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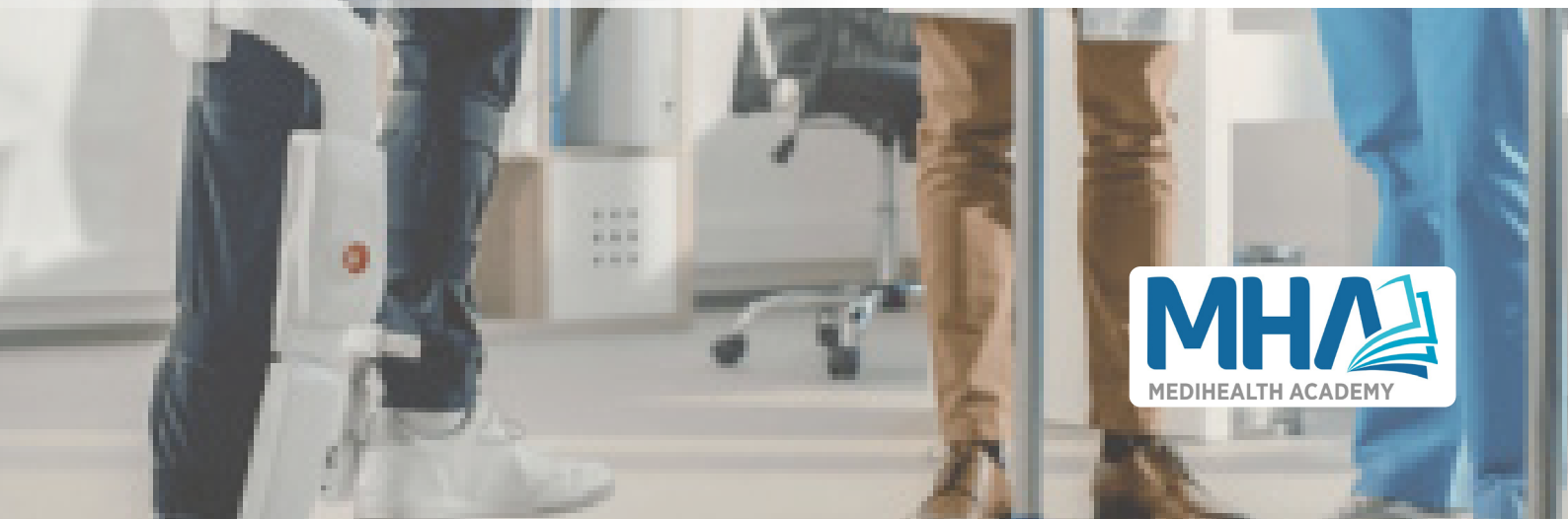

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REVIEWS

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Original Article

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A multiplanar tomographic modeling-based comparison of coracoid process transfer techniques for anterior shoulder instability

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ABSTRACT

Aims: This study aimed to compare the standard and congruent arc Latarjet techniques in anterior shoulder instability using a multiplanar computed tomography (CT)-based modeling approach, with particular focus on coracoid process morphology, glenoid reconstruction capacity, and graft contact surface area.

Methods: A total of 200 patients were included for coracoid measurements and 156 patients for glenoid measurements. Coracoid length, width, and thickness were evaluated, and glenoid width was measured on CT images. The potential glenoid bone defect reconstruction capacity and graft to glenoid contact surface area were calculated for both techniques. Gender-based anatomical differences were also analyzed.

Results: Coracoid dimensions were significantly larger in males than in females. The congruent arc Latarjet technique allowed reconstruction of a larger proportion of the anterior glenoid bone defect (mean 55%) than the standard Latarjet technique (mean 37%). In contrast, the standard technique provided a larger contact surface area between the transferred coracoid graft and the glenoid (452±126 mm^2 vs. 292±105 mm^2, $p<0.001$). Smaller coracoid dimensions, particularly in female patients, were associated with a smaller graft to glenoid contact area and the need for smaller fixation screws, which may reduce the mechanical stability of graft fixation.

Conclusion: While the congruent arc Latarjet technique allows reconstruction of larger glenoid bone defects, the standard technique offers a greater contact surface area that may favor graft healing and fixation stability. Coracoid process morphology, especially in smaller-sized coracoids, should be considered during surgical planning. Preoperative evaluation of coracoid process dimensions may help optimize technique selection and reduce the risk of complications.

Keywords: Shoulder dislocation, Latarjet procedure, bone transplantation, coracoid process

INTRODUCTION

Anterior shoulder instability is one of the most common forms of joint instability and accounts for the majority of shoulder dislocations. Recurrent instability is frequently associated with anteroinferior glenoid bone loss, which directly affects treatment outcomes.[1] Biomechanical studies have demonstrated that increasing glenoid defects significantly compromise shoulder stability.[2] Although soft tissue repairs may be effective in selected cases, failure rates increase in the presence of substantial bone loss.[3] Therefore, both soft tissue and bony structures should be considered together in the evaluation of anterior shoulder instability. Accurate analysis of anatomical and biomechanical factors is critical in determining the most appropriate surgical approach.

In the surgical management of anterior shoulder instability, various techniques have been described, particularly in cases with significant bone defects. Among these, the Latarjet procedure, based on coracoid process transfer, is widely preferred due to its ability to provide both static and dynamic stability.[4] In the classic Latarjet technique, the inferior surface of the coracoid is fixed to the anteroinferior glenoid, whereas in the congruent-arc modification, the coracoid is rotated by 90° to achieve a reconstruction that better conforms to the native glenoid curvature. This modification has been shown to restore larger glenoid defects and improve articular congruency.[5] However, there is ongoing debate regarding graft fixation strength, union potential, and the risk of complications.[6] Although favorable clinical outcomes have been reported for both techniques[7,8] their biomechanical differences have not yet been fully clarified.

Although both the standard and congruent-arc Latarjet techniques are widely used in clinical practice, studies comparing these methods from anatomical and biomechanical perspectives remain limited. In particular, the impact of coracoid morphology on surgical feasibility has not been sufficiently investigated in detail.[9] Existing studies suggest that while the congruent-arc technique may restore

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larger defects, it may also present disadvantages in terms of contact surface area and fixation stability.[10] Furthermore, the influence of anatomical differences between male and female patients on surgical outcomes has not been adequately evaluated in the literature.[11] This issue should not be overlooked, as smaller coracoid dimensions may increase the risk of intraoperative fracture and inadequate fixation. Therefore, further detailed investigation of the effects of coracoid anatomy on different surgical techniques is warranted.

The aim of this study was to compare the standard and congruent-arc Latarjet techniques using a multiplanar computed tomography (CT)-based modeling approach. In this context, coracoid measurements, glenoid reconstruction capacity, and graft contact surface area were evaluated. In addition, the impact of anatomical differences between male and female patients on surgical feasibility and fixation stability was analyzed. We hypothesized that the congruent-arc technique would be able to restore larger glenoid defects, whereas the standard technique would provide a greater bone contact surface area. Furthermore, it was anticipated that fixation parameters and the risk of complications could be affected, particularly in patients with smaller coracoid dimensions.

METHODS

Ethics

In this retrospective study, shoulder joint CT images of 200 patients who presented between 2000 and 2020 were analyzed. Ethical approval was obtained the Ankara University Human Researches Ethics Committee (Date: 13.02.2020, Decision No: I1-72-20), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

Patients with acute or healed fractures involving the proximal humerus, clavicle, or scapula, radiographic evidence of glenohumeral osteoarthritis, previous shoulder surgery, congenital or acquired shoulder deformities, or CT images with motion artifacts, incomplete visualization of the anatomical landmarks, or insufficient image quality for reliable measurements were excluded.

A total of 200 patients were included for coracoid measurements, while 156 patients were included for glenoid measurements. CT images were transferred to appropriate imaging software and analyzed using the multiplanar reconstruction function. Using this method, an oblique sagittal view of the coracoid was obtained, and the distance from the tip of the coracoid to its "elbow" was measured (Figure 1). Additionally, cross-sectional images perpendicular to the axis of the coracoid were generated to obtain a mid-section view; on this section, the medial-lateral width and superior-inferior thickness of the coracoid were measured (Figure 2).

Glenoid width was measured on CT images of 156 patients, and mean values were calculated. At this stage, patients with glenoid bone defects were excluded. The presence of glenoid bone loss was assessed on sagittal CT sections using the "best-fit circle" method. For this purpose, an optimal circle was fitted to the posterior and inferior margins of the glenoid,

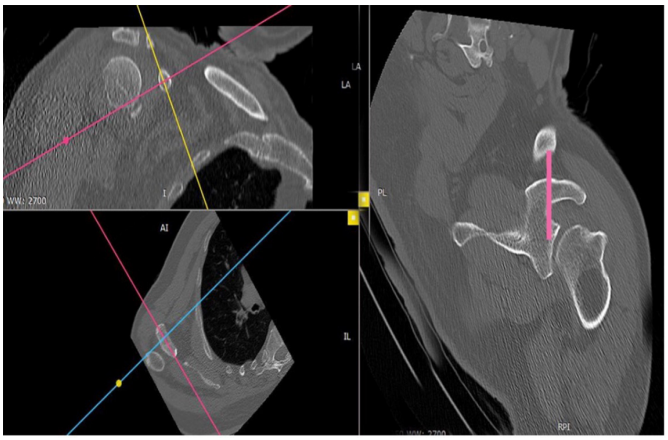

Figure 1. Oblique sagittal view of the coracoid process. The reference line was drawn through the region corresponding to the "elbow" of the coracoid

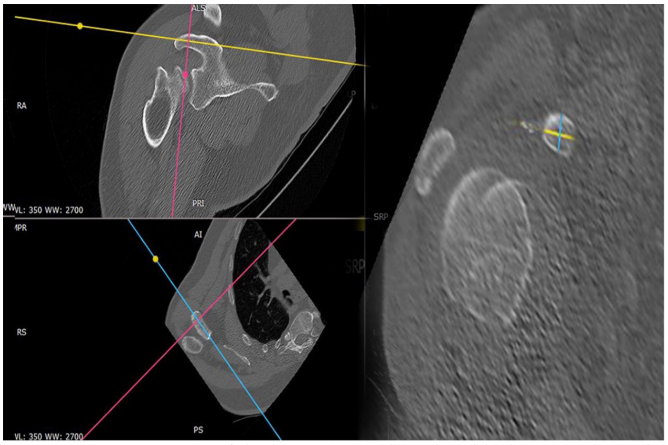

Figure 2. Measurement of thickness (vertical) and width (horizontal) on the oblique axial view of the coracoid process

and the presence of a defect was determined based on this reference (Figure 3). In these patients, the potential glenoid defect restoration ratios were calculated for both surgical techniques.

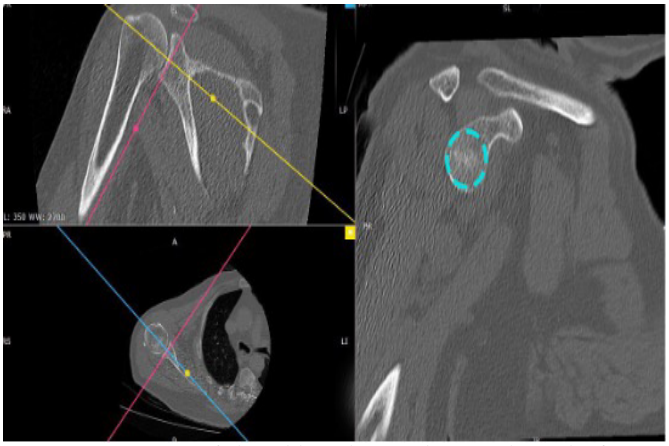

Figure 3. Assessment of glenoid bone loss on the sagittal view by fitting a best-fit circle to determine the presence of a defect

The contact surface area between the coracoid and the anteroinferior glenoid region, which is critical for bone union, was calculated based on the method described by Michel Latarjet. In the standard technique, the contact area was determined by multiplying the coracoid length by its medial-lateral width, whereas in the congruent-arc modification, it was calculated by multiplying the coracoid length by its superior-inferior thickness (Figure 4).

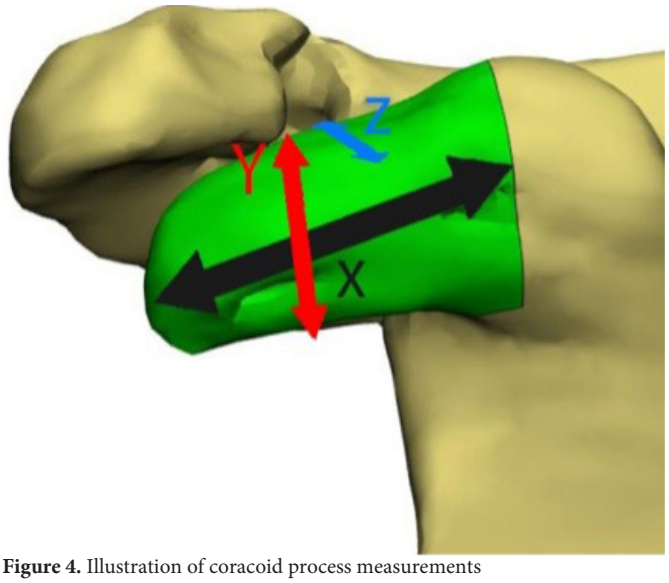

Figure 4. Illustration of coracoid process measurements

Maximum screw diameters applicable for both techniques in male and female patients were calculated based on the 40% rule for safe fixation of bone with screws.[12]

Three-dimensional visualizations of the coracoid transfer procedures were generated using Mimics Innovation Suite 22.0 (Materialise, Leuven, Belgium).

