Chapter 1

Examination Of The Factors That Have An Effect On Anterior Cruciate Ligament Injury

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Abstract

Sports injuries, which are defined as sports-specific injuries, have been significantly affected by the increasing popularity of sports and the continuous development of athletes. The knee joint, which is the largest and most complex joint of the human body, is one of the seven major joints of the body, where soft tissues such as the meniscus, femoral cartilage, tibial plateau cartilage, ligament and tendons are located. This complex joint is very susceptible to injuries due to its ability to withstand anatomical and physiological loads. Anterior Cruciate Ligament, an important component of the knee joint, has a key role in stabilizing the knee joint and in large mechanical loads. However, in some cases, sudden movements, strains, and rotations can cause serious damage to the Anterior Cruciate Ligament. The aim of this study is to examine the factors that cause Anterior Cruciate Ligament Injuries in detail from many perspectives. In the study, data related to Anterior Cruciate Ligament and Anterior Cruciate Ligament Injuries were determined by scanning the NCBI database. The data obtained as a result of the screening were included in the scope of the study. When the factors that may cause Anterior Cruciate Ligament Injuries are carefully evaluated, it has been determined that biomechanical and genetic factors are important risk factors in these injuries. To the best of our knowledge, the location of the Anterior Cruciate Ligament in the knee joint and the loads to which it is exposed are important biomechanical causes of injury to this region. In addition, some genes can seriously change, due to the proteins they decode, the structural integrity of soft tissues. Considering that sports have a complex

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structure, other factors that may cause Anterior Cruciate Ligament Injury should also be investigated meticulously.

Introduction

In today's world, the number and type of injuries tend to increase in parallel with the increasing interest in physical activities. Physical activity-related injuries are a comprehensive type of injury that all individuals, from athletes to sedentary individuals, frequently experience (Werner et al., 2023). The positive effects of physical activities on human health may be an important reason for this result (Renton et al., 2021). In addition, the efforts of athletes to improve sports performance may also have an impact on injuries.

Sports injuries, which are defined as sports-specific injuries, have been significantly affected by the increasing popularity of sports and the continuous development of athletes. Additionally, sports injuries are a condition that has significant financial consequences and negative effects (Kimura et al., 2023; Tranaeus et al., 2024). Sports injuries are classified differently according to the side of injury and tissue structure. Soft tissue injuries are defined as damage to muscles, tendons, fascia, ligaments, bursa, bones, cartilage, blood vessels, etc (Xiong et al., 2025). In this sense, soft tissues may have important roles in maintaining the joint integrity of body limbs during biomechanical movement.

The knee joint, which is the largest and most complex joint of the human body, is one of the seven major joints of the body, where soft tissues such as the meniscus, femoral cartilage, tibial plateau cartilage, ligament and tendons are located. This complex joint is very susceptible to injuries due to its ability to withstand anatomical and physiological loads (Flandry and Hommel 2011; Li et al., 2024). ACL (Anterior Cruciate Ligament), an important component of the knee joint, has a key role in stabilizing the knee joint and in large mechanical loads (Sha et al., 2022; Kacprzak et al., 2024). However, in some cases, sudden movements, strains, and rotations can cause serious damage to the ACL. For this reason, ACLI (Anterior Cruciate Ligament Injury) is a common type of injury among skeletal-muscle injuries in athletes (Stańczak et al., 2025). Many factors such as biomechanical, anatomical, genetic, environmental, etc. have an impact on ACLI (Baker et al., 2017; Maniar et al., 2022; Candela et al., 2024; Tosarelli, ve diğerleri, 2024). In the literature review, it was reported that many factors that caused these injuries were evaluated in a one-dimensional manner in studies on ACLI. To our knowledge, the deficiencies in the studies in which these factors are examined in the multidisciplinary field are remarkable. In light of this, the aim of this study is to examine the factors that cause ACLI in detail from many perspectives. It is predicted that the study will make valuable contributions to the existing literature in this field.

Material and Methods

Selection of Data

In the study, data related to ACL were determined by scanning the NCBI database. To this end, the biomechanical and anatomical structure of ACL, the factors that cause ACL, the economic impact of ACL, the relationship between sports and genetics, and the effect of genetic factors on ACL were written in the NCBI content and screened. The data obtained as a result of the screening were included in the scope of the study. Editorial notes, conferences and non-original publications were not evaluated. The present study, MeSH (Medical Subject Headings) was used to determine the terminology equivalents of the data. MeSH is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed.

