

Polymorphisms of Lower Limb Sports Injuries in Weightlifters: Meta-Analysis

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Abstract

Introduction: The high incidence of sports injuries in elite athletes is a concern in sports medicine, a broad vision of sport injuries in Colombia and its pathophysiology can be achieved in the scope of genomics, which could respond to numerous sports injuries from the Identification of single nucleotide polymorphism that affect the health of athletes and often distance them from the field of play.

Objective: To determine the incidence of nucleotide polymorphisms (SNPs) in sports injuries of weightlifters. Material and methods. We searched in the databases PubMed, ScienceDirect and EBSCO for studies experimental published to January 2020, including studies in English and Portuguese, corresponding to case-control clinical studies, where the experimental group were weightlifters and controls were supposedly healthy people. The final papers were assessed for quality and bias using the Jadad scoring scale or Oxford quality scoring system. From the data obtained, heterogeneity was identified with the I2 test and the Q statistic, for the estimation of the effect in the cohort studies the odds ratio (OR) and P value <0.05 were used, obtaining the forest plots of each gen. Results. 4 out of 1220 studies were selected, finding a degree of heterogeneity in all studies, such as the risk of injury for the SNPs of the ACNT3 and COL5A1 genes.

Conclusion: The existence of genetic polymorphisms interacts in the integrity of the muscular and tendon system, which allows the incidence of sports injury in weightlifters to be higher, as well as the need to delve into the subject from the prevention of injury and health promotion in elite athletes.

Introduction

Since the advances that have been generated with the analysis of the human genome [1], various studies propose the explanation of multiple pathologies with the presence of Single Nucleotide Polymorphisms (SNPs), that is why research was sought to link certain SNPs with sports injuries in weightlifters and, from this, obtain a clear basis for conducting an exploratory study in a population of athletes who presented sports injuries. Olympic weightlifting are the most commonly practiced strength sports where maximal strength in one repetition is the primary focus. In weightlifting there are two events: the snatch and the clean and jerk. Powerlifting consists of three events: the squat, bench press

and deadlift. The goal of sports is to lift the maximum weight in each event [2]. Sports injuries have been described as acute, being common in weight training such as sprains, strains, tendon avulsions, and compartment syndromes. Common chronic injuries have also been characterized, including rotator cuff tendinopathy and stress injuries in the vertebrae, clavicles, and upper extremities [3]. The origins of sports injuries are diverse; some authors cite physical and physiological factors that are associated with lifestyle habits such as diet and sleep; others indicate that injuries are associated with age, sex, the training process, and fatigue [4]. Currently, information on the frequency and location of sports

injuries in weightlifters is limited, and even more so when studying the presence of single nucleotide polymorphisms associated with sports injuries in weightlifters.

The studies by Rodas et al. [5], cite a high tendency for injuries in a competition, of which 30 to 40% are of muscular origin, which implies an injury risk of almost 2 per 1,000 hours of exposure [6], in the same way, other studies report between 50 and 60% of injuries related to the articular and ligament system [7]. Undoubtedly, the constant physical exercise in high performance athletes generates adaptations and changes in their physiological functions [8], that result in metabolic adjustments, which impact the cardiac and pulmonary systems, among others. At a molecular level, this is evident in the phenotypic changes of soft tissues [9], accompanied by the activation or repression of specific signaling in gene expression pathways [10], a relevant aspect when identifying the high rate of sports injuries. Sports injuries depend largely on external and internal factors [11], related to vulnerability to these kind of injuries. External factors like the frequency of the exercise, intensity, and workload [12] are overcome by designing a tailored routine for the player. On the other hand, some intrinsic factors are associated with genetic susceptibility [13], where several single nucleotide polymorphisms (SNPs) are related. They are located in genes responsible for encoding structural, and soft tissue regulatory proteins that are involved in the lesions [14]. Some research refers to genetic markers in relation to some parameters of sports performance [15], where the relationship of the SNPs with various pathologies as populations, an example of this are the ACTN genes [16], COL1A1 [17], COL5A1 [18], a fact that led to the search for relevant information on these genes with sports injuries and which were taken into account for the performance of this meta-analysis.