Statistical Analysis

All data analysis of the data was performed using IBM SPSS Statistics version 15.0. Descriptive statistics were expressed as mean and standard deviation (SD) for normally distributed continuous variables, and as number (n) and percentage (%) for categorical variables. Student's *t*-test was used to compare coracoid measurements between male and female patients, as well as the contact surface areas between the coracoid and the anteroinferior glenoid in both techniques. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 200 patients (129 males, 71 females) were included for coracoid measurements, and 156 patients (94 males, 62 females) for glenoid measurements. The mean age of the patients was 42 years (range, 17-70). When all patients were evaluated, the mean coracoid length was 27.4±3.6 mm, the medial-lateral width was 16.2±2.7 mm, and the superior-inferior thickness was 10.4±2.7 mm (Table 1).

Table 1. Coracoid process measurements

	Coracoid length (X) (mm)	Coracoid width (Y) (mm)	Coracoid thickness (Z) (mm)
Mean	27.4±3.6	16.2±2.7	10.4±2.7
Minimum	20.6	11.1	5.8
Maximum	32.8	20.1	14.9

Values are presented as mean±standard deviation

In the gender-based analysis, coracoid length (29.4±1.6 mm), width (17.4±1.4 mm), and thickness (11.5±1.5 mm) were significantly greater in males compared to females. In females, these values were 23.1±1.9 mm, 13.0±1.4 mm, and 7.0±1.4 mm, respectively (Table 2). The mean glenoid width was 28.1±1.3 mm, with values of 30.5±1.3 mm in males and 24.6±1.0 mm in females (Table 3).

Table 2. Comparison of coracoid process measurements between males and females

	Male (mm)	Female (mm)	p-value
Coracoid length	29.4±1.6	23.1±1.9	<0.001
Coracoid width	17.4±1.4	13.0±1.4	<0.001
Coracoid thickness	11.5±1.5	7.0±1.4	<0.001

Values are presented as mean±standard deviation

Table 3. Glenoid width measurements

	All patients (mm)	Males (mm)	Females (mm)
Glenoid width	28.1±1.3	30.5±1.3	24.6±1.0

Values are presented as mean±standard deviation

The proportion of glenoid bone defect that could potentially be reconstructed by the coracoid process was found to be a mean of 37% (23-44%) with the standard Latarjet technique and 55% (44-61%) with the congruent-arc technique (Table 4). When analyzed by sex, these values were 37% (25-44%) and 57% (47-61%) in males, and 28% (23-41%) and 52% (44-61%) in females for the standard and congruent-arc techniques, respectively (Table 5, 6).

Table 4. Restorable glenoid ratios with both techniques

	Mean (%)	Min (%)	Max (%)
Standard Latarjet	34	23	44
Congruent-arc Latarjet	55	44	61

Min: Minimum, Max: Maximum

Table 5. Restorable glenoid ratios with both techniques in male patients

	Mean (%)	Min (%)	Max (%)
Standard Latarjet	37	25	44
Congruent-arc Latarjet	57	47	61

Min: Minimum, Max: Maximum

Table 6. Restorable glenoid ratios with both techniques in female patients

	Mean (%)	Min (%)	Max (%)
Standard Latarjet	28	23	41
Congruent-arc Latarjet	52	44	61

Min: Minimum, Max: Maximum

Regarding the bone contact surface area, the mean value was 452±126 mm² for the standard Latarjet technique and 292±105 mm² for the congruent-arc technique (Table 7), with a statistically significant difference between the two (p<0.001).

Table 7. Mean screw diameters applicable for both techniques in males and females

	Male (mm)	Female (mm)
Standard Latarjet	7.0	5.0
Congruent-arc Latarjet	4.5	2.8

Based on the mean coracoid values in male and female patients, the maximum screw diameters applicable for both surgical techniques were calculated. Accordingly, in

the standard Latarjet technique, the use of screws with a mean diameter of 7 mm in males and 5 mm in females was considered appropriate. In the congruent-arc Latarjet technique, these values were calculated as 4.5 mm in males and 2.8 mm in females (Table 8).

Table 8. Statistical comparison of coracoid contact surface area between both techniques

	Standard Latarjet (mm^2)	Congruent-arc Latarjet (mm^2)	p-value
Coracoid contact area	452±126	292±105	<0.001

Values are presented as mean±standard deviation

DISCUSSION

In this study, the standard and congruent-arc Latarjet techniques were compared using a multiplanar tomographic modeling approach. Coracoid and glenoid morphology were evaluated in detail, and for both techniques, glenoid reconstruction capacity, contact surface area, and potential fixation parameters were analyzed. In addition, the impact of anatomical differences between male and female patients on surgical feasibility was investigated. The findings demonstrated notable biomechanical differences between the two techniques.

In the literature, coracoid morphology has been reported to differ between genders, with males generally exhibiting larger coracoid dimensions than females. Studies by Young et al.[13] and Ljungquist et al.[14] have demonstrated that coracoid length typically ranges between approximately 26 and 28 mm. In our study, the mean coracoid length was 29.4 mm in males and 23.1 mm in females, with this difference being statistically significant. Similarly, width and thickness measurements were also significantly greater in males. These findings are consistent with the existing literature and support the reliability of the multiplanar reconstruction method used in our study.

The impact of glenoid bone defects on shoulder stability is well established, and it is widely accepted that soft tissue repair alone is insufficient in defects exceeding 25-30%.[15] Previous studies have reported that the congruent-arc technique can restore larger defects, whereas the classic Latarjet technique typically achieves reconstruction rates of approximately 30-36%.[16] In our study, the mean glenoid reconstruction was 37% with the standard technique and 55% with the congruent-arc technique. These results are consistent with the literature and suggest that the congruent-arc technique provides an advantage in the management of larger defects. However, this advantage should be interpreted in conjunction with other biomechanical parameters.

Although glenoid reconstruction is important, it has been shown that stability is not solely dependent on bony restoration. Yamamoto et al.[17] reported that the dynamic sling effect plays a significant role in the Latarjet procedure. Furthermore, while increased restoration of the glenoid surface may theoretically normalize contact pressures, articular incongruity may pose a risk for the development of osteoarthritis. Our findings indicate that although the congruent-arc technique provides greater reconstruction, its potential clinical implications should be carefully considered.

Previous studies have demonstrated that the standard Latarjet technique provides greater primary fixation stability, whereas the congruent-arc technique may fail under lower loads.[16,18] This difference is thought to be related to the contact surface area between the graft and the glenoid. In our study, consistent with these findings, the contact surface area was 452 mm^2 in the standard technique and 292 mm^2 in the congruent-arc technique. A smaller contact surface area may represent a disadvantage in terms of both bone union and fixation stability, and this issue may be particularly relevant in patients with smaller coracoid dimensions.[16]

In terms of screw fixation, the literature generally reports the use of screws with diameters ranging from 3.5 to 4.5 mm. However, according to AO principles, the screw diameter should not exceed 40% of the bone diameter.[12] In our study, coracoid thickness was significantly lower in female patients, and smaller screw diameters were required, particularly in the congruent-arc technique. This may compromise fixation stability and increase the risk of intraoperative fracture and nonunion. Therefore, consideration of coracoid dimensions during surgical planning is of great importance.

Studies evaluating Latarjet outcomes specifically in female patients are limited in the literature.[11] Available data suggest that the incidence of instability in females is not markedly different from that in males.[19,20] However, our findings indicate that smaller coracoid dimensions in female patients may lead to biomechanical disadvantages, particularly with the congruent-arc technique. Accordingly, gender-related anatomical differences should be taken into account when selecting patients and determining the surgical technique.

Limitations

This study has several limitations. First, its retrospective design and reliance on data from a single center may limit the generalizability of the findings. Additionally, the analyses were based on static measurements, and physiological loading conditions as well as dynamic muscle forces were not incorporated into the model. Furthermore, the lack of clinical outcome assessment restricts the direct clinical applicability of the results.

Despite these limitations, the study also has notable strengths. The use of multiplanar tomographic analysis enabled a detailed and quantitative evaluation of coracoid and glenoid morphology, thereby enhancing the reliability of the findings. Moreover, the comparison of both the standard and congruent-arc Latarjet techniques within the same model allowed for a clearer demonstration of biomechanical differences between the techniques. In addition, the evaluation of sex-related anatomical differences provides a unique contribution to the existing literature.

CONCLUSION

This study demonstrated that the standard and congruent-arc Latarjet techniques used in anterior shoulder instability exhibit distinct biomechanical characteristics. While the congruent-arc technique was found to restore larger glenoid bone defects, the standard Latarjet technique provided a greater contact surface area. In addition, significant differences in coracoid measurements were observed between male and female patients, suggesting that these anatomical

variations may influence surgical feasibility. The smaller coracoid dimensions observed particularly in female patients result in the need for smaller screw diameters and a more limited contact surface area in the congruent-arc technique. This may reduce fixation stability and increase the risk of complications. Our findings indicate that surgical decision-making should consider not only the size of the glenoid defect but also the morphology of the coracoid process. In patients with smaller coracoid dimensions, techniques that provide a larger contact surface area may be more appropriate.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ankara University Human Researches Ethics Committee (Date: 13.02.2020, Decision No: İ1-72-20).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: AA, MA; Design: AA, AM, SNA; Control: MK, MA; Resources: AA; Materials: AA; Data Collection and/or Processing: AA; Analysis and/or Interpretation: AA; Literature Review: AA, MK, SNA; Writing the Article: AA, MK, MA; Critical Review: AA, MK, SNA, MA.

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Journal of Orthopedics Research and Rehabilitation

Original Article

DOI: 10.51271/JORR-0073

An investigation of the relationship between quadriceps femoris and hamstring muscle strength and balance in individuals with pes planus

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ABSTRACT

Aims: This study aimed to examine the relationship between quadriceps femoris and hamstring muscle strength and balance in individuals with pes planus.

Methods: The study was conducted with 64 participants with pes planus, including 48 female and 16 male. Individuals were identified using the navicular drop test and the Feiss line test. Based on the Feiss line test results 29 of the participants had grade 2, 24 of participants had grade1 and 11 of participants had grade 3 pes planus. Muscle strength was assessed using the Lafayette Manual Muscle Tester. Balance measurements were performed using the Biodex Balance System under three different conditions: double-leg stance with eyes closed, single-leg stance on the pes planus side with eyes open, and single-leg stance on the pes planus side with eyes closed. In these measurements, we examined the Anteroposterior Index (APSI), Mediolateral Index (MLSI) and Overall Stability Index (OSI). The Spearman's correlation analysis was performed to evaluate the relationship between variables.

Results: In the single-leg stance with eyes closed the OSI, APSI and MLSI were recorded as 2.39±1.18, API 1.87±1.10 and 1.10±0.64 respectively. A weak, statistically significant positive correlation was found between the MLSI values obtained during single-leg stance with eyes closed and quadriceps femoris muscle strength (rho=0.270, p=0.031). A weak, statistically significant positive correlation was also found between the MLSI value obtained under the same single-leg, eyes-closed condition and hamstring muscle strength (rho=0.293, p=0.019). In the double-leg stance with eyes closed, OSI, APSI, and MLSI were determined to be 0.98±0.53, 0.83±0.49 and 0.38±0.26, respectively. In the single-leg stance with eyes open, the OSI, APSI, and MLSI were found to be 0.79±0.56, API 0.54±0.44 and 0.42±0.35, respectively. No statistically significant relationship was found between quadriceps femoris and hamstring muscle strength with OSI (p>0.05) and with APSI (p>0.05).

Conclusion: Our results demonstrated that, in balance measurements performed in individuals with pes planus, only the MLSI showed weak positive correlation with quadriceps femoris and hamstring muscle strength. OSI and APSI values were independent of muscle strength. These findings suggest that dynamic balance performance, particulary in terms of mediolateral stability, may vary depending on task difficulty and visual input in individuals with pes planus.

