are very important for the physiological development of organs and tissues, and 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.⁸ In addition, some biomechanical properties of the musculoskeletal system seem to be affected by hormonal diseases.⁹ Recently, some Authors have focused their studies on the influence of hormones and metabolic diseases on tendon health. In this article, we review the current knowledge about the influence of lipids, glucose and thyroid hormones on tendons.

The role of cholesterol and lipids

Hypercholesterolemia and obesity has been recently indicated as important risk factor for musculoskeletal diseases and tendinopathies.¹⁰ Lipid related changes are known to affect several tendon mechanical properties, including stiffness and Young modulus, in uninjured and injured tendons. Cholesterol can accumulate in tendons, causing structural disruption of a tendon's collagen matrix, and in high cholesterol environments (e.g. familial hyperlipidemia), lipids accumulate within the tendon ECM and form deposits called xanthomas.¹¹ The incidence of Achilles tendinopathy can increase 6-fold in patients with tendon xanthoma¹² and symptoms have been reported to improve in more than half of patients after lipid-lowering treatment.¹³

Laboratory and animal studies have been performed to examine the possible influence of cholesterol and lipids on tendon's health. In rats, biomechanical testing revealed a significant reduction in normalized stiffness in hypercholesterolemic rats compared with controls, whereas histologic analyses showed no significant differences in collagen organization, cellularity, or cell shape between the two models.¹⁴ In a rotator cuff animal model, stiffness and elastic modulus of supraspinatus rat's tendons were increased in a high cholesterol environment.¹⁵ The effect of hypercholesterolemia on uninjured tendon has also been studied across multiple species using supraspinatus tendons from Apolipoprotein E (ApoE) knockout mice, rats Hypercholesterolemic diet (HC diet), and monkeys (HC diet).¹⁶ Tendon stiffness was significantly increased in HC mice and rats, and there was a trend toward increased stiffness in HC monkeys. Tendon elastic modulus was significantly increased in HC mice and monkeys, and there was a trend toward increased modulus in HC rats.

Taken together, these data suggest that exposure to a high cholesterol environment negatively impact tendon healing, as demonstrated by decreased normalized maximum tendon stress in ApoE mice and decreased normalized stiffness in rats fed a HC diet. Moreover, the reduction in tendon healing observed in the 40-week (but not 14-week) age group of mice may be explained by a process that allows for accumulation over time, such as the intratendinous cholesterol deposition, or relative tissue ischemia due to vascular impairment.

Although current literature shows some association between hypercholesterolemia, obesity and tendon injuries, no level I

studies are available, and the design of the published studies does not allow identifying a precise cause-effect relationship, and their specific role independently of other risk factors. Abboud and Kim¹⁷ reported that patients with rotator cuff tears were more likely to have hypercholesterolemia than the control group. Lee et al.¹⁸ retrospectively reviewed patients with lateral epicondylitis (LE) who presented to their institution between 2011 and 2015. In this study, patients with LE had higher triglycerides (TC) levels than the healthy controls. The incidence of hypercholesterolemia was higher in LE patients than in controls. In addition, subjects with hypercholesterolemia were more likely to experience LE than those with normal cholesterol levels after adjustment for Body Mass Index (BMI) and glucose levels. Five case-control level II studies (14–18) investigated the role of obesity on tendinopathy and tendon ruptures, concluding that people with higher BMI (BMI ≥ 30) had an higher risk to develop a tendon injury compared to normal-weight people, with odds ratios ranging from 1.9 (95% CI: 1.1–2.2) to 5.6 (1.9–16.6).¹⁰ In particular, a statistical significant association has been reported between higher BMI and an increased risk of rotator cuff ruptures (O.R. 3.1 for males, O.R. 3.5 for females),¹⁹ an increased risk to develop lateral epicondylitis (OR 1.41),²⁰ and achilles tendinopathy (OR 6.6).²¹

The pharmacological treatment of hypercholesterolemia – using statins, bile acid sequestrants, ezetimibe, and niacin has been associated with regression of tendon xanthomas.^{22,23} Despite allowing for normalization of tendon thickness in at least a subset of patients, the use of lipid-lowering medication to treat hyperlipidemia may also result in at least transient changes that are detrimental to tendon structure and function. Statins are the most prescribed. Tendon injury accounts for 2.1 % of reported statin related side effects. 59 % of injuries occur within the first year of therapy, and median time from statin initiation to tendon injury is 8–10 months.²⁴

