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Review

The pathogenesis of Achilles tendinopathy: A systematic review

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ABSTRACT

Achilles tendinopathy is a degenerative, not an inflammatory, condition. It is prevalent in athletes involved in running sports.

A systematic literature review on Achilles tendon tendinopathy has been performed according to the intrinsic (age, sex, body weight, tendon temperature, systemic diseases, muscle strength, flexibility, previous injuries and anatomical variants, genetic predisposition and blood supply) and extrinsic risk factors (drugs and overuse), which can cause tendon suffering and degeneration. Different theories have been found: Neurogenic, Angiogenic, Impingement and "Iceberg" Hypotheses.

Multiple databases were utilized for articles published between 1964 and 2013.

The different hypothesis were analyzed, differently considering those concerning the pathogenesis of tendinopathy and those concerning the etiology of complaints in patients.

This review of the literature demonstrates the heterogeneity of Achilles tendinopathy pathogenesis. Various risk factors have been identified and have shown an interaction between them such as genes, age, circulating and local cytokine production, sex, biomechanics and body composition.

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1. Introduction

The Achilles tendon is one of the most frequently injured tendons in the human body despite its strength [1]: it not only is the commonest tendon to rupture but also, along with the patellar tendon, it represents one of the two tendons most frequently impaired as a result of overuse [2]. Overuse is by definition a repetitive strain acting on a tendon, so that it can no longer endure stress and tension, but other factors may also play a role: the non-athletic population can be frequently affected [3], 30% of patients referred, do not regularly participate in sport [4]. Patients with Achilles tendinopathy commonly refers to pain in the tendon during initial loading, subsiding with continued activity; as the condition becomes chronic, pain can be persistent, resulting in activity curtailment or cessation [5,6]. Infact Maffulli et al. [7] recently defined Achilles tendinopathy as a clinical syndrome characterized by three elements, pain, swelling and functional impairment, corresponding to the histological pattern of "tendinosis", a term that indicates a degenerative non-inflammatory process with a disorganized collagen structure. However, it must be kept in mind that since up to 34% of asymptomatic tendons show histopathological changes [8]: this finding leads to suppose

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that the intratendinous degenerative changes may not be directly the cause of pain. So overuse is considered to induce the condition but the etiology and pathogenesis have not yet been scientifically clarified; the same is for the source of pain and the background of the pain mechanisms. Many different explanations have been raised and consequently the range of conservative and surgical treatment options is actually very wide [8]: a summary of the current hypotheses is provided, analyzing separately those concerning the pathogenesis of tendinopathy and those concerning the etiology of complaint in patients.

2. Materials and methods

Prisma guidelines were followed for this systematic review

Multiple databases, as PubMed, Google Scholar, Academic Search Complete, and Health and Wellness Resource Center, were searched for articles published between 1964 and 2013 concerning informations about the etiology of Achilles tendinopathy using the following search filter: "Achilles tendinopathy" and "Achilles pathogenesis" that identified a total of 480 articles dated from 1967 to 2013. The articles were combined into EndNote and reviewed manually in order to exclude repetitions and to select those specifically related to the argument; among the remaining 362 pertinent articles case reports and articles referring to options of treatment for tendinopathy were excluded (some of these have been considered for the discussion and conclusion).

A total amount of 139 articles were reviewed for inclusion based on the pathogenesis of Achilles tendon with its intrinsic and extrinsic factors, and the various theories formulated in this regard.

3. Results

3.1. Etiology of intratendinous degenerative changes

It is widely acknowledged that causes of intratendinous changes could be divided into intrinsic and extrinsic factors; extrinsic factors play a major role in the acute lesions of the Achilles tendon, while most commonly will be a combination of both extrinsic and intrinsic factors in chronic tendinopathy [9].

According to the intrinsic risk factors, 68 articles describe the various risk factors involved [8,10–74].

19 articles [8,12–29] out of 68, reported that age affects the tendon matrix in different ways. Of these 19 studies, 2 are on animal models [27,28] and they have been shown that also skeletal maturity play a major role in the biomechanical properties.

A total of 10 from 68 articles refer to sex as an intrinsic risk factor [30–39] and men are the most common patients with a tendon overuse injury. Body weight, instead, is indicated in 1 article [40].

Five studies [10,41–44] out of 68 reported that another factor that might predispose avascular tissue for degeneration is its poor capability to regulate the tissue temperature.

The systemic diseases are reported in 4 articles [12,45–47] out of 68 and they compromise tendon strength and elasticity or result in inflammation of the tendon or its insertion (Table 1), while muscle strength, flexibility, previous injuries and anatomical variants are mentioned in 2 studies [22,48] out of 68.

In 23 articles out of 68 the blood supply is indicated as a very important intrinsic risk factor [11,49–70] and it is correlated to the pathogenic role of hypoxia as indicated in 2 of these studies conducted on animals [50,63].

Among the intrinsic factors many are complex phenotypes determined by an interaction between genetic and environmental factors. Four out of 68 are the articles that talks about the genetic predisposition of tendinopathy [71–74].

According to the extrinsic risk factors, 49 articles describe the risk factors involved [12,22,75–120].

The use of several drugs has been associated with tendinopathy and they are mentioned in 10 studies [75–85] out of 49. In 1 of them corticosteroids have been tested on animal tendons [81].

Training errors, environmental conditions, shoes, equipment, surfaces and physical activity/sport are reported in 13 studies out of 49 as extrinsic risk factors [22,86–97].

The "neurogenic hypothesis" is mentioned in 10 articles [95–104], while the role of nitric oxide (NO) and tendom stem cells (TSCs) in 11 [105–116] and 4 studies [117–120] respectively out of 49.

3.2. Etiology of complaint

It is recently hypotesised that the main cause of pain in patients with symptomatic mid-portion Achilles tendinopathy does not arise from the tendon proper but is generated by its surrounding tissues. This concept was elaborated in 7 articles [121–127].

Table 1
Systemic diseases affecting tendons.

	Disease	Structural effect on tendon
Inherited disorders	Homocystinuria (Ochronosis)	Deficient/abnormal collagen and elastin cross-linking
	Aspartylglycosaminuria (AGU)	
	Menkes kinky hair syndrome	
	Marfan syndrome	Abnormal fibril structure
	Myopathies and dystrophies	
	Haemocromatosis	Accumulation of iron in matrix
	Mucopolysaccharidoses	Abnormal collagen fibrils, increased GAGs
	Ehlers–Danlos syndromes	Various defects in collagen processing and structure
	Osteogenesis imperfecta	Genetic defects in type I collagen
	Lipid storage diseases (familial hypercolesterolaemia and cerebrotendinous xanthomatosis)	Xanthomas: slow growing lipid deposits together with inflammatory cells and fibrous reaction
Endocrine and metabolic diseases	Diabetes mellitus	Increased glycation and cross-linking of collagen
	Adrenal disorders	Altered collagen metabolism
	Thyroid and parathyroid disorders	Calcification and accumulation of deposits
	Amyloidosis	Accumulation of deposits between fibrils
	Renal disease	Elastosis, destruction of collagen fibers
Rheumatological diseases	Rheumatoid arthritis	Destruction of collagen: inflammatory infiltrate
	Reactive arthritis and Reiter's syndrome	Inflammation at insertion
	Gout	Urate crystal deposits and inflammation
	Pseudogout	Calcium pyrophosphate deposits and inflammation
	Spondylarthropathies (such as psoriasis)	Inflammation at insertion, fibrosis and calcification