Keywords: Pes planus, quadriceps femoris, hamstring muscles, postural balance, muscle strength

INTRODUCTION

Pes planus is a common condition in which the entire plantar surface of the foot contacts the ground during both static and dynamic movements. Evidence suggests that asymptomatic pes planus affects 13.60% to 26.62% of the population.[1] In individuals with pes planus, disruption of the medial longitudinal arch may lead to excessive pronation of the foot and may result in excessive inward rotation of the foot during running or walking. The medial longitudinal arch provides shock absorption and stability during weight-bearing activities and plays an important role in foot biomechanics. Over time, this condition may affect not only the feet but also other lower-extremity components, such as the knee and hip, in terms of musculoskeletal problems due to altered alignment and mechanical factors. Comparisons of range of motion and muscle strength between individuals with pes planus and those with a normal medial longitudinal arch indicate that the severity of pes planus deformities in adults and children is associated with reduced flexibility.[2] In a study by Son et al.[3] investigating tibiotalar joint mechanics while walking in 10 individuals with pes planus and 10 healthy individuals, altered foot biomechanics were shown to increase lateral contact forces in individuals with pes planus. This highlights how structural changes related to pes planus affect overall lower-extremity biomechanics beyond merely reflecting muscle strength deficits. Abnormal foot mechanics, such as excessive pronation and supination, may disrupt load distribution in the knee joint.[4]

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Malalignment of the knee joint may cause changes in the length-tension relationship of the surrounding musculature, and these changes may result in the transmission of abnormal afferent information. It has been hypothesized that alterations in afferent input to the central nervous system may affect efferent output to the muscles, inhibit the kinetic response of the muscle, and consequently lead to muscle atrophy.[5] In a study conducted by Chang et al.,[6] electromyographic (EMG) measurements revealed significant differences in muscle activation between individuals with pes planus and healthy controls, specifically affecting both distal and proximal musculature, including the tibialis anterior, gastrocnemius, vastus lateralis, and biceps femoris. The loss of supportive function in the medial longitudinal arch in individuals with pes planus leads to increased compensatory activation in the proximal musculature surrounding the knee and hip joints, thereby triggering proximal compensation mechanisms. Subtalar joint closed-chain pronation is characterized by calcaneal eversion alongside talar adduction and plantarflexion. Due to its position within the ankle mortise, the talus serves as a linkage mechanism, converting foot pronation into tibial rotation across both the subtalar and midtarsal joints. This rotation functions in temporal coordination with hip kinematics, in which rearfoot pronation corresponds to femoral internal rotation, while rearfoot supination coincides with hip external rotation. Impairments in this kinematic coupling mechanism are considered to be a contributing factor to various musculoskeletal injuries of the lower extremity.[7] Although the literature indicates that lower extremity biomechanics and balance control are altered in individuals with pes planus, studies directly examining the relationship between quadriceps femoris and hamstring muscle strength and balance performance across different support conditions remain limited. Therefore, the primary objective of this study was to determine the relationship between quadriceps femoris and hamstring muscle strength and balance performance under various support base conditions in individuals with pes planus. We hypothesize that lower quadriceps femoris and hamstring muscle strength in individuals with pes planus would be significantly associated with reduced balance performance, particularly under conditions with reduced base of support (single-leg stance).

METHODS

Ethics

Ethical permission and approval for the study were obtained from the Gazi University Rectorate Institute of Health Sciences Ethics Committee (Date: 03.07.2025 Decision No: 26/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Individuals were included in the study after completing the informed consent form required by the relevant ethics committee.

Study Design

This study was a correlational study investigating the relationship between quadriceps femoris and hamstring muscle strength and balance in individuals with pes planus. The study was conducted between September 2025 and June 2026 with the participation of 64 individuals with pes planus (48 female, 16 male). Volunteers aged 18-35 years were included in the study. The inclusion criteria for the study were as follows: individuals aged between 18 and 35 years, with a body-mass index (BMI) of less than 30 kg/m^2, and identified with pes planus based on the Navicular Drop Test, Additionally, participants report no pain during daily living activities, and voluntarily agree to participate in the study by signing an Informed Consent Form. The exclusion criteria were scoliosis or postural deformities (such as genu valgum,genu varum), lower-extremity injury or surgery with in six months, lower limb length discrepancy, a history of neurological or rheumatological disease, malignancy, and pregnancy. Lastly candidates with psychiatric or cognitive impairments that could impede communication were excluded from study. The study was conducted in the Orthopedics Unit of the Faculty of Health Sciences, Gazi University.

The sample size was determined using G*Power. Based on α=0.05, α power of 80% (β=0.20), and effect size of 0.3, α minimum total of 64 participants was required for the study. Of the 71 individuals who agreed to participate in the study, one could not participate due to scoliosis, two due to chronic ankle instability, and four due to meniscal rupture in the knee. Therefore, the study was completed with a total of 64 participants. Both feet were evaluated during the study; however, only the side presenting with pes planus was included in the analysis. Participants were identified using the navicular drop test, and their pes planus grade was then recorded using the Feiss line test. Consequently, participants were definitively diagnosed with pes planus if they exhibited a navicular drop test result of ≥10 mm in conjunction with a grade 1 or higher displacement on the Feiss Line Test assessment.

The participants' age, height, body weight, gender, dominant side, side with pes planus, and pes planus grade were recorded. Quadriceps femoris and hamstring muscle strength were measured on the side with pes planus, and balance was assessed. These measurements were completed on the same day. In the literature, the dominant side of the lower extremity is defined as the side used for mobilization during activities, whereas the side providing support and stabilization is defined as the non-dominant side.[8]

Navicular Drop Test

The navicular drop test is applied in sitting and standing positions to determine the change in medial longitudinal arch height. The navicular tuberosity is marked while the participant is seated, and the distance between the tuberosity and the floor is recorded in millimeters on a card. The participant is then asked to stand up and after weight bearing, the navicular tuberosity is marked again on the same card, and the distance in millimeters between the two lines is recorded as navicular drop. A navicular drop of 6-9 mm is classified as normal, whereas 10 mm or more is classified as pes planus.[9]

Feiss Line Test

The Feiss line method was used to determine the degree of pes planus in the participants. During the measurements, participants were asked to stand upright on a firm surface while distributing weight equally on both feet. For the assessment, a reference Feiss line was drawn by connecting the center of the medial malleolus to the midpoint of the first

metatarsophalangeal joint. Based on the principle that the navicular tuberosity should lie on this line in a healthy foot, pes planus was graded according to the amount of downward displacement of the tuberosity below the line. Accordingly, if the navicular tuberosity dropped by one-third of the distance between the Feiss line and the floor, it was classified as grade 1 pes planus; if it dropped by two-thirds, it was classified as grade 2 pes planus; and if it was in complete contact with the floor, it was classified as grade 3 pes planus.[10]

Muscle Strength Assessment

The strength of the quadriceps femoris and hamstring muscles was measured using a Nicholas Manual Muscle Tester (model 01160, The Lafayette Instrument Company, Lafayette, Indiana, USA). For the quadriceps femoris measurement, the participant was seated with the legs hanging over the edge of the examination table and the knee flexed at 90 degrees; the participant was asked to fully extend the knee, and measurement was performed during this maneuver. For hamstring muscle strength, the participant was positioned prone with the knee flexed at 45 degrees and was asked to pull the heel toward the buttock; measurement was performed during this maneuver.[11] All measurements were repeated three times, and the mean value was recorded.

Balance Assessment

Static balance assessments were conducted via the Biodex Balance System. Three different measurements were performed on a stable surface using the Biodex Balance System.[12] Before the measurements, each participant completed a 10-second demonstration test to adapt to the test procedure with both feet on the balance platform and the eyes open. Participants were asked to keep the point, which moved according to their weight shifts without moving their feet, in the exact center of the circle. Participants were asked to maintain an upright position and minimize the movement as much as possible during the testing procedure. Because participants performed practice trials on both feet balance platform with eyes open during the demonstration phase, this position was not included in the main experiment. The first measurement was performed with both feet on the balance platform and the eyes closed. Each measurement lasted 20 seconds and was repeated three times, with 10-second rest periods between repetitions. The second measurement was performed on the pes planus side with the eyes open and again consisted of three 20-second trials. The final measurement was performed on the pes planus side with the eyes closed, again with three 20-second repetitions and 10-second rest periods. The test was repeated for all participants who lost balance or moved their foot. As a result of the tests, the Anteroposterior Index (APSI), Mediolateral Index (MLSI), and Overall Stability Index (OSI) were obtained.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics 30.0 (SPSS Inc., Chicago, IL, USA). The normality of numerical variables was examined using visual methods (histograms and probability plots) and analytical methods (Shapiro-Wilk test, skewness and kurtosis values, and coefficient of variation). Descriptive statistics were presented as frequency and percentage for categorical variables and as mean and standard deviation, median, and minimum-maximum values for numerical variables.[13,14] The Spearman correlation test was used to examine relationships between variables because the data did not meet the assumption of normal distribution. Correlation coefficient values were interpreted as follows: 0.00-0.20, very weak; 0.21-0.40, weak; 0.41-0.60, moderate; 0.61-0.80, strong; and 0.81-1.00, very strong.[13,14] Results with a type I error level below 5% were considered statistically significant.

RESULTS

Selected sociodemographic and clinical characteristics of the participants are presented in **Table 1**. The mean age of the participants was 24.17+/-3.68 years. Mean body weight was 70.47+/-12.29 kg, mean height was 166.98+/-9.16 cm, and mean BMI was 25.27+/-2.92 kg/m^2. When gender distribution was examined, 75% of the participants were female (n=48) and 25% were male (n=16). In terms of dominant side, right-side dominance was identified in 85.94% of the participants (n=55), whereas left-side dominance was identified in 14.06% (n=9). Pes planus was present in the right foot in 70.31% of participants (n=45) and in the left foot in 29.69% (n=19). According to the Feiss line test results, grade 2 pes planus was detected in 45.31% of participants (n=29), grade 1 in 37.50% (n=24), and grade 3 in 17.19% (n=11).

Table 1. Sociodemographic and clinical characteristics of the participants (n=64)

	X̄±SD	Median (min/max)
Age (years)	24.17+/-3.68	23.50 (19/34)
Body weight (kg)	70.47+/-12.29	70 (51/95)
Height (cm)	166.98+/-9.16	165 (152/192)
BMI (kg/m^2)	25.27+/-2.92	25.29 (17.51/27.23)
	n	**%**
Gender		
Male	16	25
Female	48	75
Dominant side		
Right	55	85.94
Left	9	14.06
Side with pes planus		
Right	45	70.31
Left	19	29.69
Feiss line test		
Grade 1	24	37.50
Grade 2	29	45.31
Grade 3	11	17.19

SD: Standard deviation, Min: Minimum, Max: Maximum, BMI: Body-mass index

The quadriceps femoris and hamstring muscle strength values of the participants are presented in **Table 2**. Mean quadriceps femoris muscle strength was 186.49+/-44.65 N, and mean hamstring muscle strength was 154.15+/-60.87 N.

Table 2. Muscle strength values of the participants (n=64)

	X̄±SD	Median (min-max)
QF muscle strength (N)	186.49+/-44.65	181.37 (120.50/316.33)
Hamstring muscle strength (N)	154.15+/-60.87	148.60 (55.23/363.50)

SD: Standard deviation, Min: Minimum, Max: Maximum, QF: Quadriceps femoris, N: Newton

The Biodex balance measurement results of the participants are presented in Table 3. In double-leg stance with eyes closed, the OSI was 0.98+/-0.53, the APSI was 0.83+/-0.49, and the MLSI was 0.38+/-0.26. In single-leg stance with eyes open, OSI was 0.79+/-0.56, APSI was 0.54+/-0.44, and MLSI was 0.42+/-0.35. In single-leg stance with eyes closed, OSI was 2.39+/-1.18, APSI was 1.87+/-1.10, and MLSI was 1.10+/-0.64.

Table 3. Balance measurement values of the participants (n=64)

		X̄±SD	Median (min-max)
Double-leg stance (eyes closed)	OSI	0.98+/-0.53	0.85 (0.20/2.70)
	APSI	0.83+/-0.49	0.70 (0.20/2.40)
	MLSI	0.38+/-0.26	0.30 (0.10/1.10)
Single-leg stance (eyes open)	OSI	0.79+/-0.56	0.60 (0.30/3.30)
	APSI	0.54+/-0.44	0.40 (0.20/3.10)
	MLSI	0.42+/-0.35	0.30 (0.10/1.80)
Single-leg stance (eyes closed)	OSI	2.39+/-1.18	2.10 (1/7.70)
	APSI	1.87+/-1.10	1.60 (0.60/7)
	MLSI	1.10+/-0.64	0.90 (0.40/4.60)

SD: Standard deviation, Min: Minimum, Max: Maximum, OSI: Overall Stability Index, APSI: Anterior-posterior Stability Index, MLSI: Mediolateral Stability Index

The relationship between participants' muscle strength values and balance measurement results was examined using Spearman correlation analysis, and the results are presented in Table 4. A weak, statistically significant positive correlation was found between the MLSI value obtained during single-leg stance with eyes closed and muscle strengths of both the quadriceps femoris (rho=0.270, p=0.031) and hamstring (rho=0.293, p=0.019). Conversely no statistically significant correlation was found between eighter quadriceps femoris and hamstring muscle strength and any of the balance indices (OSI, APSI) during the double leg eyes closed and single leg eyes open conditions, nor with OSI and APSI values during the single leg eyes closed condition. (p>0.05).

Table 4. Relationship between participants' muscle strength values and balance measurement results (n=64)

			QF muscle strength	Hamstring muscle strength
Double-leg stance (eyes closed)	OSI	rho	-0.082	-0.186
		p	0.519	0.140
	APSI	rho	-0.111	-0.172
		p	0.384	0.173
	MLSI	rho	0.011	-0.103
		p	0.932	0.417
Single-leg stance (eyes open)	OSI	rho	-0.102	-0.174
		p	0.424	0.168
	APSI	rho	-0.102	-0.173
		p	0.424	0.172
	MLSI	rho	-0.088	-0.149
		p	0.488	0.239
Single-leg stance (eyes closed)	OSI	rho	0.203	0.205
		p	0.107	0.105
	APSI	rho	0.178	0.139
		p	0.159	0.273
	MLSI	rho	0.270	0.293
		p	0.031	0.019

rho: Spearman correlation coefficient, QF: Quadriceps femoris, OSI: Overall Stability Index, APSI: Anterior-Posterior Stability Index, MLSI: Mediolateral Stability Index

DISCUSSION

The primary aim of this study was to examine the relationship between quadriceps femoris and hamstring muscle strength and balance parameters in individuals with pes planus. The notable statistical finding was that, during single-leg stance with eyes closed, both quadriceps femoris and hamstring muscle strength showed weak positive correlations with the MLSI (rho=0.270, p=0.031; and rho=0.293, p=0.019, respectively).

