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Systematic Review

Relationship between foot and ankle tendinopathies and dyslipidemia: a literature review

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Abstract

Objectives: Dyslipidemia is a multifactorial condition related to genetic factors, dietary patterns, sedentary habits, and socioeconomic conditions. Foot and ankle tendinopathies are a common problem in orthopedic consultations and can represent up to 30%, highlighting some risk factors, such as metabolic disorders.

Methods: This study is an integrative review of the literature addressing the correlation between foot and ankle tendinopathy and dyslipidemia. The keywords used were: "tendinopathy," "foot and ankle," and "dyslipidemia," with the operators "AND" and "OR" for the search. The following inclusion criteria were established: case reports, cohort studies, case and control studies, clinical trials, and biomechanical studies published between 2013 and 2024, indexed in the following databases: Pubmed (Medline), Scielo, Lilacs, and Scopus, published in English, Spanish, and Portuguese.

Results: Several mechanisms have been proposed to explain the correlation between tendinopathies and dyslipidemia, although there is still no absolute clarity; it was shown that the Achilles tendon is the main tendon affected in the foot and ankle, especially by xanthomas, which lead to an increase in the area size, causing pain, edema, difficulty in movement and changes in gait.

Conclusion: It is believed that females with dyslipidemia, elderly patients, and individuals with a body mass index below 18.5kg/m^2 are more prone to tendinopathies.

Level of evidence II; Diagnostic studies.

Keywords: Tendinopathy; Foot and ankle; Dyslipidemia.

Introduction

Dyslipidemia is a multifactorial condition related to genetic factors, dietary patterns, sedentary habits, and socioeconomic conditions[1,2]. This disease stands out due to its harmful effects on various body systems, including the musculoskeletal system[3-5]. In this case, tendons are frequently affected by injuries ranging from xanthomas[6] to tendinopathies[7]. However, the mechanisms underlying this relationship are not well elucidated yet[8]. It is believed that there are numerous actions of cholesterol in tendons, such as changes in the microenvironment, accumulation of cholesterol in the intertendinous matrix, and inflammatory lipid effects[9,10].

The consequences of hypercholesterolemia in the shoulder, knee, and hand diseases are well reported in the literature[11]. In energy-stored tendons such as the Achilles and the quadriceps femoris[12-14], it is believed that dyslipidemia has the potential to alter their functional and histological characteristics[15]. Some studies have demonstrated that the formation of xanthomas may be an initial clinical manifestation of familial hypercholesterolemia[16].

A study in Sweden with 120 volunteers, 60 individuals with Achilles tendinopathy, and 60 controls observed that patients with tendon pathology presented concomitantly with dyslipidemia, low HDL, and waist circumference bigger than the controls[17].

Study performed at the Universidade Federal de Alfenas, Alfenas, MG, Brazil.

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Foot and ankle tendinopathies are a common problem in orthopedic consultations[18] and can represent up to 30%[19,20], highlighting some risk factors, such as advanced age, metabolic disorders, and use of medications like corticosteroids and statins[21]. These impact the patient's quality of life, causing impairments in gait, work functions, and financial conditions, as they sometimes require complex treatment[22].

Through this literature review, the objective of the study is to discuss and highlight the relationship between dyslipidemia and foot and ankle tendinopathies.

Methods

This literature review followed the steps of producing an integrative review, with the definition of the theme and objectives, choice of keywords and their use in the literature search, definition of inclusion and exclusion factors, selection of studies through the application of these factors, data collection, analysis of the data obtained and their presentation in detail.

The literature search was guided by the question: "Is there a relationship between dyslipidemia and foot and ankle tendinopathies?" The guiding question was elaborated on using the PICO strategy. The keywords used were: "tendinopathy," "foot and ankle," and "dyslipidemia." Such descriptors were used with the operators "AND" and "OR" for the search.

The following inclusion criteria were established: case reports, cohort studies, case and control studies, clinical trials, and biomechanical studies published between 2013 and 2024, indexed in the following databases: Pubmed (Medline), Scielo, Lilacs, and Scopus, published in English, Spanish, and Portuguese and addressing the correlation between foot and ankle tendinopathy and dyslipidemia.

