

Considering Genetics in Tendinopathy Management



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Introduction

Tendinopathy is a common condition that affects a large portion of the population [1]. Chronic tendinopathy is frequent in both elite and recreational athletes, but sedentary subjects may also develop tendinopathy in the absence of any history of increased physical activity [2]. Tendinopathy is an umbrella term for clinical presentation of tendon pain during loading, often accompanied by loss of function [3]. Tendinopathies make up 30% of all musculoskeletal injuries and are the most prevalent tendon disorder [4]. The patella, Achilles, lateral elbow and rotator cuff are the most frequent locations of tendinopathy for the lower and upper limbs, respectively [1]. Currently, tendinopathy is considered as a continuum of changes that can move from an acute, inflammatory response to non-pathologic stages or to more advanced stages with degenerative changes [3]. The etiology and development of the tendon injury is considered multifactorial and involves a complex interaction of extrinsic and intrinsic factors that can predispose the person to injuries [5].

Genetics is one of the intrinsic factors that may play a role in the pathogenesis of tendinopathy [6]. Certain genetic alterations make some people more susceptible to developing tendinopathy, even in spite of carrying loads of the same magnitude as other healthy people [7]. This could also explain why there is an increased risk of contralateral rupture of the Achilles tendon in subjects with a previous rupture [8]. Although this pathology often manifests in the dominant extremity, it is also possible to occur in the non-dominant side or bilaterally, even in regions of the tendon in which the load does not reach its maximum. This is another indication suggesting that other mechanisms are involved in the development of this pathology beyond the actual load to which the tendon is subjected. These are reasons why the importance of the genetic component of each individual has emerged as a possible cause of susceptibility to injury in recent years [9].

Clearly, the load (tensile and compressive) has been identified as the greatest variable in inducing damage in the tendon, but how

this load affects the tendon varies according to how it is modulated by individual extrinsic and intrinsic factors [5]. Therefore, it is clear that not all tendons react in the same way to the same load stimulus [3]. To date, several studies have described the contribution of genetic factors to the presence of Achilles, patellar, and rotator cuff tendinopathy [9]. Vaughn et al. [9]. in a systematic review of genetic factors and tendon injury found strong associations of tendinopathy with polymorphism of genes involving type V collagen A1, tenascin-C, matrix metalloproteinase-3, and estrogen-related receptor beta, with the association between tendon injury and COL5A1 having the most support. Although most of these studies describing the contribution of genetic factors to the presence of tendinopathies are developed in lower limbs, there are also emerging indications for rotator cuff or lateral elbow tendinopathy, with new evidence for upper limb tendinopathies being desirable.

In addition to the above mentioned, several specific genetic mutations have been linked to tendon injury involving single nucleotide polymorphisms (change in a nucleotide of a given gene). Altinisik et al. [10] developed the first study reporting that rs12722 and rs13946 single nucleotide polymorphisms are genetic risk factors for tennis elbow, generating high likelihood of developing symptoms in carrier subjects. What's more, the authors reported a protective effect of the CC genotype in development of elbow tendinopathy for this specific single nucleotide polymorphism. There is international consensus about the best treatment for tendinopathy: prevention, which is quite a complex task. Indeed, there are a number of studies which show that injury prediction is a non-linear complex problem [11]. However, in the scientific literature about injury prevention there are several publications in which analytical statistical techniques are used. A reflection in this way may be done in order to apply the appropriate statistical approach [12].

In the study of risk factors for musculoskeletal soft tissue injuries, including tendinopathies, finding a statistically significant

association between a test result and tendinopathy is not sufficient evidence to use the test to predict the risk for injury. It is likely that the individual influence of each potential risk factor for tendinopathy is small, irrelevant or even not statistically significant unless it is analyzed in conjunction with other known factors simultaneously, as a complex event [11]. For this reason, in the artificial intelligence framework, the use of statistical approaches (Machine Learning and Neuronal Networks) could help us to better understand the set of factors and variables that determines the development of a tendinopathic process, and the complex interactions among them [13]. Currently, there are interesting lines of research in progress on prediction of sports injuries with this approach that consider this complexity [13,14].

In this regard, the methodology of genetic profile studies could help in the future to classify the general population, and athletes in particular, according to their level of risk of suffering tendinopathy, although it cannot be considered as a prognostic element [15]. Obviously, having certain genetic polymorphisms associated with tendinopathy is not a sufficient condition for the development of this pathology [16]. This is not as simple as it seems. But considering genetic predisposition as another risk factor in the multifactorial equation, together with other intrinsic and extrinsic factors, would be useful from a clinical and preventive perspective [17,18] for example, to design personalized exercise programs to prevent and even treat this injury, select a sport discipline to practice with less risk of injury to the tendon, or modify the exposure of an individual to other modifiable factors that could trigger the injury with greater probability. Finally, a new focus of interest for researchers in this area is epigenetic risk factors that might predispose an individual to suffer tendinopathy. These are elements which can influence gene expression. One that has received a great deal of attention is DNA methylation in certain genes that have been shown to have differential levels of expression in tendinopathy patients compared to controls.

We will have to pay attention in the future because it really seems to be a variable conditioning the expression of certain genes associated with the risk of suffering tendinopathy. In conclusion, there is increasing evidence that the genetic profile of an individual may predispose them to tendinopathy. However, this is not a unique condition, since it requires interaction with other factors in a complex and unknown equation to finally induce a tendon injury. Although it may seem somewhat futuristic for now, these genetic aspects should be seriously considered in the future for the management of tendinopathy.

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