The literature indicates that pes planus deformity alters the kinematics of the ankle and proximal joints and therefore affects balance. Studies examining the effects of foot posture on dynamic balance have shown that individuals with pes planus have increased postural sway and that this negatively affects balance strategies.[15] In our study, the unfavorable change in balance strategies observed particularly during single-leg stance with eyes closed supports this view in the literature.

In our study, the weak positive relationship found between MLSI values during single-leg stance with eyes closed and quadriceps femoris and hamstring muscle strength indicates that as muscle strength increased, the MLSI also increased, reflecting an unfavorable change in balance. Given the weak statistical results, further clinical studies are required, and these finding do not warrant a definitive conclusion. This finding can be explained by compensatory mechanisms in the presence of pes planus. It has been reported that lower-extremity alignment disorders in individuals with pes planus may alter loads on the knee and hip joints, potentially causing excessive contractions in proximal muscle groups.[16] In conditions in which the eyes are closed and mechanoreceptors on the sole of the foot are insufficient because of pes planus deformity, the body places greater demand on the knee and hip joints to maintain balance. According to the "Foot Core System" theory, when intrinsic muscle activation in the foot is insufficient, extrinsic muscles and larger proximal muscles attempt to assume the role of stabilization.[16] Therefore, it is likely that the individuals with pes planus in our study used proximal muscle groups, namely the quadriceps femoris and hamstring muscles, more intensively as a compensatory strategy to control MLSI values. As a potential biomechanical hypothesis, the increased MLSI associated with higher proximal muscle strength may reflect a compensatory strategy.[16,17] In individuals with pes planus, insufficient intrinsic foot muscle activation might lead to an over-reliance on larger proximal muscles to maintain stability. This proximal co-contraction strategy could result in increased joint stiffness unintentionally increasing balance sway.[18,19] Future studies combining EMG and 3D motion analysis are warranted to test this hypothesis.

The contribution of muscle groups around the knee to mediolateral stability, rather than anterior-posterior stability, in foot deformities remains debated in the literature. The relationship between lower-extremity muscle strength and pes planus has been examined during gait, and impairments in foot mechanics have been shown to create direct changes in loading at the knee joint.[17] In our study, the fact that the correlation was observed only for MLSI supports the interpretation that subtalar joint eversion and internal rotation torque in individuals with pes planus destabilize the trunk more in the medial-lateral axis and that the knee joint is affected more in this axis than in the anterior-posterior axis.

Limitations

This study has several limitations. Although the sample consisted of 64 participants, most participants were female when the gender distribution was examined. This distribution, with a higher number of female participants, limits the generalizability of the data obtained. Although our findings showed a relationship between muscle strength and the MLSI under eyes-closed conditions, participants' joint position sense or ankle proprioception levels were not objectively measured. Another limitation of this study is the absence of a healthy control group, which restricts the ability to make direct comparative evaluations. Additionally, the side presenting with pes planus deformity did not correspond to the dominant side in all participants, representing another limitation regarding functional side to side symmetry. A further limitation is that the quadriceps to hamstring strength ratio was not included in the analysis, limiting deeper insights into agonist-antagonist muscle balance. Finally, EMG and muscle firing patterns were not recorded in this study, nor were proprioception parameters directly evaluated.

Future studies should include a more homogeneous sample according to pes planus grade and gender distribution. In addition, including ankle proprioception parameters in the assessment process would help future studies obtain more objective results.

CONCLUSION

As a result, this study demonstrates that young adults with unilateral pes planus exhibit significant deficits in proximal muscle strength, particularly in the quadriceps femoris and hamstring on the affected side, which are weakly associated with impaired medioateral stability index. While proximal muscle strength plays a contributing role in lower extremity control, the weak correlation magnitudes suggest that proximal capacity alone is insufficient to fully compensate for distal biomechanical alterations during dynamic single-leg tasks. Clinicians should therefore adopt an integrative rehabilitation approach that combines proximal muscular strengthening with distal structural and sensorimotor interventions rather than relying solely on proximal training to enhance postural control in individuals with pes planus. From a clinical perspective, these findings suggest that while proximal muscle capacity plays a contributing role in lower extremity stabilization, relying solely on proximal muscle strengthening in rehabilitation programs may not be sufficient to fully restore dynamic postural balance in individuals with pes planus. Therefore, clinicians are encouraged to adopt a comprehensive treatment paradigm that integrates proximal muscle training with distal structural support and sensorimotor re-education. Future research should incorporate EMG muscle activation patterns, ankle biomechanics, and proprioceptive tracking to further clarify the underlying motor control mechanisms and proximal compensation strategies during functional tasks.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Gazi University Rectorate Institute of Health Sciences Ethics Committee (Date: 03.07.2025 Decision No: 26/03).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: İY, SÇ; Design: İY, SÇ; Control: İY, SÇ; Resources: İY, SÇ; Materials: İY, SÇ; Data Collection and/or Processing: İY, SÇ; Analysis and/or Interpretation: İY, SÇ; Literature Review: İY, SÇ; Writing the Article: İY, SÇ; Critical Review: İY, SÇ.

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Review

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From cortex to quadriceps: understanding and treating arthrogenic muscle inhibition (AMI) after ACL injury

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ABSTRACT

Arthrogenic muscle inhibition (AMI) limits voluntary quadriceps activation after anterior cruciate ligament (ACL) injury despite preserved muscle structure. This review aims to synthesize current evidence on the neurophysiopathology of AMI, measured via electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS), and on rehabilitation strategies targeting AMI. A scoping review was undertaken. A comprehensive literature search was conducted in PubMed, Web of Science, and the Cochrane Library to identify studies examining the neurophysiological mechanisms underlying AMI, and evaluating interventions aimed at restoring quadriceps function. A total of 30 studies were included in the neurophysiological basis of AMI: 11 employing EEG, 8 using fMRI, and 11 utilizing TMS. These studies characterized the neurophysiological basis of AMI, demonstrating local joint inhibition, altered afferent signaling, cortical reorganization, and reduced corticospinal excitability, all contributing to impaired quadriceps activation. Twenty intervention studies showed that multiple strategies can enhance quadriceps activation and strength, particularly when applied early or in a phase-specific manner. Importantly, AMI is progressively reversible but leaves a subset of motoneurons difficult to recruit voluntarily, highlighting the need for interventions that specifically target the central nervous system, in addition to the muscle, to optimize neuromuscular recovery. AMI is driven by complex interactions between peripheral and central neural mechanisms, measurable via EEG, fMRI, and TMS. Early identification and targeted interventions can restore quadriceps function and mitigate long-term deficits. Understanding both neurophysiological alterations and effective therapeutic strategies is essential for designing individualized, evidence-based rehabilitation programs for ACL-injured patients.

Keywords: ACL, neuroscience, EEG, fMRI, TMS, therapeutic strategies

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is among the most common and severe knee injuries, with an annual incidence of approximately 0.03% in the general population and between 0.15% and 3.67% among professional athletes.[1] Each year, an estimated 250,000 new ACL ruptures occur in the United States, primarily during pivoting or rapid change-of-direction activities.[2] The injury predominantly affects active young adults aged 15 to 30 years and is more frequent in female due to specific biomechanical and hormonal factors.[3] Although ACL rehabilitation is well standardized in clinical practice, return-to-sport (RTS) outcomes remain suboptimal. A recent meta-analysis reported that while 82% of patients resume some level of sport after ACL reconstruction (ACLR), only 44% return to their preinjury competitive level.[4]

Quadriceps activation failure is frequent and persistent impairment following ACL rupture or reconstruction.[5] This deficit not only affects the injured limb but also extends to the contralateral, uninjured side.[6] Such findings suggest a mechanism beyond local disuse or atrophy secondary to pain or immobilization. This phenomenon is attributed to arthrogenic muscle inhibition (AMI), a neurophysiological process characterized by altered excitability within the motor pathways, resulting in insufficient quadriceps activation.[7] The bilateral nature of AMI supports the involvement of centralized neurophysiological mechanisms. Altered sensory input from the injured joint modulates spinal and supraspinal circuits, leading to decreased motoneuron excitability and reflex inhibition of periarticular musculature-even in the contralateral limb.[8-10] This highlights the central, rather than

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purely peripheral, role of AMI in post-injury neuromuscular dysfunction.

AMI has been identified in over half of patients with acute ACL rupture.[5] Its consequences are clinically significant and include extension deficits, gait abnormalities, quadriceps atrophy, reduced function, persistent pain, dynamic instability, and early-onset osteoarthritis.[11] These effects often persist after returning to unrestricted physical activity and may contribute to recurrent injuries and long-term disability.[12] Preoperative identification of AMI is crucial in patients awaiting ACLR, as its presence increases the risk of postoperative stiffness and delayed recovery. Surgical intervention should be postponed until targeted rehabilitation protocols have addressed these deficits.[10] Warning signs suggestive of AMI include joint effusion, high pain scores, a short interval between injury and assessment, multi-ligament involvement, crutch dependence, and nocturnal knee support.[5] Sonnery-Cottet et al.[10] proposed a classification system for AMI based on the reversibility of vastus medialis oblique (VMO) inhibition, which can guide individualized treatment strategies.

AMI represents a major barrier to effective ACL rehabilitation.[11] It impairs voluntary muscle activation, leading to strength loss, proprioceptive deficits, and compromised motor control-factors that increase reinjury risk. Its bilateral impact further complicates recovery, prolongs rehabilitation, and contributes to persistent asymmetries. Moreover, AMI may affect patient motivation and engagement, adding a psychological dimension to its management. Recent advances in neurorehabilitation have challenged traditional paradigms of post-ACL care. Emerging interventions aim to restore quadriceps activation by targeting joint mechanoreceptors, peripheral neural structures, or directly modulating central nervous system excitability.[13,14] This shift reflects a growing recognition that successful rehabilitation requires addressing not only the "hardware" (the knee and its mechanical integrity) but also the "software" (the brain and its neural control).[15]

Despite increasing attention in AMI with a growing number of studies emphasizing its importance and clinical impact, its pathophysiology remains incompletely understood, particularly the contribution of cortical and subcortical mechanisms. A deeper understanding of the neurophysiological pathways involved in AMI is essential to develop more effective interventions and reduce recurrence following ACL rupture or reconstruction. Therefore, the purpose of this scoping review is to (1) examine the neural mechanisms underlying AMI and (2) discuss evidence-based therapeutic strategies for its management in patients after ACL rupture or reconstruction.

METHODS

This study is a scoping review of the literature designed to explore the neural mechanisms involved in the pathophysiology of AMI, as well as the therapeutic strategies used to manage it in patients following ACL rupture or reconstruction.

Search Strategy

The literature search and study selection process were conducted in a structured and transparent manner following the principles outlined in the PRISMA-ScR guidelines to ensure methodological rigor.[16] A comprehensive search was performed in PubMed, Web of Science, and the Cochrane Library databases between September and December 2025. The search was conducted in two stages to address the review objectives. Abstract screening and full-text eligibility assessment were conducted independently by two reviewers. Any disagreements regarding study inclusion were resolved through consensus discussion.

In the first stage, the search focused on the pathophysiology of AMI and the involvement of neural pathways following ACL rupture or reconstruction. Keywords and specific term combinations were formulated in English, using Boolean operators (AND, OR) to refine results. The primary search terms included: "AMI" (OR "Quadriceps weakness") AND "Neuroplasticity" (OR "Neural mechanisms", "TMS", "EEG", "fMRI") AND "ACL injury" (OR "ACL rupture", "ACL reconstruction").

In the second stage, the search targeted rehabilitation and therapeutic strategies addressing AMI after ACL rupture or reconstruction. The following search terms and combinations were used: "AMI" (OR "Quadriceps weakness") AND "Rehabilitation strategies" AND "ACL injury" (OR "ACL rupture", "ACL reconstruction").

Additionally, a manual search of the reference lists of included studies was performed to identify further relevant publications. This systematic approach ensured comprehensive coverage of the literature on both the neurophysiological mechanisms of AMI and innovative therapeutic interventions designed to address it.

Study Selection

Inclusion criteria comprised studies investigating the neural mechanisms underlying AMI or exploring treatment and rehabilitation interventions aimed at treating AMI in patients with ACL rupture or reconstruction, with no restriction on publication date. Exclusion criteria included studies on other forms of muscle atrophy unrelated to AMI, those that did not explicitly address neural pathway involvement, and studies that lacked a comparison between a control group and a patient group with AMI following ACL rupture or reconstruction. Only full-text articles published in English or French were included. Single case reports and author commentaries were excluded from the analysis.

Data Extraction

Data extraction focused on several key elements to address the objectives of this review. The following information was collected: author, study title, year of publication, journal, and study objective. Regarding participant characteristics, the sample size was recorded, distinguishing between the study group and the control group. Particular attention was given to the methods used to assess neural activity, transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG). The outcome measures and main findings reported in each study were extracted to analyze the neural pathways involved in AMI.

For studies focusing on the management of AMI in patients with ACL rupture or reconstruction, the therapeutic

strategies, their application protocols, and their effects on AMI were also extracted and analyzed.

