Acta Kinesiologica 17 (2023) Issue.2
DOI. 10.51371/issn.1840-2976.2023.17.2.10

Review

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

Alessio Giai Via[a], Giuseppe Discalzo[b], Gennaro Pipino[c], Francesco Oliva[d], Francesco Cuozzo[e*], Emanuela Marsilio[f], Nicola Maffulli[g]

[a]Department of Orthopaedic and Trauma surgery, San Camillo-Forlanini Hospital, Circ. ne Gianicolense, 87, 00152 Rome (RM), Italy, [b]Department of Orthopaedic Surgery and Traumatology, Circolo e Fondazione Macchi Hospital, Viale Borri 57,21200 Varese, Italy, [c]Department of Orthopaedic and Trauma surgery, Villa Erbosa Hospital, Bologna, Italy. University San Raffaele, Milan, Italy, [d]Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome, Italy, [e]Department of Musculoskeletal Disorders, School of Medicine and Surgery, University of Salerno, Salerno, Italy, [f]Department of Musculoskeletal Disorders, School of Medicine and Surgery, University of Salerno, Salerno, Italy, [g]Faculty of Medicine and Psychology, University of Rome La Sapienza, Rome, Italy. Queen Mary University of London, Barts and the London School of Medicine and Dentistry, Center for Sports and Exercise Medicine, Mile End Hospital, 275 Bancroft Road, London E1 4DG, England

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 xanthoma [12] 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 intratendineous 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 Kim[17] 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 $\geq$ 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 increate 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 synthetize 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, Biglican 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

ORCID

Alessio Giai Via ID http://orcid.org/0000-0002-5943-081X
Francesco Oliva ID http://orcid.org/0000-0002-6734-5308
Emanuela Marsilio ID http://orcid.org/0000-0001-6934-1506
Nicola Maffulli ID http://orcid.org/0000-0002-5327-3702

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.

References

1. Maffulli N, Wong J, Almekinders LC. Types and epidemiology of tendinopathy. *Clin Sports Med*. Oct 2003;22(4):675-92. doi:10.1016/s0278-5919(03)00004-8
2. Kastelic J, Galeski A, Baer E. The multicomposite structure of tendon. *Connect Tissue Res*. 1978;6(1):11-23. doi:10.3109/03008207809152283
3. Kannus P. Structure of the tendon connective tissue. *Scand J Med Sci Sports*. Dec 2000;10(6):312-20. doi:10.1034/j.1600-0838.2000.010006312.x
4. Riley GP. Gene expression and matrix turnover in overused and damaged tendons. *Scand J Med Sci Sports*. Aug 2005;15(4):241-51. doi:10.1111/j.1600-0838.2005.00456.x
5. Bailey AJ, Paul RG, Knott L. Mechanisms of maturation and ageing of collagen. *Mech Ageing Dev*. Dec 1 1998;106(1-2):1-56. doi:10.1016/s0047-6374(98)00119-5
6. Sharma P, Maffulli N. Tendon injury and tendinopathy: healing and repair. *J Bone Joint Surg Am*. Jan 2005;87(1):187-202. doi:10.2106/JBJS.D.01850
7. Maffulli N, Cuozzo F, Migliorini F, Oliva F. The tendon unit: biochemical, biomechanical, hormonal influences. *J Orthop Surg Res*. Apr 21 2023;18(1):311. doi:10.1186/s13018-023-03796-4
8. Oliva F, Piccirilli E, Berardi AC, Frizziero A, Tarantino U, Maffulli N. Hormones and tendinopathies: the current evidence. *Br Med Bull*. Mar 2016;117(1):39-58. doi:10.1093/bmb/ldv054
9. Oliva F, Misiti S, Maffulli N. Metabolic diseases and tendinopathies: the missing link. *Muscles Ligaments Tendons J*. Jul 2014;4(3):273-4.
10. Franceschi F, Papalia R, Paciotti M, et al. Obesity as a risk factor for tendinopathy: a systematic review. *Int J Endocrinol*. 2014;2014:670262. doi:10.1155/2014/670262
11. Tsouli SG, Xydis V, Argyropoulou MI, Tselepis AD, Elisaf M, Kiortsis DN. Regression of Achilles tendon thickness after statin treatment in patients with familial hypercholesterolemia: an ultrasonographic study. *Atherosclerosis*. Jul 2009;205(1):151-5. doi:10.1016/j.atherosclerosis.2008.10.032
12. Beeharry D, Coupe B, Benbow EW, et al. Familial hypercholesterolaemia commonly presents with Achilles tenosynovitis. *Ann Rheum Dis*. Mar 2006;65(3):312-5. doi:10.1136/ard.2005.040766
13. Klemp P, Halland AM, Majoos FL, Steyn K. Musculoskeletal manifestations in hyperlipidaemia: a controlled study. *Ann Rheum Dis*. Jan 1993;52(1):44-8. doi:10.1136/ard.52.1.44
14. Hast MW, Abboud JA, Soslowsky LJ. Exploring the role of hypercholesterolemia in tendon health and repair. *Muscles Ligaments Tendons J*. Jul 2014;4(3):275-9.
15. Beason DP, Tucker JJ, Lee CS, Edelstein L, Abboud JA, Soslowsky LJ. Rat rotator cuff tendon-to-bone healing properties are adversely affected by hypercholesterolemia. *J Shoulder Elbow Surg*. Jun 2014;23(6):867-72. doi:10.1016/j.jse.2013.08.018
16. Beason DP, Hsu JE, Marshall SM, et al. Hypercholesterolemia increases supraspinatus tendon stiffness and elastic modulus across multiple species. *J Shoulder Elbow Surg*. May 2013;22(5):681-6. doi:10.1016/j.jse.2012.07.008
17. Abboud JA, Kim JS. The effect of hypercholesterolemia on rotator cuff disease. *Clin Orthop Relat Res*. Jun 2010;468(6):1493-7. doi:10.1007/s11999-009-1151-9
18. Lee SH, Gong HS, Kim S, Kim J, Baek GH. Is There a Relation Between Lateral Epicondylitis and Total