SNPs contribute to inter-individual variations in the structural and functional properties of muscle and tendon, which could be involved in the susceptibility of the lesion [19], this is how the literature presents a series of SNPs associated with sports injuries in some genes like ACTN3, a gene that encodes the α -actinin-3 protein, a structural component of the Z disk where the thin filaments of actin are anchored to keep the myofibrillar matrix of fast muscle fibers [20]. Its absence affects the functionality of skeletal muscle when strong contractions are generated [21]. One of the cases presented in recent investigations with athletes of various modalities shows that the SNPs R577 of the ACTN3 gene expresses the substitution of a cytosine (C) for a thymine (T) at nucleotide number 1747 of the DNA sequence in the exon 16, which replaces the synthesis of an arginine with a stop codon [22], causing the production of a protein of only 577 amino acids and thus generating two allele variants: a functional R allele and a non-functional X allele [23,24]. Type V collagen may be a structurally minor player in the collagen hierarchy but is functionally prominent where it plays an important role in regulating fiber diameter as well as assembly (fibrillogenesis) of collagen fibers [25]. Type V collagen protein is encoded by the

collagen type V alpha 1 chain (COL5A1) gene, located on the long (q) arm of chromosome 9 [26] and is expressed in both tendons and ligaments. This leads us to review the bibliography related to the association of single nucleotide polymorphisms (SNPs) with sports injuries in soccer. The objective is to strengthen the field of sports genomics, since it has been little explored in Colombia and fundamental for the generation of personalized sports actions, which would give the opportunity to direct preventive actions and timely intervention to lessen the impact of injuries and thus answer the research question about ¿what are the single nucleotide polymorphisms associated with sports injuries in weightlifters?

Methods and Materials

A meta-analysis was carried out, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. The systematic review of the literature was done until January 2020, there were searched studies published in the last 6 years in the databases indexed in PubMed, ScienceDirect and EBSCO, taking into account that the latest relevant advances in sportomic were present since 2013 [28]. Additional publications were also considered by cross-referencing. Also, a manual search was carried out in the Pubmed databases for the references of the 5 selected articles that served as support for the study. It was used a combination of keywords to detect potentially relevant studies such as sports injury, muscle strain, muscle damage, sports trauma, sports genetics, weightlifters injury, polymorphisms or gene or SNPs, and genotype.

Study Selection

All publications retrieved were screened by title and any duplicates or those irrelevant to the research question were removed. Abstracts of the remaining studies were then similarly screened, and 4 studies were selected for full-text assessment against the predetermined inclusion and exclusion criteria outlined below.

Inclusion and Exclusion Criteria

The present review included case-control studies and genomic association. To be included, the studies had to provide data on the genotypes associated with the state of the population, whose methodology will perform DNA extraction and quantification. The studies should be written in English or Portuguese. There were no restrictions applied regarding the age, gender, or ethnicity of the participants.

Studies were excluded if they were:

- a) review articles, congress abstracts, editorials or other non-original articles
- b) reported in a language other than English. Overall, 26 studies were included for qualitative synthesis. The study selection process and reasons for exclusion are in Figure 1.

Data Extraction and Quality Assessment

For all selected studies, the following data were extracted:

- a) name of first author
- b) date of publication
- c) characteristics of the participants
- d) study design (Table 1).

Table 1: Characteristics in included Studies.

Authors	Year	Sample (n)	N Experimental	N Control	Age Experimental	Age Control
Kim h, et al.	2014	975	121	854	22,2	32,6
Clos, et al.	2019	66	23	43	28	27,8
Brown Kl, et al.	2017	242	112	130	31,6	33,9
Lulińska-kuklik, et al . [38]	2018	421	192	229	23.4	25.3
Total		2069	644	1425	26,66±4,149	32,48±3,725

Risk of Bias Assessment Quality Evaluation

The risk of bias of individual studies was assessed using the Cochrane Collaboration’s risk of bias tool [30]. Studies were given an overall risk of bias grade of either “high”, “unclear” or “low” calculated from the following five domains:

- a) sequence generation
- b) allocation concealment
- c) blinding
- d) Incomplete outcome data
- e) selective reporting of results.

If details for a particular domain were insufficient, the risk of bias was assessed as “unclear” (Table 2). Studies were assessed for inclusion by authors, with disagreements resolved by discussion, and arbitration from the third author if necessary. If a decision on whether to include or exclude a paper could not be made from the title and abstract, the full text was obtained and checked.