The role of diabetes mellitus

Diabetes Mellitus has been associated with compromised tendon function, increased susceptibility to tendon injury, and reduced healing ability.²⁵ In diabetic patients the tendons are thicker, shorter and have increase stiffness compared to normal controls. Boivin et al.²⁶ showed that diabetic mice Achilles tendon at 16 weeks of age had inferior biomechanical proprieties compared to control mice. A significant decrease in maximum load, maximum stress, elastic modulus, and stiffness have been described.²⁶

Connective tissue stiffness has been shown to further increase with diabetes.²⁷ This tissue stiffening has been associated with non-enzymatic, oxidative reaction between glucose and collagen which lead to the formation of so-called Advanced Glycation End-products (AGEs).^{28,29} AGEs accumulation occur is particular in long live protein, such as collagen. Some AGEs can bridge between proteins to form intermolecular crosslinks. There is no direct experimental evidence linking AGEs with increased in collagen fibril stiffness, but this seems to be plausible because of the correlation between AGEs markers and increasing tissue stiffness. AGEs formation affects the interactions between collagen fibers, ECM protein, and tenocytes.³⁰ These changes have been associated with both reduced healing capacity and altered mechanical properties of connective tissues. The effects of AGEs on the mechanical properties of tendons have been studied in a rat model.²⁵ The formation of AGEs would change the way tendons respond to loading, in particular reducing tissue viscoelasticity by severely limiting fiber-fiber and fibril-fibril sliding, making tendon more susceptible to injury. Recently, Gautieri et al. confirmed these results in their vitro study.³¹ Interestingly, Chung et al. found a significantly overexpression

of MMP-9 and IL-6 genes in the torn supraspinatus tendon of diabetic patients compared to controls, concluding that the increased MMP-9 and IL-6 synthesis might significantly compromise the integrity of tendon ECM and predispose patients with diabetes to tendinopathy or rupture.²⁷

Clinical studies showed that the incidence of tendinopathies and tendon ruptures are higher in patients with type 2 diabetes compared to non-diabetic patients.^{32,33} In particular, people with type II diabetes have a higher risk to suffer a rotator cuff tears, the results after repair are often poorer, and the re-rupture incidence is higher compared to non-diabetic controls.³⁴ Achilles tendon are strongly disarranged in diabetic patients,³⁵ especially in men younger than 44 years old,³⁶ as confirmed by an ultrasounds study.³⁷ Diabetes mellitus has been also related to calcific tendinopathy. We recently reported in an epidemiological study that patients affected by diabetes mellitus have higher risk to develop calcific insertional tendinopathy of the Achilles tendon compared to general population (OR 3.04).³⁸ These data have been confirmed by a systematic review of literature,³⁹ which reported a strong evidence that diabetes is associated with higher risk of tendinopathy, that symptoms are directly proportional with duration of diabetes, and tendons of diabetic patients thicker than controls.

The role of thyroid hormones

Thyroid hormones (THs), T3 and T4, play an essential role in the development and metabolism of many tissues and organs, and exert profound metabolic effects in adult life, including changes in oxygen consumption, protein, carbohydrate, lipid, and vitamin metabolism.⁴⁰

T3 and T4 play an antiapoptotic role on tenocytes, causing an increase in vital tenocytes isolated from tendons *in vitro* and a reduction of apoptotic ones; they are also able to influence extra cellular matrix proteins secretion *in vitro* from tenocytes, enhancing collagen production.⁴¹

Ayala et al.⁴² in 1991 identified by immunocytochemical techniques the expression of T3 on tenocytes, within the cell nucleus and between the heteroeuchromatin transition zone in chicks. The authors were able to show that all the chicks that underwent tenotomy showed a decrease of the number of T3 receptors of collagen-forming fibroblasts as the tendons healed, and their capacity to synthesize collagen diminished. Furthermore, the relationship between thyroid disorders and collagen has been long described.⁴³ In particular, hyperthyroidism is accompanied by increased rates of catabolism of both soluble and insoluble collagen, and hypothyroidism is accompanied by decreased rates of catabolism of collagen.

Many studies indicate that THs regulate several functions of tenocytes. One such function is proliferation. Oliva et al. examined the action of T3 and T4 in *in vitro* on cell proliferation by time course, and in a dose dependent manner. Tenocytes have been harvested from 5 patients who underwent surgical reconstruction of rotator cuff tears. The data from this study showed that both T3 and T4 act on cell growth in dose dependent manner. At 72 hours of hormone treatment at concentration of 10⁻⁷M, they found a significant higher proliferation (19%) for T3 and T4 (10%) compared with primary tenocytes grown without thyroid hormones.⁴⁴ Furthermore, thyroid hormones were also able to counteract tenocytes apoptosis in a dose- and time-dependent manner.

The action of thyroid hormones on cell growth has been demonstrated both *in vitro* and *in vivo*.⁴⁵

THs treatment, in synergism with amino acids, increases the production of collagen I, Biglycan and COMP.