RESULTS

Neurophysiopathology of AMI

The initial literature search across PubMed, Web of Science, and the Cochrane Library identified 473 articles, supplemented by 13 additional studies from other sources. After removing duplicates, 312 articles remained and were screened based on titles and abstracts, leading to the exclusion of 226 articles deemed irrelevant. A total of 86 full-text articles were then assessed for eligibility. Of these, 66 were excluded due to case-series design, lack of direct association with ACL injury, or duplication of data previously published in other studies. Ultimately, 30 studies were included in the qualitative synthesis: 11 employing EEG[17-27] (**Table 1**), 8 fMRI[28-35] (**Table 2**) and 11 utilizing TMS (**Table 3**).[36-46] The study selection process is summarized in the PRISMA flow diagram (**Figure 1**).

Table 1. Summary of studies using EEG

Author/year	Population	Technique	Results
Piskin[17]	15 healthy vs. 10 ACLR	Spectral power analysis during a kicking task	Significant increase in frontal theta power and decrease in posterior alpha power in the ACLR group.
Bush[18]	20 healthy vs. 10 ACLR	Spectral power analysis during a knee proprioception test (JPS).	Increase in bilateral frontal theta power, although not statistically significant, and a slight increase in parietal alpha-2 power in the ACLR group.
An[19]	15 healthy vs. 15 ACLR	Spectral power analysis during a single-leg stance (first 3 seconds).	Increase in theta power in the contralateral primary motor cortex (frontal), and an increase in alpha-2 power in the ipsilateral premotor cortex in the ACL group, but not statistically significant.
Miao[20]	15 healhty vs 16 ACLD	Spectral power analysis during the following activities: walking, light jogging, and landing	Significant increase in spectral power across all frequency bands, and for all tasks, in the ACLD group.
Baumeister[21]	9 healthy vs 9 ACLR	Spectral power analysis during knee extension	Significant increase in frontal theta power (F3 and Fz) in ACLR patients.
Baumeister[22]	12 healthy vs 10 ACLR	Spectral power analysis during 40° knee flexion.	Significant increase in frontal theta band power (F3, F4, F8) and parietal alpha-2 power (P3, P4) in ACLR patients.
Iwasa[23]	8 healthy vs. 39 ACLR	ACL somatosensory evoked potentials (SEPs) during arthroscopy.	Reproducible SEPs were observed in all healthy patients and in 39 out of 45 ACLR patients.
Ochi[24]	19 healthy vs. 45 ACLD vs. 42 ACLR	ACL somatosensory evoked potentials (SEPs) during arthroscopy.	Reproducible SEPs were observed in 58% of ACL-deficient patients, 86% of ACLR patients, and 100% of individuals with a healthy ACL.
Ochi[25]	14 healthy vs 32 ACLD vs 23 ACLR	ACL somatosensory evoked potentials (SEPs) during arthroscopy.	Reproducible SEPs were observed in 47% of ACL-deficient patients, 96% of ACLR patients, and 100% of individuals with a healthy ACL.
Lavender[26]	4 healthy vs 7 ACLD	ACL somatosensory evoked potentials (SEPs) during arthroscopy.	All intact ACLs showed reproducible SEPs, whereas torn ACLs did not show reproducible SEPs.
Valeriani[27]	20 healthy vs 19 ACLD	Somatosensory evoked potentials (SEPs) of the common peroneal nerve	Seven participants in the ACL-deficient group showed SEP abnormalities following stimulation of the common peroneal nerve.

EEG: Electroencephalography, ACLR: Anterior cruciate ligament reconstruction, ACLD: Anterior cruciate ligament deficient, JPS: Joint position sense, ACL: Anterior cruciate ligament, SEPs: Somatosensory evoked potentials, F3, F4, F8, Fz, P3, P4: Standard EEG electrode positions (frontal and parietal regions)

Table 2. Summary of studies using fMRI

Author/year	Population	Results
Culiver[28]	15 healthy vs. 15 ACLR	Decreased activity: ipsilateral M1 and S1, contralateral S1, SMA, and precuneus in ACL-reconstructed individuals.
Guan[29]	15 healthy and 15 ACLD	Decreased connectivity between cerebellar regions and large cortical regions (occipital, parietal, and frontal cortices), as well as reduced fronto-parietal and parieto-occipital connections in ACL-deficient participants.
Baez[30]	12 healthy vs. 12 ACLR	Increased activity: inferior parietal lobule, mediodorsal thalamus, cerebellum, and inferior occipital regions in ACL-reconstructed participants.
Criss[31]	15 healthy vs. 15 ACLR	Increased activity: intracalcarine cortex, lingual gyrus, occipital fusiform gyrus, lateral occipital cortex, angular gyrus, and superior parietal lobule in ACL-reconstructed individuals.
Diefkuss[32]	12 healthy vs. 3 ACLD	Decreased connectivity between ipsilateral S2 and ipsilateral SMA, contralateral premotor cortex, contralateral SMA, ipsilateral S1, and ipsilateral M1 in ACL-deficient individuals.
Diefkus[33]	8 healthy vs. 2 ACLD	Decreased connectivity between left S1 and the right posterior cerebellar lobe in ACL-deficient individuals
Grooms[34]	Healthy vs. 15 ACLR	Increased activity: contralateral M1, lingual gyrus, and contralateral S2 in ACL-reconstructed participants. Decreased activity: ipsilateral M1 and cerebellum in ACL-reconstructed participants.
Kapreli[35]	18 healthy vs. 17 ACLD	Decreased activity: contralateral thalamus, posterior parietal cortex, S1, external pallidum, S2, cingulate motor area, premotor cortex, and ipsilateral cerebellum (vermis and anterior lobe), and ipsilateral SM1 in ACL-deficient individuals. Increased activity: SMA, posterior S2, and posterior inferior temporal gyrus in ACL-deficient individuals.

fMRI: Functional magnetic resonance imaging, ACLR: Anterior cruciate ligament reconstruction, ACLD: Anterior cruciate ligament deficient, M1: Primary motor cortex, S1: Primary somatosensory cortex, S2: Secondary somatosensory cortex, SMA: Supplementary motor area, ACL: Anterior cruciate ligament, SM1: Sensorimotor cortex

Table 3. Summary of studies using TMS

Author/year	Population	Measurement	Results
Scheure[33]6	16 healthy vs. 16 ACLR	-TMS/EMG: AMT, SICI, ICF - Dynamometer: MVIC -EMG/dynamometer: CAR	- AMT significantly higher in the ACLR group compared to controls. - MVIC significantly lower in the injured limb compared to the uninjured and control limbs. - No significant difference in CAR, SICI, or ICF.
Zarzycki[37]	18 healthy vs. 18 ACLR	-TMS/EMG: SICI, ICF - Dynamometer: MVIC	-ACLR group showed significantly reduced intracortical facilitation (ICF) in the operated limb compared to the contralateral limb, but no difference compared to controls. - No significant difference in SICI.
Lepley[38]	11 healthy vs. 11 ACLR	-TMS/EMG: AMT, MEP -EMG: H/M - Dynamometer: MVIC - fMRI -Structural MRI: Quadriceps muscle volume	- MVIC and muscle volume were lower in the injured limb compared to the contralateral and control limbs. - AMT higher bilaterally in the ACLR group vs. controls. - Smaller MEPs in the injured limb compared to contralateral and controls. - No difference in H/M ratio. - ACLR group showed greater activation in brain regions involved in pain perception: frontal lobe regions, inferior frontal gyrus, paracingulate gyrus, and anterior cingulate gyrus.
Norte[39]	30 healthy vs. 72 ACLR	-TMS/EMG: AMT - Dynamometer/EMG: MVIC, CAR -EMG: H/M	No significant differences.
Zarzycki[40]	18 healthy vs. 18 ACLR	TMS/EMG: RMT, MEP, SICI, ICF EMG: Hoffman reflex	- Higher RMT and greater MEP amplitudes in the ACLR group. - No significant difference for ICF, SICI, or H/M reflex.
Ward[41]	18 healthy vs. 18 ACLD	-TMS/EMG: MEP, AMT, CsP, SICI	-CsP was higher in the injured limb compared to the non-injured limb in ACLD -No significant difference was observed for corticospinal excitability (MEP, AMT) or SICI.
Petrosimone[42]	29 healthy vs. 28 ACLR	TMS/EMG: AMT EMG: H/M Dynamometer/EMG: CAR	-CAR was lower bilaterally compared to controls. -AMT was higher in the injured limb compared to the contralateral limb and to controls. -Higher H/M ratios in both limbs of ACLR participants.
Kuenze[43]	24 healthy vs. 22 ACLR	TMS/EMG: AMT Dynamometer / EMG: MVIC, CAR EMG: H/M	-AMT higher in the ACLR group. -MVIC and CAR lower in the ACLR group. -No difference in H/M ratio.
Lepley[44]	20 healthy vs. 20 ACLR	TMS/EMG: AMT, MEP Dynamometer/EMG: MVIC, CAR	-AMT significantly higher in the injured limb and contralateral limb compared to controls. -No significant difference in MEP. -MVIC and CAR lower in both limbs of ACLR participants compared to controls.
Lepley[45]	29 healthy vs. 29 ACLR	TMS / EMG: AMT EMG: H/M Dynamometer/EMG: MVIC, CAR	-AMT higher in the ACLR group. -H/M reflex higher in the ACLR group. -MVIC and CAR lower in both limbs compared to controls.
Heroux[46]	4 healthy vs. 10 ACLD	-TMS / EMG: RMT, MEP, SR curve -EMG: H/M	-RMT significantly reduced in ACLR compared to controls. -No significant difference in MEP, SR curve, or H/M reflex.

TMS: Transcranial magnetic stimulation, ACLR: Anterior cruciate ligament reconstruction, ACLD: Anterior cruciate ligament deficient, EMG: Electromyography, AMI: Arthrogenic muscle inhibition, SICI: Short-interval intracortical inhibition, ICF: Intracortical facilitation, MVIC: Maximal voluntary isometric contraction, CAR: Central activation ratio, AMT: Active motor threshold, CsP (CSP): Cortical silent period, EEG: Electroencephalography, fMRI: Functional magnetic resonance imaging, H/M ratio: Hoffmann reflex to M-wave ratio, MEP: Motor evoked potential, MRI: Magnetic resonance imaging, RMT: Resting motor threshold, SR curve/SR slope: Stimulus-response curve/slope

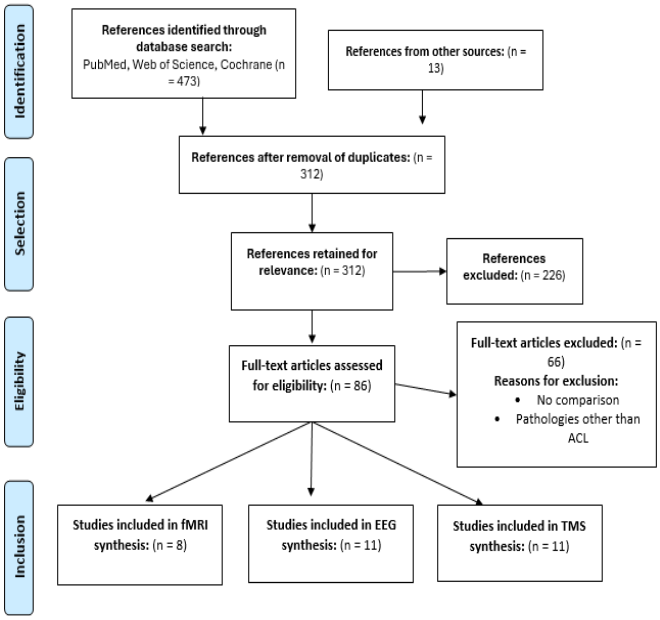

Figure 1. PRISMA diagram of studies included in the pathophysiology of AMI

PRISMA: Preferred reporting items for systematic reviews and meta-analyses, AMI: Arthrogenic muscle inhibition, ACL: Anterior cruciate ligament, fMRI: Functional magnetic resonance imaging, EEG: Electroencephalography, TMS: Transcranial magnetic stimulation

Therapeutic Strategies Targeting AMI

The search for studies addressing therapeutic strategies targeting AMI following ACL injury was conducted in PubMed, Web of Science, and the Cochrane Library, yielding 242 references, supplemented by 21 additional articles from other sources. After duplicate removal, 202 unique references were retained and screened for relevance based on titles and abstracts. At this stage, 145 articles were excluded for lack of direct relevance to AMI management. A total of 57 full-text articles were then reviewed for eligibility. Among these, 24 studies were excluded-primarily due to the absence of quadriceps strength assessments or inclusion of populations unrelated to ACL pathology (e.g., patients with prosthetic knees). Finally, 20 studies[47-66] (**Table 4**) met the inclusion criteria and were included in the synthesis. Given the limited number of comparative studies available, all identified articles were included, regardless of study design, and comparison group presence was not considered an exclusion criterion in this section of the analysis. This rigorous selection process enabled the construction of a focused and comprehensive narrative synthesis, as illustrated in the PRISMA flow diagram (**Figure 2**).