Cholesterol Levels? *Arthroscopy*. May 2019;35(5):1379-1384. doi:10.1016/j.arthro.2019.01.048
19. Wendelboe AM, Hegmann KT, Gren LH, Alder SC, White GL, Jr., Lyon JL. Associations between body-mass index and surgery for rotator cuff tendinitis. *J Bone Joint Surg Am*. Apr 2004;86(4):743-7. doi:10.2106/00004623-200404000-00011
20. Titchener AG, Fakis A, Tambe AA, Smith C, Hubbard RB, Clark DI. Risk factors in lateral epicondylitis (tennis elbow): a case-control study. *J Hand Surg Eur Vol*. Feb 2013;38(2):159-64. doi:10.1177/1753193412442464
21. Scott RT, Hyer CF, Granata A. The correlation of Achilles tendinopathy and body mass index. *Foot Ankle Spec*. Aug 2013;6(4):283-5. doi:10.1177/1938640013490019
22. Lind S, Olsson AG, Eriksson M, Rudling M, Eggertsen G, Angelin B. Autosomal recessive hypercholesterolaemia: normalization of plasma LDL cholesterol by ezetimibe in combination with statin treatment. *J Intern Med*. Nov 2004;256(5):406-12. doi:10.1111/j.1365-2796.2004.01401.x
23. Kane JP, Malloy MJ, Tun P, et al. Normalization of low-density-lipoprotein levels in heterozygous familial hypercholesterolemia with a combined drug regimen. *N Engl J Med*. Jan 29 1981;304(5):251-8. doi:10.1056/NEJM198101293040502
24. Marie I, Delafenetre H, Massy N, Thuillez C, Noblet C, Network of the French Pharmacovigilance C. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990-2005 and review of the literature. *Arthritis Rheum*. Mar 15 2008;59(3):367-72. doi:10.1002/art.23309
25. Snedeker JG, Gautieri A. The role of collagen crosslinks in ageing and diabetes - the good, the bad, and the ugly. *Muscles Ligaments Tendons J*. Jul 2014;4(3):303-8.
26. Boivin GP, Elenes EY, Schultze AK, Chodavarapu H, Hunter SA, Elased KM. Biomechanical properties and histology of db/db diabetic mouse Achilles tendon. *Muscles Ligaments Tendons J*. Jul 2014;4(3):280-4.
27. Chung SW, Choi BM, Kim JY, et al. Altered Gene and Protein Expressions in Torn Rotator Cuff Tendon Tissues in Diabetic Patients. *Arthroscopy*. Mar 2017;33(3):518-526 e1. doi:10.1016/j.arthro.2016.08.017
28. Saito M, Marumo K. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. *Osteoporos Int*. Feb 2010;21(2):195-214. doi:10.1007/s00198-009-1066-z
29. BenjaminM,KaiserE,MilzS.Structure-functionrelationships in tendons: a review. *J Anat*. Mar 2008;212(3):211-28. doi:10.1111/j.1469-7580.2008.00864.x
30. Li Y, Fessel G, Georgiadis M, Snedeker JG. Advanced glycation end-products diminish tendon collagen fiber sliding. *Matrix Biol*. Apr 24 2013;32(3-4):169-77. doi:10.1016/j.matbio.2013.01.003
31. Gautieri A, Passini FS, Silvan U, et al. Advanced glycation end-products: Mechanics of aged collagen from molecule to tissue. *Matrix Biol*. May 2017;59:95-108. doi:10.1016/j.matbio.2016.09.001
32. Rechardt M, Shiri R, Karppinen J, Jula A, Heliovaara M, Viikari-Juntura E. Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. *BMC Musculoskelet Disord*. Jul 20 2010;11:165. doi:10.1186/1471-2474-11-165
33. Abate M, Schiavone C, Salini V. Sonographic evaluation of the shoulder in asymptomatic elderly subjects with diabetes. *BMC Musculoskelet Disord*. Dec 7 2010;11:278. doi:10.1186/1471-2474-11-278