Evaluation of Data

A repository was created for the data obtained from the NCBI database. Then, the data suitable for the purpose of the study from the pool were ranked from general to specific. The data of the general information were presented in the introduction of the present study. In the findings part of the study, the data emphasizing the ultimate purpose of the subject were evaluated and explained in detail. A common evaluation was reached with the data obtained in the conclusion part of the study. In the evaluation, preparation for the subject in general information, determination of the source of the problem in the findings, and more inclusive information in the conclusion section were determined as the basic criteria.

Anatomy of the Anterior Cruciate Ligament and Its Biomechanical Function in Injury

Collagen plays an important role as a major structural protein in ligaments and tendons in mammals and is frequently found in connective tissues such as muscles, bones, cartilage, tendons, ligaments, meniscus, skin, etc. (Guo et al. 2024). These structures, which include the soft tissues of the body, have different functions and tasks in the body. For this purpose, the knee joint has a key role in the stability of the knee due to the collagen structures it contains.

The flat physis of the distal femur provides support for approximately 70 % of the whole femur length and 37 % of the whole limb length in skeletal development, at a growth rate of 10 mm per year. The proximal tibial physis supports approximately to 55% of the whole tibial length and 25% of the whole limb length in skeletal development, at a growth rate of 6.4 mm per year (Cancino et al. 2022) . The complex structure of the knee joint is shown in Figure 1 (Boyan et al. 2013; Kean et al. 2017).

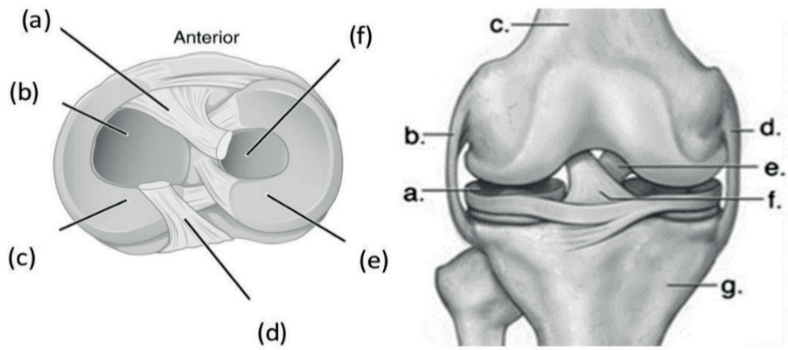

Figure 1. Left to right; a- ACL b- Articular cartilage on the medial tibial condyle c- Medial meniscus d- Posterior cruciate ligament (PCL) e- Lateral meniscus f- Articular cartilage on the lateral tibial condyle. a- Meniscus b- Lateral collateral ligament c- Distal femur d- Medial kollateral bağ e- PCL f- ACL g- Proximal tibia.

The ACL is a double-bundled structure composed of anterio-medial (AM) and posterio-lateral (PL) collagen bundles (Beaulieu et al. 2021). The length of the ACL, which prevents excessive stretching by providing stability of the knee joint, is approximately 25 to 35 mm in length and 4 to 10 mm in breadth (Marieswaran et al. 2018). The measurement of the dimensions of the ACL using the caliper is shown in Figure 2 (Śmigielski et al. 2015).

Figure 2. Measurement of the medium material width, thickness and long axis of the ACL.

ACL plays a critical role in the movement of the knee joint. For this reason, ACL has a feature that supports anterior tibial translation (ATT) and internal rotation (IR) of the knee. This functional role of the ACL is realized due to the tense characteristics of the ligaments and the anatomical structure of this region. When the knee is in the extension position, while standing, the ATT is a maximum of 2 mm, when the external anterior-posterior load is applied in knee flexion, when walking, the ATT increases up to 3 mm. When anterior tibial load is applied, ATT may reach 5 mm (Markolf et al. 1976; Freeman and Pinskerova, 2005; Domnick et al. 2016).

The ACL has a biomechanics that regulates the internal rotation of the tibia and the angle of valgus rotation (Matsumoto et al. 2001). There are some negative conditions that affect this biomechanical structure. ACLI, which is the most important of these, occurs in most cases as a result of the PL bundle being exposed to more load in the position where the knee is in full extension. This result is influenced by the fact that the PL bundle is an important structure that regulates the overall biomechanical stability (Siegel et al. 2012). Another biomechanical effect for ACLI is the deterioration of the valgus angle of the knee. Dynamic valgus for ACLI occurs when the distal femur approaches the midline of the body or when the distal tibia moves away from the midline of the body. Images of the dynamic valgus angle are shown in Figure 3 (Hewett et al. 2005; Arhos et al. 2021).