Table 2: Assessing risk of bias in included Studies.

Authors	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting of Results	Age Control
Kim H, et al.	+	+	-	?	-	32,6
Brown Kl, et al.	+	+	+	+	+	27,8
Clos E, et al.	+	?	-	-	?	
Lulińska-Kuklik E, et al . [38]	+	+	-	-	?	
Total	+	+	?	+	?	

Data

For the quality of the studies the Oxford quality scoring system was used [31,32]. This scale presents a quality score of five points. Additionally, it includes two criteria for an appropriate randomization method and stealth placement, which range from 0 (weak) to 5 (good) (Table 3). The analyzed studies presented a score of 4.1 points out of 5 was obtained, indicating that the studies have a higher quality than the expected average.

Table 3: Oxford Quality scoring system.

1. Is the study is described as randomized?	Yes=1, no= 0
2. The method used to generate the randomization sequence is described and is this the appropriate one?	Yes=1, no= 0
3. The method used to generate the randomization sequence is the adequate?	Yes=1, no= 0

4. Is the study described as double-blind?	Yes=1, no= 0
5. Is the method of blinding described (masking)?	Yes=1, no= 0
6. The masking (or blinding) method appropriate?	Yes=1, no= 0
7. Is there a description of follow-up losses and dropouts?	Yes=1, no= 0

Statistical Analysis

The random-effects models were used to perform the meta-analysis using the free online software version of Cochrane Review Manager (RevMan) version 5.3. The degree of heterogeneity between the results of the study was evaluated with the statistical I2. The significant association between polymorphisms and sports injuries in soccer was estimated by odd relationships (OR) at a 95% confidence intervals (CI). The comparison of the soccer players with the controls of the healthy population was made with RevMan to build Forest Plot [33].

Results

Once the non-relevant articles were discarded, the PubMed, ScienceDirect, EBSCO databases were used with the cross combination of keywords: sports injury, muscle strain, muscle damage, sports trauma, sports genetics, polymorphisms or gene or SNP, genotype. Then, the inclusion criteria were designed as shown in Figure 1. The general characteristics of the 4 studies corresponding to the control and experimental groups are shown in Table 1. The random-effects model (Odds Ratio) was used

due to population heterogeneity. Below is the subgroup analysis performed according to the different polymorphisms found. The association between ACTN3 polymorphism, and the risk of sports injury is shown in Figure 2, whose heterogeneity is high (I² of 61%), which leads to a risk of injury of OR 0.98, indicating that the risk of injury is greater in the healthy population, CI of 98% (0.64-1.50), statistically significant (P 0,03). The results show that the COL5A1, whose heterogeneity is high (I² of 52%), which leads to a risk of injury of OR 0.98, indicating that the risk of injury is greater in the healthy population, CI of 95% (0.70-1.37), as shown in Figure 3.

Identification	Records identified through database searching (n = 1220)	Additional records identified through other sources (n = 1)
Screening	Records after duplicates removed (n = 222)	
	Records screened (n = 26)	
Eligibility	Full-text articles assessed for eligibility (n = 5)	
	Studies included in qualitative analysis (n = 1)	
Included	Studies included in quantitative synthesis (meta-analysis) (n = 3)	

Figure 1: The study selection process.