Table 4. Summary of strategies targeting AMI in ACL reconstruction patients

Author/year	Population	Treatment	Measurement	Results
Zarzycki[47]	20 ACLR	One session of transcranial direct-current stimulation (tDCS)	- Corticospinal excitability: AMT, SR slope - Dynamometer: Strength	No significant difference observed
Dos Anjos[48]	30 ACLR	Neuromotor program (motor imagery+low-frequency sound stimulation)	- Electromyographic activity - Knee extension deficit - Subjective knee value	- EMG activity significantly increased by 45% - Knee extension deficit significantly improved - SKV significantly increased
Khan[49]	60 ACLR	TENS; in 2 groups: - TENS therapy+exercises and ice packs (n=30) - Exercises+ice packs only (n=30)	- Dynamometer: Strength - Pain: VAS (Visual Analog Scale) - Function: Lysholm and IKDC scores - Thigh circumference	- Significantly lower VAS pain scores, greater muscle strength, and better Lysholm and IKDC scores in the TENS group - No significant difference in mean thigh circumference
Sherman[50]	20 ACLR vs. 20 healthy controls	External focus during single-leg stance under four conditions: - TENS - External focus based on an object - External focus based on a target - Internal focus	EEG: pectral analysis of theta and alpha activity	- ACLR individuals showed higher motor-planning activity, reduced sensory activity, and decreased motor activity - External focus based on a target reduced motor-planning activity and increased bilateral visual, sensory, and motor activity - No significant differences between other groups
Kim[51]	13 ACLR vs. 13 healthy	Effect of kinesiophopia → Observations of an action during a vertical drop jump	- fMRI - TSK 11: Psychological fear score	- Lower brain activity in the right ventrolateral prefrontal cortex, including the precentral gyrus, middle frontal gyrus, and corticospinal tract in the ACLR group - Higher TSK-11 scores in the ACLR group
Bodkin[52]	10 ACLR	Visuomotor therapy (visual biofeedback)	- TMS: MEP	Significant increase in MEP
Rush[53]	10 ACLR	tDCS: One session of transcranial direct-current stimulation	- EMG: MVIC - Pain and symptoms	No significant difference after a single session
Mendias[54]	19 ACLR	Hormone therapy: Growth hormone, two groups: - Treatment group: 9 - Control group: 10	- Dynamometer: Muscle strength - MRI: Muscle volume -PROMs	- Significant increase in muscle strength in the treatment group - No significant difference in muscle volume or PROMs
An[55]	20 ACLR vs. 20 healthy	Psychological effect → Response to three types of emotionally evocative negative images (fear or knee-injury-related images)	- EEG: Frontal and parietal electrodes - ROM	- Increased frontal and parietal spectral frequency in the ACLR group - Increased rigidity in the ACLR group
Lepley[56]	5 ACLR	Cross-eccentric exercises (nondominant limb)	- Brain activity: fMRI - EMG: H-reflex - TMS: AMT, MEP - PROMs: Pain, symptoms, function	- fMRI: Reduced neuronal activity in the frontal cortex - Significant increase in H-reflex and MEP - Significant improvements in PROMs
Lowe[57]	9 ACLR vs. 9 healthy	Hamstring fatigue → Induced by performing squats	-CAR	Significant increase in CAR in the ACLR group
Oliveira[58]	47 ACLR	Kinésio-taping, 3 groupes: - Control group - Placebo group - Taping group	- EMG/dynamometer: CAR - MVIC - Baropodometry: Postural balance	No significant difference
Lepley[59]	36 ACLR vs. 10 healthy	NMES/eccentric exercises, 4 groups: 1-NMES+eccentric exercises 2-Eccentric exercises only 3-NMES only 4-Standard rehabilitation	- MVIC - CAR	- CAR: Higher in the eccentric-exercise-only group - MVIC: Higher in the NMES and eccentric-only groups
Hart[60]	30 ACLR	Cryotherapy 3 groupes: 1-20 minutes of cryotherapy 2-One hour of rehabilitation exercise. 3-Cryotherapy followed by exercises	- MVIC - Reflex H/M	- Significant increase in MVIC in the cryotherapy+exercises group - No significant difference in H/M reflex
Baltaci[61]	30 ACLR	Biofeedback+motor imagery (Nintendo Wii Fit) Two groups: - Treatment group: 15 - Control group: 15	- Dynamometer: Knee strength - Coordination tests - Functional test: Squat	No significant difference
Maddison[62]	21 ACLR	Motor imagery (visual+kinesthetic), two groups: - Treatment group: 13 - Control group: 8	- Dynamometer: Knee strength - KT1000 arthrometer: Laxity - Psychological effect (Questionnaire-AIESQ)	- No significant difference in knee strength or in the AIESQ questionnaire - Significantly lower laxity in the treatment group
Lebon[63]	12 ACLR	Kinesthetic motor imagery, two groups: - Treatment group: 7 - Control group: 5	- EMG: Electromyographic activity - LEFS to assess ability to perform daily activities - Anthropometric data: joint ROM, effusion resorption - Pain: VAS	- Greater electromyographic activity in the treatment group - No difference in anthropometric measures, LEFS scores, or VAS pain
Ohta[64]	44 ACLR	Blood flow restriction Two groups: - Treatment group: 22 - Control group: 22	- Dynamometer: Muscle strength - Pre/post ratio of quadriceps cross-sectional area	- Significant increases in muscle strength. - Significant improvement in the preoperative/postoperative ratio of quadriceps cross-sectional area at 16 weeks in the treatment group.
Cupal[65]	30 ACLR	Intervention: Motor imagery (visual+kinesthetic) three groups - Treatment group: 10 - Standard physiotherapy group: 10 - Placebo group: 10	- Dynamometer: Muscle strength - Reinjury anxiety (questionnaire) - Pain	- Significantly higher muscle strength in the treatment group. - Significantly lower pain and reinjury anxiety in the treatment group.
Draper[66]	30 ACLR	EMG Biofeedback/TENS, two groups: -TENS group: 15 -EMG biofeedback group: 15	-Dynamometer: Muscle strength	The biofeedback group recovered significantly greater muscle strength compared to the electrical stimulation (TENS) group.

AMI: Arthrogenic muscle inhibition, ACL: Anterior cruciate ligament, ACLR: Anterior cruciate ligament reconstruction, tDCS: Transcranial direct current stimulation, TENS: Transcutaneous electrical nerve stimulation, NMES: Neuromuscular electrical stimulation, AMT: Active motor threshold, SR slope: Stimulus-response slope, EEG: Electroencephalography, fMRI: Functional magnetic resonance imaging, AIESQ: Athletic Injury Self-Efficacy Questionnaire, BFR: Blood flow restriction, CAR: Central activation ratio, EMG: Electromyography, H/M ratio: Hoffmann reflex to M-Wave ratio, IKDC: International Knee Documentation Committee score; KT: Kinesio taping, MEP: Motor evoked potential, MRI: Magnetic resonance imaging, VMO: Vastus medialis oblique, MVIC: Maximal voluntary isometric contraction, PROMs: Patient-reported outcome measures, ROM: Range of motion, SKV: Subjective knee value, TMS: Transcranial magnetic stimulation, TSK-11: Tampa Scale of Kinesiophobia-11 items, LEFS: Lower Extremity Functional Scale, VAS: Visual Analog Scale

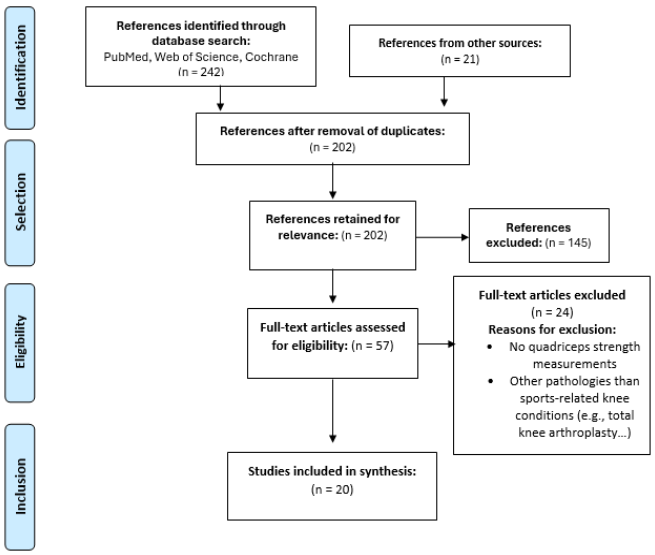

Figure 2. PRISMA diagram of studies included in the review of therapeutic strategies targeting AMI

PRISMA: Preferred reporting items for systematic reviews and meta-analyses, AMI: Arthrogenic muscle inhibition

DISCUSSION

AMI is a long-recognized neurophysiological phenomenon first described in 1965, when researchers demonstrated that experimentally induced knee effusion produced reflexive quadriceps inhibition through altered capsular feedback.[67] Subsequent work in the 1980s confirmed that the magnitude of inhibition was proportional to the volume of effusion, highlighting the strong link between disrupted joint afference and reduced muscle activation.[68,69] Although the association between reflex inhibition and muscle weakness was known for decades, AMI was formally defined only in 2000 by Hopkins and Ingersoll as a persistent reflex inhibition of the alpha-motoneuron resulting from altered afferent input from an injured joint.[70] Since this definition, research on AMI-particularly in the context of ACL injury-has advanced substantially.

Neurophysiopathology of AMI

Current evidence indicates that AMI is a multifactorial process involving interacting local, spinal, and supraspinal mechanisms.[71] Local factors such as damaged proprioceptors, inflammatory "biochemical soup," joint effusion, and mechanical instability disrupt sensory transmission to the central nervous system.[72-75] These altered afferents contribute to higher-level changes, including disrupted sensory integration (EEG), altered cortical connectivity (fMRI), and impaired descending motor drive (TMS), ultimately resulting in deficits in voluntary quadriceps activation.[71]

Sensory afferent pathway (EEG): Eleven studies investigated sensory afferent pathways in individuals with ACL injury using EEG, including power spectral analysis and somatosensory evoked potentials (SEP).[17-27] EEG provides an initial window into supraspinal mechanisms contributing to AMI by capturing cortical responses to altered proprioceptive input.

Across studies, spectral analysis consistently demonstrated increased frontal theta activity during sensorimotor tasks, interpreted as enhanced engagement of cortical networks supporting anticipatory motor control in the context of reduced proprioceptive reliability.[17,18,20-22] Several investigations also reported increased parietal alpha activity-typically associated with cortical deactivation-suggesting challenges in sensory processing or attentional allocation.[19] Conversely, reduced posterior alpha observed in ACL-reconstructed individuals during complex or dynamic tasks indicates a greater reliance on visual processing to compensate for sensory-motor deficits.[17]

SEP findings further characterized the integrity of afferent pathways by examining cortical responses following peripheral nerve or ACL stimulation. Although the overall transmission of sensory information to the cortex appeared preserved, studies consistently noted reduced reproducibility and stability of SEP waveforms in individuals with ACL injury.[23-27] These alterations suggest that despite intact structural pathways, the quality and consistency of proprioceptive input reaching the somatosensory cortex are compromised. Such disruptions in afferent signal processing likely contribute to the central component of AMI and may influence subsequent motor control adaptations

Cortical connectivity (fMRI): Neuroplastic reorganization following ACL injury reflects the brain's adaptive response to altered sensory-motor input. Functional MRI provides a window into these adaptations by quantifying blood-oxygen-level-dependent (BOLD) activity and mapping functional connectivity within networks responsible for motor planning and execution. Across eight comparative studies, consistent patterns of neurofunctional change have been identified in individuals with ACL injury, using both resting-state and task-based paradigms.[28-35]

A primary finding is the reduced activation of key motor and sensory regions, particularly the primary motor cortex (M1), primary somatosensory cortex (S1), and supplementary motor area (SMA).[28,29,34] This hypoactivation is commonly interpreted as impaired descending motor drive or a persistent centrally mediated inhibitory state, likely arising from partial deafferentation following ligament injury. At the same time, increased activation within associative and visual regions-including the thalamus, superior parietal cortex, angular gyrus, and inferior parietal lobule-suggests a compensatory shift toward heightened multisensory integration and cognitive control.[30,31] These changes indicate that individuals may rely more heavily on visual and higher-order cortical processing to compensate for degraded proprioceptive input during lower-limb tasks.[34]

Alterations in functional connectivity complement these activation patterns. Several studies report decreased connectivity between sensory and motor regions, such as between S1 and SMA or between premotor areas and M1, reflecting a disruption of motor network organization.[29,32,33] Conversely, increased connectivity within cognitive and premotor circuits has been observed, which may represent adaptive recruitment of alternative pathways to support movement planning and execution.[34,35] Together, these findings support the concept of a reorganized but less efficient motor control strategy, potentially contributing to persistent AMI and long-term deficits following ACL injury.

Motor efferent pathway (TMS): Eleven studies have used TMS to investigate alterations in efferent motor pathways following ACL injury.[36-46] TMS, typically combined with

EMG and dynamometry, allows simultaneous evaluation of corticospinal excitability, motor output, and voluntary activation.