34. Via AG, De Cupis M, Spoliti M, Oliva F. Clinical and biological aspects of rotator cuff tears. *Muscles Ligaments Tendons J*. Apr 2013;3(2):70-9. doi:10.11138/mltj/2013.3.2.070
35. Batista F, Nery C, Pinzur M, et al. Achilles tendinopathy in diabetes mellitus. *Foot Ankle Int*. May 2008;29(5):498-501. doi:10.3113/FAI-2008-0498
36. Holmes GB, Lin J. Etiologic factors associated with symptomatic achilles tendinopathy. *Foot Ankle Int*. Nov 2006;27(11):952-9. doi:10.1177/107110070602701115
37. de Jonge S, Rozenberg R, Vieyra B, et al. Achilles tendons in people with type 2 diabetes show mildly compromised structure: an ultrasound tissue characterisation study. *Br J Sports Med*. Aug 2015;49(15):995-9. doi:10.1136/bjsports-2014-093696
38. Giai Via A, Oliva F, Padulo J, Oliva G, Maffulli N. Insertional Calcific Tendinopathy of the Achilles Tendon and Dysmetabolic Diseases: An Epidemiological Survey. *Clin J Sport Med*. Jan 1 2022;32(1):e68-e73. doi:10.1097/JSM.0000000000000881
39. Ranger TA, Wong AM, Cook JL, Gaida JE. Is there an association between tendinopathy and diabetes mellitus? A systematic review with meta-analysis. *Br J Sports Med*. Aug 2016;50(16):982-9. doi:10.1136/bjsports-2015-094735
40. Brent GA. Tissue-specific actions of thyroid hormone: insights from animal models. *Rev Endocr Metab Disord*. Jan 2000;1(1-2):27-33. doi:10.1023/a:1010056202122
41. Oliva F, Berardi AC, Misiti S, Maffulli N. Thyroid hormones and tendon: current views and future perspectives. Concise review. *Muscles Ligaments Tendons J*. Aug 11 2013;3(3):201-3.
42. Oliva F, Marsilio E, Asparago G, et al. Achilles Tendon Rupture and Dysmetabolic Diseases: A Multicentric, Epidemiologic Study. *J Clin Med*. Jun 27 2022;11(13) doi:10.3390/jcm11133698
43. Kivirikko KI, Laitinen O, Aer J, Halme J. Metabolism of collagen in experimental hyperthyroidism and hypothyroidism in the rat. *Endocrinology*. Jun 1967;80(6):1051-61. doi:10.1210/endo-80-6-1051
44. Oliva F, Berardi AC, Misiti S, Verga Falzacappa C, Iacone A, Maffulli N. Thyroid hormones enhance growth and counteract apoptosis in human tenocytes isolated from rotator cuff tendons. *Cell Death Dis*. Jul 4 2013;4(7):e705. doi:10.1038/cddis.2013.229
45. Oliva F, Gatti S, Porcellini G, Forsyth NR, Maffulli N. Growth factors and tendon healing. *Med Sport Sci*. 2012;57:53-64. doi:10.1159/000328878
46. Maffulli N, Ewen SW, Waterston SW, Reaper J, Barrass V. Tenocytes from ruptured and tendinopathic achilles tendons produce greater quantities of type III collagen than tenocytes from normal achilles tendons. An in vitro model of human tendon healing. *Am J Sports Med*. Jul-Aug 2000;28(4):499-505. doi:10.1177/03635465000280040901
47. Vesentini S, Redaelli A, Gautieri A. Nanomechanics of collagen microfibrils. *Muscles Ligaments Tendons J*. Jan 2013;3(1):23-34. doi:10.11138/mltj/2013.3.1.023
48. 48. Oliva F, Osti L, Padulo J, Maffulli N. Epidemiology of the rotator cuff tears: a new incidence related to thyroid disease. *Muscles Ligaments Tendons J*. Jul 2014;4(3):309-14.
49. Chang J, Most D, Thunder R, Mehrara B, Longaker MT, Lineaweaver WC. Molecular studies in flexor tendon