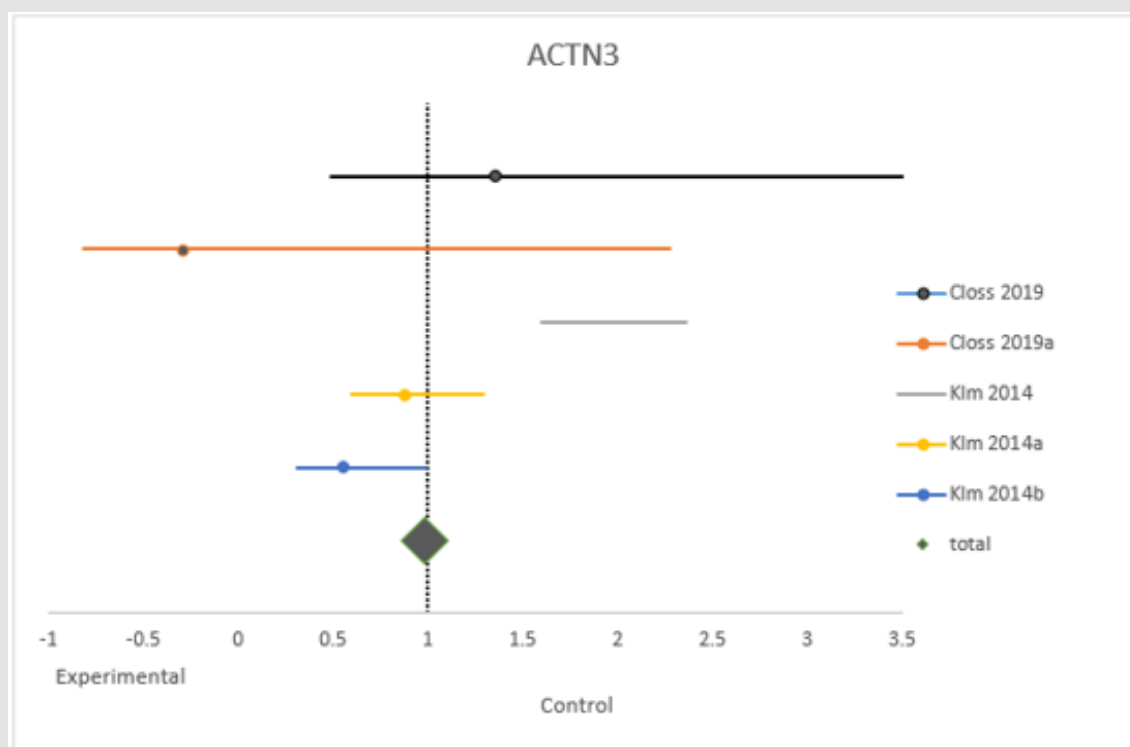


Figure 2: Forest Plot ACTN3.

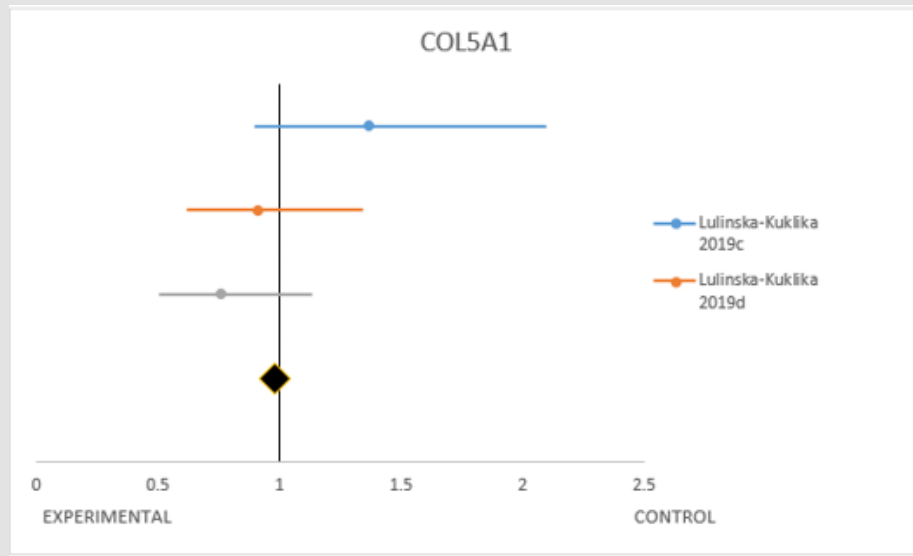


Figure 3: Forest Plot COL5A1.

Discussion

The new sports genomics field focus on research of the SNPs of the genes involved in sports injuries with the aim to evaluate the correlation between a personalized workout with specific SNPs combinations in high performance athletes. This approach is in agreement with Sarzynski MA, Ghosh S, Bouchard [34], where it is proposed to establish future training models, design, and plan sports follow-up processes based on the present polymorphisms that have a lower risk [35]. In general, this meta-analysis delimited which polymorphisms in COL5A1 (rs12722) and ACTN3 (Rx577R) are determinants for the analysis and relationship with sports injuries, which gains importance in the diagnostic and treatment processes. Genetic variations of the COL5A1 gene affect mRNA stability and its export from the nucleus after transcription, where regulatory sequences control gene expression at the post-transcriptional level [36]. Therefore, mutations or variations of a single nucleotide within this region can alter the secondary structure of mRNA and, therefore, the characteristics of proteins [37]. leads to poorly organized fibrils, decreased tensile strength, and reduced stiffness of connective tissue [38]. Functionally, rs12722 variants are believed to alter the stability of COL5A1 mRNA.