Across studies, individuals with ACL injury consistently demonstrate reduced corticospinal excitability, evidenced by elevated active motor thresholds (AMT) and diminished motor evoked potentials (MEP) amplitudes in the injured limb compared with the contralateral side or healthy controls.[42,44,45] These findings suggest weakened descending drive and impaired transmission along the corticospinal tract. Evidence regarding intracortical mechanisms is more variable: while several studies report no significant changes in short-interval intracortical inhibition (SICI) or intracortical facilitation (ICF), others identify prolonged cortical silent period (CSP) duration, consistent with enhanced intracortical inhibition and a persistent limitation in motor output.[37,38]

Three recent meta-analyses provide additional clarity and reinforce the strength of the evidence. Across 13-14 studies and samples ranging from 381 to 611 participants, they consistently report bilaterally elevated AMT, reflecting a generalized decrease in cortical excitability after ACL injury. MEP amplitudes demonstrate asymmetrical reorganization, typically reduced in the injured limb while relatively preserved in the uninjured limb, suggesting compensatory redistribution of descending motor drive.[76-78]

Synthesis: AMI arises from the interaction between peripheral joint pathology and central nervous system adaptations following ACL injury. Locally, damage to ligamentous mechanoreceptors combined with pain, effusion, and inflammation disrupts proprioceptive afferent input and triggers protective inhibitory reflexes. EEG studies show altered cortical processing of this degraded sensory information, characterized by increased frontal activity and changes in sensorimotor rhythms, indicating greater cognitive demand and reduced efficiency of motor control. fMRI findings further reveal maladaptive cortical reorganization, with decreased activation of primary sensorimotor areas and compensatory recruitment of visual and associative regions. These supraspinal alterations translate into impaired descending motor drive, as confirmed by TMS studies demonstrating reduced corticospinal excitability and altered intracortical inhibition. Together, these local and central mechanisms explain the persistent inability to fully activate the quadriceps despite preserved muscle structure.

Therapeutic Strategies Targeting AMI

Most studies addressing AMI focus on individuals with ACL injury or reconstruction (43.9%) and almost exclusively target the knee joint (97.4%), highlighting the central role of AMI in knee pathology. Therapeutic interventions predominantly address the quadriceps, which is particularly susceptible to AMI following ACL reconstruction, whereas the hamstrings are less frequently targeted, mainly due to their contribution to dynamic knee stability and co-activation with the quadriceps.[14]

To improve clinical recognition and management, Sonnery-Cottet and colleagues[10] proposed in 2022 a graded clinical classification of knee AMI based on vastus medialis oblique (VMO) activation and knee extension deficit. This system distinguishes reversible forms that respond to simple in-clinic exercises from more severe forms requiring prolonged, targeted rehabilitation or, in chronic cases, surgical intervention. Early identification and treatment of reversible AMI are critical to restoring quadriceps function and preventing persistent deficits. Clinical management focuses on reducing reflexive inhibition through hamstring fatigue, addressing hemarthrosis when present, and re-establishing active quadriceps and VMO activation to restore full knee extension.[10] A prospective 2024 study of 300 patients with recent ACL injuries (<6 weeks) found that over 55% exhibited AMI, with nearly 80% being easily reversible through simple exercises; more severe forms (grades 1B and 2B) accounted for approximately 12% and required longer, specific rehabilitation.[5]

Overall, AMI is progressively reversible but leaves a subset of motoneurons difficult to recruit voluntarily, reinforcing the need for phase-specific neuromuscular interventions. In this review, therapeutic strategies are structured according to the recovery phases after ACL injury, following the framework of Norte et al.,[14] which considers both time and the evolving neurophysiological state of the patient, according to their mechanisms of action on neuromuscular inhibition. This phase-based organization is intended to facilitate clinical interpretation; however, rehabilitation progression in practice is often criterion-based rather than strictly time-dependent, and several interventions may overlap across recovery phases depending on individual patient presentation and rehabilitation goals.

Acute phase: 0-6 weeks: During the acute phase, AMI is maximal, primarily due to pain, edema, and inflammation. Voluntary quadriceps activation, as measured by the central activation ratio (CAR), can drop below 20%.[7,70] Despite a structurally intact muscle, ACL injury or reconstruction disrupts proprioceptive signaling through mechanoreceptor damage and nociceptive afferents. This triggers protective inhibitory reflexes at both the spinal and cortical levels, limiting motoneuron availability.[14] Early rehabilitation aims to reduce pain, effusion, and inflammation; promote muscle activation; and limit atrophy.

Cryotherapy: Targeted cryotherapy around the joint appears to attenuate AMI by modulating nociceptive and thermosensory afferents, enhancing motoneuron excitability and voluntary muscle activation.[79] It reduces nociceptor activity while stimulating thermoreceptors, decreasing inhibitory signals transmitted via small-diameter afferents and facilitating motor disinhibition.[80] Typically, ice or a cooling device is applied circumferentially for 20-30 minutes immediately prior to therapeutic exercises. Hart et al.[60] demonstrated that combining cryotherapy with exercise significantly improved quadriceps strength (MVIC) without affecting the H/M reflex.

Transcutaneous electrical nerve stimulation (TENS): TENS is frequently used in the acute phase to limit AMI. By modulating sensory afferent pathways, particularly small-diameter fibers, TENS can mask nociceptive signals responsible for reflexive motoneuron inhibition. This transient disinhibition helps restore motor pool excitability and facilitates voluntary quadriceps activation.[81] Sessions of 20-30 minutes at high frequency (120-150 Hz) before

or during exercise appear optimal. Khan et al.[49] reported reductions in pain (VAS) and improvements in muscle strength and functional scores (IKDC, Lysholm) when TENS was combined with exercise.

Neuromuscular electrical stimulation (NMES): NMES is widely used early in rehabilitation to bypass AMI. Its primary goals are to enhance intramuscular blood flow, maximal force, endurance, and prevent early atrophy.[82] NMES stimulates intramuscular nerve branches to elicit muscle contractions. Repeated depolarization of motor neurons produces involuntary maximal contractions to limit atrophy in inhibited muscles.[83] NMES is most effective in the early recovery phase, with diminishing returns as voluntary strength and activation improve.[82] Combined NMES and exercise, particularly eccentric training, has been shown to significantly increase quadriceps MVIC.[59]

Cross-education eccentric exercises: Cross-education exercises performed on the contralateral limb can stimulate muscle activation on the injured side via supraspinal mechanisms. This approach relies on interhemispheric communication activated during voluntary contractions of the healthy limb.[84] In the acute phase, when loading the injured joint is limited, cross-education offers a safe method to maintain neuromuscular excitability.[82] Lepley et al.[56] reported that a 4-week intervention increased H/M reflex and MEP responses and improved functional scores despite no direct work on the operated limb.

Blood flow restriction (BFR) training: BFR is a valuable option during the acute phase when high loads are contraindicated. By inducing localized muscular hypoxia, BFR activates metabolic pathways that promote anabolic growth factors, fast-twitch fiber recruitment, and myostatin inhibition, thereby limiting muscle atrophy.[86] Ohta et al.[64] demonstrated that a 16-week BFR program significantly increased quadriceps strength and cross-sectional area without heavy resistance. While BFR does not directly address AMI mechanisms, it supports early muscle preservation.

EMG biofeedback: EMG biofeedback provides patients with real-time feedback on muscle activation, enhancing conscious control over descending motor pathways.[87] This voluntary cortical engagement helps bypass spinal inhibitory reflexes and restore quadriceps activation. A 2023 meta-analysis of eight studies conducted 1-16 weeks post-ACL reconstruction found EMG biofeedback improves quadriceps strength and knee extension, though effects on pain and Lysholm scores were limited.[88] Draper et al.[66] reported significantly greater strength recovery with EMG biofeedback compared to TENS, and Pietrosimone et al.[42] observed increases in MEP and muscle strength in healthy subjects after isometric training with EMG-BF, suggesting a corticospinal activation effect.

Subacute phase: 6 weeks-6 months: During the subacute phase, AMI gradually decreases but remains present. Some motoneurons regain availability; however, the motor system often struggles to recruit them effectively, a phenomenon known as central activation failure.[42,59] Despite apparent physical recovery, voluntary quadriceps activation (CAR) often remains below 50%,[42,45] largely due to persistent cortical alterations detected by TMS, even when the muscle is structurally intact. Pain, effusion, and inflammation typically diminish during this phase. The main goals are to progressively increase joint load, continue muscle strengthening, and enhance voluntary activation.

Antagonist muscle fatigue: After ACL injury, antagonist muscles may become hyperactive via supraspinal mechanisms to stabilize the joint and protect intra-articular tissues. This overactivation inhibits agonist activity, such as the quadriceps, through reciprocal inhibition.[89] Voluntary fatigue of the hamstrings reduces this antagonistic inhibition, facilitating quadriceps activation.[90] While primarily applied in the subacute phase, antagonist fatigue can also be useful in the acute phase to counter early spinal reflex inhibition. Lowe et al.[57] demonstrated a significant increase in CAR following targeted antagonist fatigue exercises in ACL patients.

Eccentric exercises: Eccentric training targeting strength and voluntary activation effectively improves CAR, a key indicator of quadriceps activation after ACL injury.[14] Lepley et al.[59] reported that participants performing only eccentric exercises had significantly higher CAR compared with other groups, indicating enhanced voluntary activation via supraspinal and spinal excitatory pathways. Integrating eccentric exercises into ACL rehabilitation can therefore restore neuromuscular activation, essential for regaining quadriceps strength and function.

Kinesio taping (KT): KT involves applying elastic tape to the skin (e.g., quadriceps in an inverted Y configuration) to stimulate cutaneous receptors and facilitate muscle activation. Oliveira et al.[58] found that, at 4 months post-ACL reconstruction, KT alone did not significantly improve MVIC or CAR in patients with AMI. This suggests limited efficacy in advanced rehabilitation but supports its use in the acute phase to enable earlier quadriceps activation when pain, edema, and reflex inhibition predominate.[91]

Return-to-sport phase: >6 months: Beyond six months, AMI can persist despite structural recovery. Lepley et al.[59] reported that 30-40% of patients still exhibit significant AMI one-year post-surgery. Although quadriceps volume is often restored, neuromuscular activation quality remains compromised. Compensatory cortical strategies, including overactivation of premotor or visual cortical regions and recruitment of alternative muscle groups, can partially mask deficits.[37,50]

Motor imagery: Motor imagery-visual or kinesthetic simulation of movement without physical execution-engages mirror neurons, activating motor regions similarly to actual movement. This strengthens corticospinal circuits and facilitates voluntary motoneuron recruitment even without physical movement.[92] Cupal et al.[65] reported significant gains in muscle strength and reductions in pain and fear of reinjury after 6 weeks of motor imagery. Lebon et al.[63] observed increased EMG activity, while Maddison et al.[62] demonstrated reduced joint laxity. More recently, Dos Anjos and colleagues,[48] using the Allyane method, reported a 45% increase in EMG activity, a significant improvement in knee-extension deficit, and a significant increase in subjective knee value (SKV), further supporting the neuromuscular benefits of motor imagery-based interventions. Although results across studies remain heterogeneous, motor imagery is safe, noninvasive strategy that can complement conventional rehabilitation. While findings are encouraging, the current level of evidence for motor imagery remains moderate and somewhat heterogeneous, with most studies involving small sample sizes and variable protocols.

Visuomotor therapy: Bodkin et al.[52] showed that a single session of visuomotor therapy elicited a greater increase in quadriceps corticospinal motor response than sham therapy, suggesting that visuomotor training may serve as an effective adjunct when upregulation of corticospinal excitability is desired. Baltaci et al.[61] investigated Nintendo Wii Fit-based rehabilitation as an interactive, visually guided approach to balance and functional training that emphasizes visual feedback, external cues, and sensorimotor integration. Wii Fit-based rehabilitation resulted in functional outcomes comparable to conventional rehabilitation after ACL reconstruction, with greater improvements in balance-related measures. However, this intervention did not provide direct evidence of neuromodulatory effects on quadriceps strength or AMI. Evidence supporting visuomotor therapy remains preliminary, and additional controlled studies are needed to determine its specific effects on AMI and quadriceps neuromuscular recovery.

Supraphysiological hormone therapy: Experimental interventions using growth hormone aim to limit AMI by targeting post-traumatic muscle catabolism when voluntary activation remains limited. Mendias et al.[54] reported increased muscle strength post-ACL reconstruction with growth hormone treatment, though effects on muscle volume and functional scores were minimal. Benefits may relate to reduced myostatin expression and modulation of anabolic pathways. Due to low evidence, regulatory limitations, and potential systemic side effects, this approach remains experimental and insufficient to support routine clinical use in AMI management.

Attentional focus: Emerging evidence suggests that external attentional focus (directed toward an object or target) may enhance voluntary quadriceps activation and facilitate motor recruitment.[93] Focusing externally improves motor performance and reduces cortical inhibition more effectively than internal focus. Sherman et al.[50] compared different unipedal stance conditions in ACL patients and found that external target-focused attention decreased motor planning activity while increasing bilateral sensory-motor activation, promoting more automatic and efficient movement. Targeting patient attention to external goals during exercise is a simple yet effective neuromuscular strategy in late-phase ACL rehabilitation.

Transcranial direct current stimulation (tDCS): tDCS is a noninvasive method to modulate cortical excitability, especially in the primary motor cortex (M1), with the goal of enhancing voluntary motoneuron recruitment via descending pathways. Typical application involves 1-2 mA anodal stimulation for 20 minutes over the motor region contralateral to the injured limb.[47,53] Rush et al.[53] reported no significant improvement in quadriceps activation or pain after a single tDCS session during treadmill walking 39 months post-ACL reconstruction. Zarzycki et al.[47] similarly observed no significant effects on strength, H/M reflex, or MEPs during cycling at 6 months post-surgery, though tDCS was well tolerated. While feasible and safe, isolated tDCS efficacy remains limited and inconclusive, despite its feasibility and favorable safety profile.