Among the exclusion criteria were articles that did not explore feet and/or ankles and articles without reference to the context of lipidic changes.

The search strategy used for this research is summarized in figure 1, as recommended by the PRISMA guidelines.

Aiming to reduce possible interpretation biases, two researchers analyzed the articles independently, selecting them based on the inclusion and exclusion criteria. Subsequently, the selection results of each researcher were compared. Selection differences were resolved through discussion between the two researchers and a third researcher. The articles were classified according to the level of scientific evidence, according to the Agency for Healthcare Research and Quality (AHRQ).

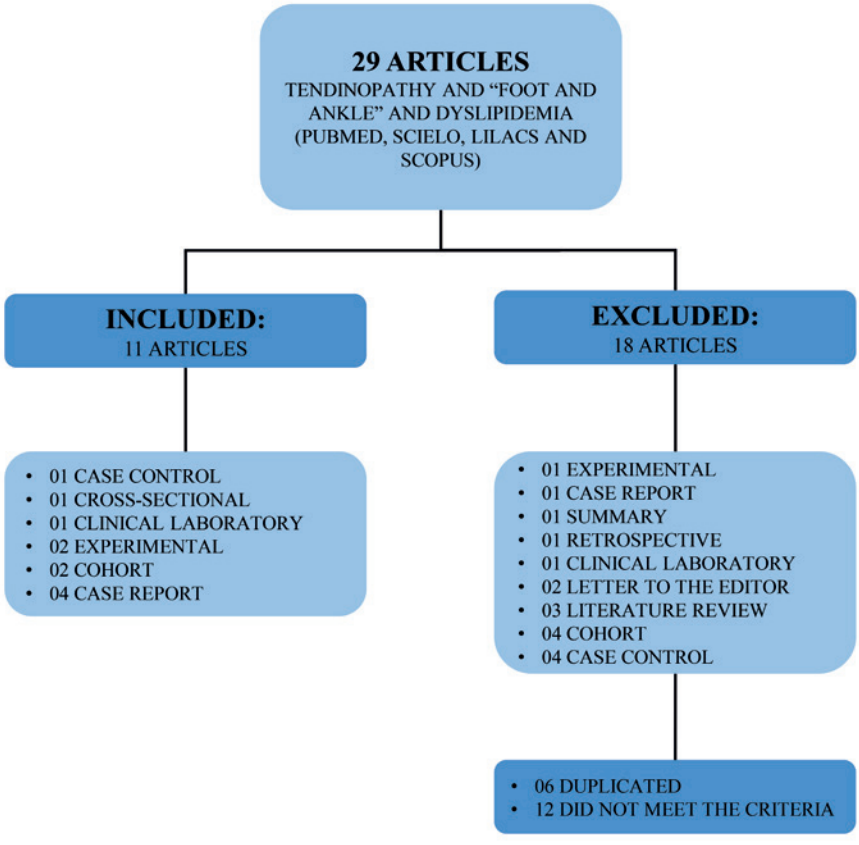

Figure 1. Systematization of articles analyzed according to the inclusion criteria.

The results were analyzed through table 1, which characterizes the publications according to authors, year of publication, type of study, objectives, and main results.

Results and discussion

The relationship between the prevalence of xanthomas, benign tendon tumors, and dyslipidemia has already been explored by many authors. Fernandes et al.[23] presented a report of a xanthoma in the Achilles tendon in a patient with a serum level of 268 mg/dL at the expense of LDL. Song et al.[24] presented another case of multiple xanthomas affecting the Achilles tendon bilaterally, hands and knees, in a 34-year-old patient with primary hyperlipidemia (233 mg/dL of total cholesterol), being treated with statins. The patient also had decreased Achilles and patellar reflexes and pain on palpation of the tendons, especially in the right lower limb[24]. The magnetic resonance imaging identified abnormalities in the Achilles, anterior and posterior tibial tendons, and peroneus longus tendons on the right. Histopathological examination of the lesions showed macrophages full of lipids. It is believed that the lesions are formed in response to an inflammatory reaction triggered by hypercholesterolemia in the tissue environment[24]. Another report by Roy et al.[25] exposed a multinodular condition, identified in the histopathological report as an extensive tuberous xanthoma, in a patient with previously unidentified familial hypercholesterolemia. The patient had abundant edema around the knee, elbow, ankle, and small joints of the feet, in addition to visible thickening and enlargement of the Achilles tendons in both lower limbs[25].