Alleles of the rs12722 SNP are proposed to have differential effects on mRNA stability. Stiffness is a complex trait defined by the mechanical property of tensile tissue to resist deformation without failure the T allele is hypothesized to increase mRNA stability by increasing the abundance of collagen V, reducing fibril diameter and increasing tissue-fibril density and tissue stiffness. Previous investigations have described the rs12722 variant genotype with phenotype associations in chronic tendon pathology [39]. The athletic population has a genetic variety being sport an important epigenetic marker for the study [29-31]. This confirms that the

field of sports genetics still lacks some answers and requires more research [40]. This is explained when physiological responses differ from one individual to another, as well as treatment protocols influence the same heterogeneity of the desired response [41]. However, this limitation is overcome by expanding research in different sports. This meta-analysis showed that the population chosen from the different articles is heterogeneous, demonstrating that the presence of certain SNPs affects the risk of sports injury. This is consistent with other similar studies [42] where an incidence of SNPs of the ACTN3 R577X gene associated with a hamstring injury affecting flexibility, and at the same time, manifesting limitations in their ranges of joint movement [43], for which the presence of this polymorphism would give rise to the increase in muscle injuries.

Sports like weightlifting and CrossFit, has the physical requirements are high [44], for which the presence of an injury is related to whether the athlete has an ACTN3 R577X polymorphism; the foregoing reflects that the risk of injury prevails over the individual who does not manifest it. This is how Miyamoto et al [45] infer that this polymorphism is responsible for changes in the sarcomeric cytoskeleton leading to muscle stiffness and prevalence of injury [46]. One of the limitations found in this study was the diversity of polymorphisms associated with sports injuries as well as the limited availability of research on a gene or a defined polymorphism. For this reason, I2 was very high in contrast to some studies in other areas for treatment [47], a situation that differs from the study proposed by Fang et al [48] who found significant associations for the alleles of the ACTN3 gene with the different sports disciplines and performance. Regarding the COL5A1 polymorphism, it was possible to estimate the statistical significance, allowing to determine that the incidence of lesions is associated with this gene, which is confirmed in other studies

[36], by indicating that type V collagen generates an important regulation in the diameter of the fibers. as in the assembly process of the collagen fiber [49], essential for the moments of traction and compression that are exerted during the start of weightlifting.

This is highlighted by Raleigh (2012) [50], when indicating about the implications of epigenetic factors in gene regulation beyond polymorphisms and modification of sports performance. Therefore, robust replication of studies in large cohorts of athletes is required before the findings can be applied to practice in sport. The limitations of the study are reflected in the limited availability of literature on the subject of sports genomics and its interaction with sports injuries, which is supported by various investigations on the subject [51,52]. Although the overall risk of bias within those included studies were considered low, some reports that were excluded had biases due to selective reports and incomplete data. Therefore, it is recommended that future studies include reporting on all measured allele frequencies rather than focusing only on the most common genetic variants.

Conclusions

The meta-analysis allowed us to determine that the field of sports genomics is poorly explored in Colombia and that it requires more research to generate genetic profiles related to sports injuries. In general, 2 possible SNPs of the different genes that are related to sports injuries have been identified, which can be used as preliminary evidence to develop an investigation focused on the polygenic nature of complex traits related to specific pathologies of the muscular system and tendinous. For the ACTN3 and COL5A1 genes, a risk and positive association were observed, with statistical significance $p < 0.05$, which allows generating new horizons from this knowledge, that help to reveal the pathophysiology of sports injuries. The Authors declare not to present any conflict of interest and their participation in the entire study process.

Ethical-Legal Aspects

This study is cataloged as a risk-free investigation by not carrying out any intervention or intentional modification of the biological, physiological, psychological, or social variables of individuals, as stipulated in resolution 8430 of 1993 [53] and following the guidelines of the declaration Helsinki as PRISMA's guide to meta-analysis. The present project was approved by the Ethics Committee of the Universidad del Cauca through code 4925 called Sports Injury Prevention.

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