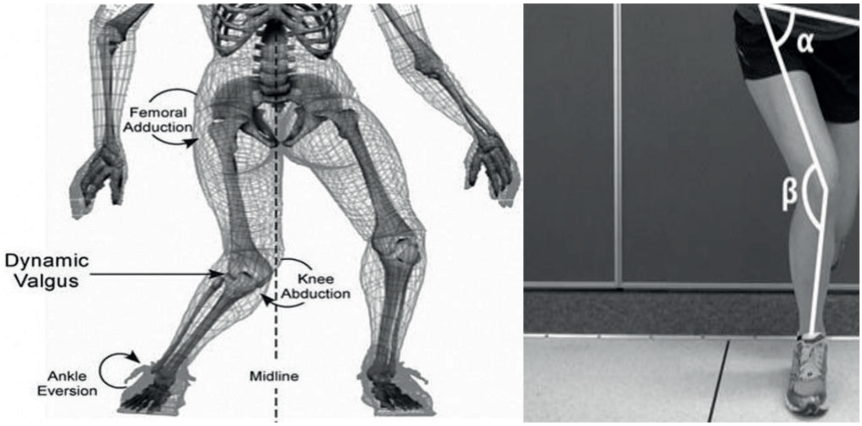

Figure 3. 3D measurement of dynamic valgus and kinematic measurements of hip (α) ***and knee*** (β).

As shown in Figure 3, biomechanical factors can have a significant impact on ACL injuries. This may be explained by the biomechanical properties of the ACL. Despite this evidence, there are other factors that may be cause ACLI. In this sense, the issue needs to be investigated in detail. During our literature review, it was also reported that there was an increasing interest in studies on the biomechanical mechanism of ACLI (Amini et al. 2022; Janani et al. 2023; Kim et al. 2023; Rai et al. 2023; Rigg et al. 2023; Loya et al. 2024; Issaoui et al. 2025; Karatekin et al. 2025; Li et al. 2025; O'Brien et al. 2025).

Rehabilitation in Anterior Cruciate Ligament Injuries

Rehabilitation practices are carried out in order to accelerate the recovery process of the athlete and support his performance after ACLI. The ultimate goal of these practices is to help the athlete quickly return to the pre-injury performance level (Kotsifaki et al., 2023).

Despite the benefits of standard rehabilitation practices applied in the treatment of ACLI, it is very difficult to achieve equal success for every individual. For this reason, potential alternatives, with the developing technology, to these standard applications have been developed. In these applications, called ACL biotherapy, patients are often treated with hyaluronic acid, self-assembling short peptides, growth factors, stem cell therapy, gene therapy, platelet-rich plasma therapy, bone marrow aspirate concentrate, extracorporeal shock wave therapy (ESWT) and electrical stimulation (Yu et al., 2024).

Although rehabilitation services play a key role in ACLI, early and accurate diagnosis of these injuries can be critical to successful rehabilitation (Hu et al., 2024; Lin et al., 2024). In this sense, knowing the susceptibility of athletes to ACLI may significantly reduce the prevalence of these injuries.

Frequency and Economic Impact of Anterior Cruciate Ligament Injuries

Ligaments are dense fibrous connective tissues that are vital for the mobility and stability of the musculoskeletal system (Bobzin et al. 2021). The most common mechanism of ligament damage is the consecutive rupture of degraded collagen fibril bundles along the connective tissue (Chekroun et al. 2022). ACLI, one of these damages, is a negative condition that occurs in the knee area and is encountered by 85% of every 100,000 patients (Granan et al. 2007; Lynch et al. 2015; Kaeding et al. 2017; Diermeier et al. 2020). In the US, 68.6% of 100,000 patients suffer from ACLI each year, and male (81.7 %) individuals were more likely to be exposed than women (55.3 %) individuals (Sanders et al. 2016). In a study of individuals aged 5 to 14 years with ACL injuries who were admitted to hospital in Australia over a 10-year period (2005-2015), It was reported that the prevalence of ACLI increased from 2.74% to 6.79% (Shaw and Finch 2017).