In a clinical trial developed by Li et al.[7], cells from murine models exposed to significant cholesterol levels (10 mg/dL) were used, and their behavior was evaluated. The study proved that cholesterol interrupted cell migration, proliferation, and division, in addition to inducing apoptosis and autophagy in tendon-derived stem cells. It is believed that such events occur through mechanisms such as producing reactive oxygen species, hyperactivation of cleaved caspase-3 and BAX, reduction of Bcl-xL expression, and accumulation of CL3-II. In this sense, the affected cells play an important role in the pathology of tendinopathy, and it is believed that this is one of the mechanisms by which dyslipidemia is related to tendinopathies, given that high cholesterol levels increase the risk of pain and rupture of the tendons[7].

Another experimental study by Grewal et al.[15], using ApoE-KO mice, whose objective was to visualize structural changes in tendons after a controlled lipid diet, did not demonstrate any cellular deformities. As a result, it was expected to visualize a

Table 1. Analysis of articles found in databases according to indexers and search criteria.

Author	Year of publication	Types of studies	Objective	Main results
Fernandes et al.	2015	Case report	Early diagnosis of tendon xanthomas is essential	Imaging diagnosis is faster
Grewal et al.	2013	Experimental study	The knock-out mice with dyslipidemia and involvement of tendon	The results were clarified in another study
Kwak et al.	2023	Cohort study	Treatment of dyslipidemia and the development of tendinopathy	The use of statin favors the development of tendinopathies
Kutkiene et al.	2019	Case-control study	Achilles tendon ultrasound in identifying an increased risk for dyslipidemia	Ultrasonography of the Achilles tendon revealed tendinopathy
Song et al.	2015	Case report	Elucidate that tendon xanthomas may be clinical manifestations of dyslipidemia	Diagnosis of dyslipidemia and xanthomas in lower limbs
Li et al.	2020	Clinical laboratory study	Analyze whether high serum cholesterol levels have biological effects on tendon-derived stem cells	Dyslipidemia induces apoptosis and autophagy of tendon-derived stem cells
Ahn et al.	2021	Cohort study	Evaluate the correlation between dyslipidemia and the risk of tendinopathy	Dyslipidemia is associated with a risk of tendinopathy and Achilles tendon rupture
Albers et al.	2016	Cross-sectional study	The incidence and prevalence of lower limb tendinopathy	Tendinopathy is associated with dyslipidemia
Waugh et al.	2023	Experimental study	The knock-out mice with dyslipidemia and involvement of tendon	The increased cholesterol alters the biomechanical properties of the Achilles tendon
Roy et al.	2020	Case report	Demonstrate that tendon xanthomas are clinical signs of familial hypercholesterolemia	A previous diagnosis of dyslipidemia, with numerous lipid deposits and thickening of the Achilles tendon
Corredoira et al.	2024	Cross-sectional study	To analyze the size of tendon xanthomas in the Achilles tendons of individuals with familial hypercholesterolemia	The tendon xanthomas have varied characteristics depending on age, sex, and LDL cholesterol concentration

change in the architecture of the tendons and high cellularity of rounded tenocytes when compared to normal tendons; however, instead of presenting Achilles tendons with wavy, discrete, and band-shaped deposits under microscopy, no changes were observed[15]. Contradictorily, a more recent trial by Waugh et al.[12], using wild-type mice and also knock-out mice for apolipoprotein E, demonstrated that even a small increase in cholesterol is capable of causing biomechanical changes in tendon structures, therefore, causing a risk of injury. According to Waugh et al.[12], the negative result in ApoE mice can be justified by the inadequacy of this biological model, given that these animals have a subtendon and, therefore, the expected changes cannot be visualized[12].