wound healing: the role of basic fibroblast growth factor gene expression. *J Hand Surg Am*. Nov 1998;23(6):1052-8. doi:10.1016/S0363-5023(98)80015-4
50. Ciardulli MC, Marino L, Lovecchio J, et al. Tendon and Cytokine Marker Expression by Human Bone Marrow Mesenchymal Stem Cells in a Hyaluronate/Poly-Lactic-Co-Glycolic Acid (PLGA)/Fibrin Three-Dimensional (3D) Scaffold. *Cells*. May 20 2020;9(5)doi:10.3390/cells9051268
51. Li K, Deng G, Deng Y, et al. High cholesterol inhibits tendon-related gene expressions in tendon-derived stem cells through reactive oxygen species-activated nuclear factor-kappaB signaling. *J Cell Physiol*. Aug 2019;234(10):18017-18028. doi:10.1002/jcp.28433
52. Fruehauf JP, Meyskens FL, Jr. Reactive oxygen species: a breath of life or death? *Clin Cancer Res*. Feb 1 2007;13(3):789-94. doi:10.1158/1078-0432.CCR-06-2082
53. Elli S, Schiaffini G, Macchi M, Spezia M, Chisari E, Maffulli N. High-fat diet, adipokines and low-grade inflammation are associated with disrupted tendon healing: a systematic review of preclinical studies. *Br Med Bull*. Jun 10 2021;138(1):126-143. doi:10.1093/bmb/ldab007
54. Li K, Deng Y, Deng G, et al. High cholesterol induces apoptosis and autophagy through the ROS-activated AKT/FOXO1 pathway in tendon-derived stem cells. *Stem Cell Res Ther*. Mar 20 2020;11(1):131. doi:10.1186/s13287-020-01643-5

Corresponding information:
Received: 22.11.2023.
Accepted: 02.12.2023.
Correspondence to: *Dr. Francesco Cuozzo M.D.
University: Department of Musculoskeletal disorders, school of medicine and surgery
University of Salerno,Via Salvador Allende
84081 Salerno, Italy
E-mail: fra.cuoz@gmail.com