The present findings, together with those they previously

reported, suggest an important role of THs on tendons, on tenocyte proliferation directly, and in synergism with other factors such as amino acids on ECM protein synthesis. The expression gene and synthesis of collagen I are significantly increased in tenocyte-like cells cultured with THs after 14 days. In contrast THs do not affect the expression of collagen III that normally is less abundant in tendon and increase only during early phase of remodeling and in tendinopathy.^{45,46} The lack of collagen III productions under TH stress should be considered a protective factor for tendons. THs increase the intracytoplasmic expression of collagen V after 7 days of culture and decrease drastically after 14 days. Collagen V it is known to regulate the characteristic of fibrillar structure in tendon.^{45,47}

An interesting retrospective observational study has been published on 441 patients who underwent arthroscopic and mini open repair for degenerative RC tears.⁴⁸ The authors found that the incidence of a thyroid dysfunction, in particular hypothyroidism, was significantly higher in compared control group patients. The incidence of hypothyroidism was also more common in females, independently to age, while males affected by a rotator cuff tear showed a high frequency for smokers and for hypercholesterolemia.

The influence of metabolism on TD-MSCs.

MSCs are ubiquitous multipotent cells which have been isolated from various tissues.

The importance of resident MSCs for the maintenance and repair of adult tissues have been widely accepted, and tendon-derived mesenchymal stem cells (TD-MSCs) have been identified.⁴⁹ The viability and tenogenic differentiation of TD-MSCs are closely associated with the maintenance of the tendon microenvironment, and recent studies suggests that dysfunctions of TD-MSCs may be involved in the pathogenesis tendinopathy.⁵⁰ Therefore, some authors recently focused their studies on the influence of metabolism on the proliferation and differentiation of resident MSCs.

Although clinical studies suggest a closed correlation between hypercholesterolemia and tendinopathy, the pathogenetic mechanism is not completely understood. Recently, Li et al.⁵¹ found that high cholesterol inhibits tendon-related gene expression in TD-MSCs, by increasing the level of reactive oxygen species (ROS) in MSCs. ROS are the active forms of oxygen, and they are generated from cellular metabolic activities.⁵² A moderate level of ROS promotes cell proliferation and differentiation, but high levels induce cell apoptosis and autophagy due to oxidative stress to lipids, proteins, and DNA. To confirm this hypothesis, the same authors found that high cholesterol induces a significantly increased production of ROS, that may induce apoptosis, autophagy of TDSCs, and tendinopathy.^{53,54}

As a statistically significant correlation between calcific tendinopathy and diabetes mellitus has been recently reported in our recent study, we then investigated the influence of hyperglycemia on MSCs. In two different studies, MSCs have been harvested from bone marrow (BM-MSCs) and from rotator cuff tendons (TD-MSCs). MSCs have been cultured with different levels of glucose, and with the addition of insulin. We found an increased expression of bone markers (Collagen type I and III, aggrecan, osteopontin, fibronectin, alkaline phosphatase) after 48 and 72 hours of culture in MSCs cultured with high level of glucose, and with glucose and the addition of insulin, compared to control cells. After 4 weeks, MSCs cultured with high dose glucose and with insulin showed an increased intracellular content of calcium.

Practical Applications

Further studies are needed to clarify the association between tendon pathologies and their pathogenetic mechanism.

Conclusions

The pathogenesis of tendinopathy is currently considered multifactorial, and it has been defined as a failure of the healing process. Beside the traditional extrinsic and mechanical risk factors, this article showed the importance of metabolism and hormones of tendon health, reinforcing the idea of their great influence on the pathogenesis of tendinopathy. Current literature indicates that hypercholesterolemia, obesity, diabetes mellitus and hypothyroidism are all risk factors for tendinopathies and tendon ruptures. However, the precise role of each predisposing factor remains incompletely understood, and further epidemiology and laboratory studies should be performed to establish the strength of the association with tendon pathologies and their pathogenetic mechanism.

Acknowledgments

The authors would like to thank the team's coaches and players for their cooperation during all data collection procedures.

Ethical Committee approval

Not request as narrative review

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Informed Consent Statement

Not request as narrative review.

Topic

Public Health, Orthopaedic.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

No funding was received for this investigation.

Declaration if used ChatGPT

We don't used ChatGPT.

Author-s contribution

AGV and GD reviewed the literature and wrote the manuscript, GP and FO reviewed the literature and collected the articles, FC, EM made a critical revision of the manuscript, MN reviewed the manuscript, and all the authors gave their final approval to publication.

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Received: 22.11.2023.

Accepted: 02.12.2023.

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