The ACLI may often be considered a critical threshold in athletes' careers. This result emphasized that ACLI was significant for sports performance (Gladstone and Andrews 2002). Although many factors are effective on ACLI, there are other dimensions of this injury. In this sense, ACLI is not only a major obstacle to sporting performance, it is also an injury that brings with it serious economic burdens. ACLI, which significantly affects both athlete and sedentary individuals, is widely treated in orthopedic surgery. To this end, in a study conducted in the US regarding the economic impact of these treatments, it was found that ACLI's lifetime burden was $7.6 billion annually, and rehabilitation costs were $ 17.7 billion (Mather et al. 2013). A similar study in the U.S. reported an increase from 86,687 cases in 1994 to 129,836 cases in 2006 (Mall et al. 2014).

Genetic Influence on Athletic Performance

Genetics, which became important after the completion of the HGP (Human Genome Project), developed rapidly with the development of DNA sequencing techniques and gene editing technologies. To this end, CRISPR/Cas (clustered regularly interspaced short palindromic repeats) systems have supported DNA sequences to be easy, fast and cost-effective (Mali et al. 2013; Tanisawa et al. 2020). The studies, due to gene sequencing system, are carried out more comprehensively (Roth et al. 2012). The development of gene sequencing methods has increased the interest in the hereditary aspect of sports performance and formed the basis of sports genetics.

As a result of the studies concluded in the scope of the relationship between sports and genetics, many gene polymorphisms that may be related to performance were identified (Buxens et al. 2011). Additionally, in the studies, it was reported that these polymorphisms may be related to muscle fibril structure, aerobic-anaerobic capacity, VO2max, strength, speed, endurance, flexibility, ligament, etc. When the data obtained were analyzed, it was determined that genetics contributed 66% to sports performance (De Moor et al. 2007). This contribution is estimated to be 44-68% in endurance performance and 48-56% in strength/power performance (Zempo et al. 2017; Miyamoto-Mikami et al. 2018; Psatha et al. 2024).

Investigation of The Relationship between ACLI and Gene

Despite the many factors that affect ACLI, there are some differences in the mechanisms of occurrence of these injuries. When the literature was reviewed, it was determined that the underlying causes of the biomechanical mechanism of ACLI may be important for these injuries. However, in some studies on ACLI, it was reported that these injuries occur non-contact. (Agel et al., 2007; Boden et al., 2010). This result may indicate that biological factors play a critical role in ACLI. To this end, Identifying genes that have the power to affect soft tissues can reveal the truth about the molecular structure of ACL. In this sense, descriptions of some genes that are assumed to have an effect on soft tissues are presented in Table 1 (Feldmann et al., 2022).

Table 1. Some genes related to soft tissue injuries and their characteristics

Gene	Encoded protein	Chromosomal Location	Variant
ACAN	Aggrecan	15q26.1	rs2351491 C/T, rs1042631 C/T, rs1516797 T/G
ADAMTS10	Metallopeptidase with Thrombospondin Type 1 Motif 10	19p13.2	rs62621197 C/T
ADAMTS17	Metallopeptidase with Thrombospondin Type 1 Motif 17	15q26.3	rs72755233 G/A
ADIPOQ	Adiponectin	3q27.3	rs1501299 G/T

ANKH	Progressive ankylosis protein homolog	5p15.2	rs3045 A/G
BGN	Biglycan	Xq28	rs1126499 C/T, rs1042103 G/A
CASP8	Caspase-8	2q33-q34	rs3834129 ins/del, rs1045485 G/C
COL1A1	Pro-α polypeptide of collagen type I	17q21.33	rs1107946 G/T
COL3A1	α1 III collagen chain	2q31	rs1800255 G/A
COL5A1	Pro-α polypeptide of type V collagen	9q34.2-q34.3	rs12722 T/C
COL11A1	α1 XI collagen chain	1p21	rs3753841 T/C, rs1676486 C/T
COL11A2	α2 XI collagen chain	6p21.3	rs1799907 T/A
COL12A1	Pro-α1 polypeptide type XII collagen	6q12-q13	rs970547 A/G rs1800012 G/T
COL27A1	α1 XXVII collagen chain	9q32	rs946053 G/T
DCN	Decorin	12q22	rs516115 A/G
DEFB1	Beta-defensin 1	8p23.1	rs1800972 C/T
EFEMP1	GF-containing fibulin-like extracellular matrix protein 1	2p16.1	rs3791679 A/G
ESRRB	Steroid hormone receptor ERR2	14q24.3	rs1676303 C/T
FBN2	Fibrillin-2	5q23-q31	rs331079 G/T
FGF10	Fibroblast growth factor 10	5p12	rs11750845 C/T, rs1011814 T/C
FGF3	Fibroblast growth factor 3	11q13.3	rs12574452 G/A
FGFR1	Fibroblast growth factor receptor 1	8p11.23	rs13317 T/C
GDF5	Growth differentiation factor 5	20q11	rs143383 T/C
IL1B	Interleukin-Iβ	2q14	rs16944 T/C
IL1RN	Interleukin-1 receptor antagonist	2q14.2	rs2234663
IL6	Interleukin-6	1q21	rs1800795 G/C
IL6R	Interleukin-6 receptor	1q21	rs2221845 A/C