Epidemiological factors demonstrate a higher prevalence of tendinopathies related to dyslipidemia in females. A case-control study by Kutkienė et al.[26] evaluated 2013 patients, of which 110 already had a previous diagnosis of dyslipidemia. The study analyzed the prevalence of Achilles tendinopathy in 42.7% of patients with severe hypercholesterolemia. When analyzing the prevalence by sex, the association between dyslipidemia and tendinopathies was greater in females[26].

Corredoira et al.[6] published a cross-sectional study including 377 patients diagnosed with familial hypercholesterolemia, in which demographic data such as age, sex, low-density lipoprotein cholesterol, and lipoprotein (a) cholesterol levels were analyzed, together with ultrasound data on the maximum thickness of the Achilles tendon. The results demonstrated that tendon xanthomas, a characteristic of familial hypercholesterolemia, are related to exposure to high cholesterol levels and individual variability, with inert factors responsible for 20% of the heterogeneity of cases[6]. A cross-sectional study by Albers et al.[22] conducted in a Dutch population evaluated the prevalence of lower limb tendinopathy and identified a greater correlation between older individuals and those with metabolic disorders[22]. Another cohort study by Ahn et al. (2021), using a population sample from the Republic of Korea, demonstrated an increased risk of Achilles tendinopathy and Achilles tendon rupture in low-weight patients (BMI < 18.5 kg/m^2), approximately 37% and 116% respectively, under the influence of high LDL cholesterol levels, while obese patients with high LDL levels having a considerably lower risk, presenting around 10% and 16% respectively[10].

Recent studies have also explored the influence of drugs used in the treatment of dyslipidemia and its relationship with tendinopathies. A cohort study by Kwak et al.[27] suggested that the use of statins, regardless of the type, is paradoxically associated with an increased risk of developing different types of tendinopathy, such as Achilles tendon tendinopathy and rupture when compared to non-users of the drugs; this risk, however, tends to reduce according to cumulative daily doses[27]. The report by Roy et al.[25] further infers that commonly prescribed statins may not be very effective in cases of homozygous familial hypercholesterolemia, making it ideal for the use of innovative therapies such as PCSK9 inhibitors or lomitapide[25].

Foot and ankle tendinopathies are a multifactorial condition that results from a complex interaction between intrinsic and extrinsic factors in the affected individual. Hypercholesterolemia is associated with tendon pathologies; however, the reasons behind this relationship are not yet fully understood. Among the studies chosen, the most explored were Achilles tendinopathies and their relationship with dyslipidemia. It was noted that female, elderly patients and those with dyslipidemia with a BMI below 18.5 kg/m^2 are more prone to tendinopathies, especially patients with a previous diagnosis of familial hypercholesterolemia, whether homozygous or heterozygous.

Understanding the relationship between dyslipidemia and foot and ankle tendinopathies is crucial for developing more effective early diagnosis, prevention, and treatment strategies. The studies included in this review emphasize the applicability of ultrasound examination to visualize tendon xanthomas, initially because it is an accessible diagnostic tool widely distributed in health units. Interventions to control dyslipidemia, such as lifestyle modifications and appropriate drug therapy, can play an important role in the prevention and management of this condition; therefore, all variables in this relationship must be evaluated with caution. The use of drugs from the statin class, used to reduce serum LDL levels, does not necessarily result in a reduced risk of developing tendinopathies; on the contrary, paradoxically, they can constitute an additional risk factor.

Conclusion

Several mechanisms have been proposed to explain the correlation between tendinopathies and dyslipidemia, although there is still no absolute clarity; it was shown that the Achilles tendon is the main tendon affected in the foot and ankle, especially by xanthomas, which leads to an increase in the size of the tendon, causing pain, edema, difficulty in movement and changes in gait. It is believed that females with dyslipidemia, elderly patients, and individuals with a BMI below 18.5kg/m^2 are more prone to tendinopathies.

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