KDR	Kinase insert domain receptor	4q11-4q12	rs2071559 A/G, rs2305948 G/A, rs1870377 T/A
LUM	Lumican	12q21.33	rs2268578 T/C
MIR608	microRNA 608	10q24.31	rs4919510 C/G
MMP1	Matrix metalloproteinase 1	11q22.3	rs1799750 1G/2G
MMP3	Matrix metalloproteinase 3	11q22.3	rs679620 A/G
MMP8	Matrix metalloproteinase 8	11q22.3	rs11225395 C/T
MMP10	Matrix metalloproteinase 10	11q22.3	rs486055 C/T
MMP12	Matrix metalloproteinase 12	11q22.3	rs2276109 A/G
THBS2	Thrombospondin-2	6q27	rs9406328 C/T
TIMP2	Metalloproteinase inhibitor 2	17q25	rs4789932 C/T
TNAP	Tissue-Nonspecific Alkaline Phosphatase	1p36.12	rs4654760 C/T
TNC	Tenascin-C glycoprotein	9q33	rs1330363 A/G, rs2104772 T/A, rs13321 G/C rs1138545 G/A, rs3789870 C/T, rs7021589 A/G rs10759753 T/C, rs72758637 G/C, rs7035322 G/T
VEGFA	Vascular endothelial growth factor A	6p21.1	rs699947 C/C, rs1570360 G/A, rs2010963 G/C

As shown in Figure 1, some genes have important, due to the proteins they encode, effects on the structural integrity of soft tissues. For this reason, considering the anatomical and biomechanical structure of the ACL, the intense protein synthesis of this structure may affect the injury susceptibility of athletes. In studies on the *COL5A1* rs12722 gene, it was determined that athletes with TT genotype and T allele were exposed to injuries more frequently due to intense collagen synthesis (Miyamoto-Mikami et al., 2019). For this purpose, Lv et al. (2017) concluded in their study that *COL5A1* rs12722 polymorphism was positively associated with tendon and ligament injuries. Individuals with TT genotype were predisposed to higher risk. The level range of motion of the soft tissues may be an important factor on this result. Increasing the level of range of motion can stimulate the development of a mechanism by which soft tissues are more resistant to injury. To this end, in the study by Petrillo et al. (2020) reported that *COL5A1* rs12722 CC showed a range of motion (ROM) of passive external rotation statistically higher compared to CT genotype and TT genotype. In the study on ACLI, Malila et al. (2011) found that the association between *MMP3* -1612 5A/6A polymorphism and ACLI was statistically significant. Posthumus et al. (2009) reported statistically significant association between *COL1A1* Sp 1 binding polymorphism TT genotype and ACLI. In another study by Posthumus et al. (2009) found that statistically significant the association between *COL5A1* BstUI RFLP (Restriction Fragment Lenght Polymorphism) and ACLI in female athletes. Contrary to these results, Lulińska et al. (2020) were reported that no *MMP1* rs1799750, *MMP10* rs486055, and *MMP12* rs2276109 polymorphims were associated with non-contact ACLI.

Conclusion

In the present study, many mechanisms acting on ACLI were examined from a broad perspective. When the factors that may cause ACLI are carefully evaluated, it has been determined that biomechanical and genetic factors are important risk factors in these injuries. To the best of our knowledge, the location of the ACL in the knee joint and the loads to which it is exposed are important biomechanical causes of injury to this region. In addition, some genes can seriously change, due to the proteins they decode, the structural integrity of soft tissues. Considering that sports have a complex structure, other factors that may cause ACLI should also be investigated meticulously.

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