Psychological factors: Psychological factors strongly influence neuromuscular recovery after ACL reconstruction. Kinesiophobia or fear of movement can disrupt motor circuits and perpetuate muscle inhibition. Kim et al.[51] found heightened activation in fear-related brain regions (amygdala, cerebellum) during observation of risky movements, correlating with high kinesiophobia scores. An et al.[55] demonstrated increased joint stiffness and elevated frontal and parietal spectral frequency in response to traumatic knee imagery. Assessing these aspects using tools like the ACL-RSI (Anterior Cruciate Ligament-Return to Sport after Injury) scale helps address confidence, emotions, and motivation.[94] Accounting for psychological barriers is essential for optimal neuromuscular recovery and sustainable return to sport.

Limitations

This scoping review has several limitations. The included studies were highly heterogeneous in terms of experimental paradigms, neurophysiological assessment methods (EEG, fMRI, and TMS), and clinical outcome measures, which limited direct comparison across studies and precluded quantitative synthesis. Most studies used cross-sectional designs, restricting interpretation of causal relationships between neurophysiological alterations and quadriceps dysfunction.

Additionally, definitions and classifications of AMI varied across studies, and AMI was often inferred indirectly rather than measured using standardized criteria. Substantial heterogeneity in patient characteristics across studies-including time since injury or surgery, graft type, concomitant injuries, gender, athletic level, pain status, and rehabilitation exposure-likely contributed to variability in neurophysiological and clinical findings and may partially explain inconsistencies between studies. Intervention studies rarely integrated neurophysiological outcomes with functional or strength-based measures, limiting conclusions regarding mechanistic links between cortical changes and clinical recovery.

Furthermore, the therapeutic evidence should be interpreted with caution, as many intervention studies were based on small sample sizes, heterogeneous rehabilitation protocols, or exploratory designs. Consequently, some interventions discussed in this review should be considered promising but preliminary, and their clinical effectiveness requires confirmation through larger, high-quality comparative and longitudinal studies.

Finally, as a scoping review, this work aimed to map and summarize the existing literature rather than formally assess methodological quality or risk of bias, and relevant studies may have been missed despite a comprehensive search strategy.

CONCLUSION

AMI is a multilevel reflex-mediated neural disorder that limits muscle activation despite preserved structural integrity. After ACL injury, alterations detected with EEG, fMRI, and TMS indicate impaired motor control and disrupted brain-muscle communication, contributing to persistent weakness beyond simple atrophy or deconditioning. These findings support the concept that effective rehabilitation should not rely solely on strength training but should also incorporate targeted neuromuscular interventions addressing both

peripheral and central mechanisms of inhibition. Clinically, early identification and classification of AMI using functional grading systems may help identify reversible forms amenable to immediate treatment. More persistent presentations require an individualized, mechanism- and recovery stage-based rehabilitation approach that considers motoneuron availability, voluntary recruitment capacity, pain, proprioceptive deficits, and psychological factors to optimize recovery and reduce long-term dysfunction. Future longitudinal and comparative studies are needed to clarify the causal relationships between neurophysiological alterations, AMI persistence, and functional recovery after ACL injury or reconstruction.

Findings

- Neurophysiological studies demonstrate that Arthrogenic Muscle Inhibition after ACL injury involves altered afferent input, cortical reorganization, and reduced corticospinal excitability, not solely peripheral quadriceps dysfunction.
- Intervention studies indicate that quadriceps activation and strength can be improved through phase-specific strategies, particularly when interventions target both neural and muscular mechanisms.

Implications

- These findings expand current understanding of AMI as a multi-level neurophysiological condition and support rehabilitation approaches that extend beyond traditional strengthening to include cortical and sensorimotor retraining.
- Clinicians should consider early identification of AMI and integrate neuromuscular and neurocognitive strategies to optimize quadriceps recovery after ACL injury.

Caution

- Most included studies were small, heterogeneous in design and outcome measures, which may limit generalizability to broader clinical populations and real-world rehabilitation contexts.

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Review

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Objectively measured physical activity after anterior cruciate ligament reconstruction: evidence from adult populations and critical gaps in pediatric patients

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ABSTRACT

Anterior cruciate ligament (ACL) injuries are increasingly common among children and adolescents, raising concerns regarding long-term joint health and physical activity behavior. Traditional outcome measures, particularly return-to-sport (RTS), do not adequately reflect habitual physical activity levels following ACL reconstruction (ACLR). This review aimed to evaluate existing evidence on objectively measured physical activity after ACLR, with a particular focus on pediatric populations. A narrative review of the literature was conducted using major electronic databases, including studies employing objective measurement tools such as accelerometers and pedometers. Current evidence demonstrates that adults following ACLR frequently exhibit reduced physical activity levels despite successful RTS. In contrast, there is a substantial lack of studies specifically investigating objectively measured long-term physical activity in pediatric populations. Available studies are limited by mixed age cohorts, short follow-up periods, and methodological heterogeneity. Overall, the findings highlight a significant gap in the literature and emphasize the need for longitudinal studies focusing exclusively on pediatric patients in order to better understand recovery trajectories and optimize long-term outcomes.

Keywords: Physical activity monitoring, accelerometry, pediatric orthopedics, motor activity, rehabilitation

INTRODUCTION

Rupture of the anterior cruciate ligament (ACL) has become increasingly common among physically active children and adolescents, with substantial implications for joint longevity and overall quality of life.[1] Over the past two decades, the incidence of ACL injuries and subsequent reconstructions in the pediatric population has risen markedly, with reports indicating a 40% to 55% increase in surgical procedures among young individuals.[2] This trend is largely attributed to early sports specialization, year-round participation in single-sport activities, increased intensity of youth competitive sports, and improved recognition of these injuries in skeletally immature patients.[3] Notably, female athletes exhibit a two- to sixfold higher risk of ACL injury compared to their male counterparts.[1]

Despite advances in surgical techniques, pediatric and adolescent patients remain at particularly high risk for secondary ACL injuries. Rates of graft failure and contralateral ACL rupture range from 17% to 30%, significantly exceeding those observed in older populations.[4,5] Furthermore, more than 30% of secondary injuries occur within the first 20 sport exposures following return to activity.[6] These findings suggest that many young athletes may not be adequately prepared-either physically or neuromuscularly-to tolerate the demands of high-level activity.[7]

Important biological and biomechanical differences distinguish pediatric patients from adults following ACL injury. Skeletally immature individuals possess open physes, ongoing musculoskeletal growth, and maturation-dependent neuromuscular characteristics that may influence both recovery and long-term physical activity behavior. Children and adolescents demonstrate age-specific movement strategies, evolving strength and coordination patterns, and growth-related changes in joint loading. In addition, psychological and social determinants of physical activity differ substantially from those observed in adults. These factors suggest that findings derived from adult ACLR populations cannot be directly extrapolated to pediatric patients and support the need for age-specific investigations.[8]

Traditionally, return-to-sport (RTS) has been considered the primary benchmark of successful recovery.[9,10] However, this binary outcome fails to capture actual daily physical activity (PA) behavior. RTS status does not necessarily reflect habitual movement patterns, and emerging evidence suggests that individuals following ACLR often fail to achieve recommended levels of physical activity despite successful return to sport.[9,11]

Furthermore, a marked disparity exists between adolescents and adults in postoperative activity profiles; while the majority

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of adults meet health-related activity recommendations after surgery, only 9.1% of adolescents achieve the recommended 60 minutes of daily moderate-to-vigorous physical activity (MVPA).[12] This discrepancy is frequently overlooked in clinical practice, as commonly used subjective assessment tools, such as the Tegner Activity Scale and the Marx Activity Rating Scale, are prone to recall bias and systematic overreporting.[13,14] These patient-reported measures primarily capture peak sport participation rather than the overall frequency, intensity, and duration of daily movement, as defined by the FITT principle. In contrast, objective physical activity monitoring using wearable technologies, such as accelerometers, provides a more accurate and comprehensive assessment of a patient's movement profile. Such approaches have demonstrated that individuals following ACLR often exhibit reduced step counts and spend less time in vigorous physical activity compared to healthy peers, even when subjective outcomes suggest satisfactory recovery.[15]

Objective monitoring is particularly important given the direct relationship between physical activity levels and long-term knee health.[16] Reduced activity and associated weight gain represent major risk factors for the development of post-traumatic osteoarthritis, which may affect more than 50% of patients within one to two decades following the initial injury.[16,17] Incorporating objective measures of physical activity into clinical evaluation may therefore enable a more comprehensive assessment of recovery, facilitating individualized rehabilitation strategies aimed at maintaining an active lifestyle and minimizing the risk of reinjury. The aim of this review was to evaluate existing evidence on objectively measured physical activity after ACL reconstruction and to assess the availability of data in pediatric populations.

METHODS

Study Design

A structured narrative review of the literature was performed to identify studies evaluating objectively measured physical activity following anterior cruciate ligament reconstruction (ACLR). Relevant articles were retrieved through electronic database searches in PubMed, Scopus, and Web of Science, covering the period from January 2000 to January 2026.

The search strategy included combinations of keywords related to ACL reconstruction and objective physical activity assessment, such as "anterior cruciate ligament reconstruction", "ACL reconstruction", "physical activity", "motor activity", "accelerometer", "objective measurement", and "step count". To specifically assess the availability of evidence in younger populations, additional terms including "pediatric", "children", and "adolescent" were incorporated into the search.

Studies were considered for inclusion if they reported physical activity outcomes following ACL reconstruction and utilized objective measurement methods, including accelerometers, pedometers, or wearable activity tracking devices. Only studies conducted in human subjects and published in English were considered. Studies based solely on subjective assessment tools or not reporting physical activity outcomes were excluded from further analysis.

Only studies with a minimum follow-up of one year after ACL reconstruction were considered eligible, as earlier assessments primarily reflect postoperative recovery rather than habitual physical activity behavior. Because this was a narrative review, study-specific accelerometer protocols were accepted; however, particular attention was paid to commonly reported validity criteria, including a minimum wear time of approximately 10 hours per day and at least four valid monitoring days when such information was available. Only full-text articles published in English were included.

The identified literature was reviewed with particular emphasis on distinguishing between adult and pediatric populations. Special attention was given to the presence, methodology, and scope of studies involving individuals younger than 18 years, in order to evaluate the extent to which objectively measured physical activity has been investigated in this group.

Due to the expected variability in study design, measurement techniques, and reported outcomes, the findings were synthesized descriptively. The available evidence was analyzed with the aim of summarizing current knowledge in adult populations and identifying gaps in the literature regarding pediatric patients.

Objective Physical Activity Monitoring Methods

The transition from traditional RTS metrics and subjective assessments toward objective monitoring represents an important shift in the evaluation of patients following ACLR. In the context of this review, objectively measured physical activity refers primarily to data obtained using research-grade monitoring devices, such as ActiGraph and activPAL accelerometers. These instruments provide standardized raw movement data and have been validated against criterion methods including indirect calorimetry and doubly labeled water.[18,19] Consumer wearables, such as commercial smartwatches and fitness trackers, were not considered equivalent because of proprietary algorithms, limited transparency regarding data processing, and reduced comparability across studies.[19] Conventional outcome measures often fail to capture actual daily movement patterns and adherence to health-related physical activity (PA) recommendations.[9] In contrast, objective monitoring enables quantification of PA in free-living conditions according to the frequency, intensity, time, and type of movement, as defined by the FITT principle.[13]

Research-grade accelerometers are currently considered the most practical and valid tools for objective assessment of habitual physical activity.[19] Devices such as the ActiGraph (e.g., wGT3X-BT, GT9X Link) use triaxial sensors to capture body acceleration and convert it into activity counts reflecting movement intensity. These monitors are typically worn at the hip, allowing accurate assessment of whole-body movement.[13] The activPAL device, worn on the thigh, enables precise differentiation between sitting, standing, and stepping, providing additional insight into sedentary behavior and postural transitions.[20]

Physical activity data are most commonly expressed through MVPA and daily step count. MVPA represents time spent in activities ≥3 metabolic equivalents and is the primary indicator for meeting health-related guidelines.[9] Importantly, the use of age-specific cut-points is required in pediatric populations to avoid misclassification of activity intensity.

Daily step count provides a simple measure of total activity volume and has been shown to be reduced in patients following ACLR compared to healthy controls, with reported deficits of approximately 1,600-2,000 steps per day.[11]

The validity of accelerometry has been confirmed against gold-standard methods such as indirect calorimetry and doubly labeled water.[18] In addition, high adherence to device wear has been reported, supporting the feasibility of this approach in clinical and research settings.[21]

Compared to subjective questionnaires, objective monitoring offers clear advantages. Patient-reported measures, such as the Tegner Activity Scale, Marx Activity Rating Scale, and IPAQ, are prone to recall bias and frequently overestimate physical activity levels.[13] Moreover, they primarily reflect perceived or peak activity rather than total daily movement, and often show poor correlation with objectively measured outcomes such as MVPA and step count.[14]

Overall, objective monitoring provides a more accurate representation of habitual physical activity following ACL reconstruction, enabling the identification of reduced activity levels that may not be apparent through traditional clinical assessment.[22]

Evidence in Adult Population

The transition from clinical RTS clearance to habitual movement behavior remains a significant challenge in the adult population following ACLR. Although RTS is frequently achieved, objective monitoring indicates that many adults fail to reach physical activity (PA) levels required for long-term joint and overall health.[9]

Device-based evidence demonstrates that adults with a history of ACLR are 2.36 times less likely to meet recommended aerobic physical activity guidelines, such as 150 minutes of MVPA per week, compared to healthy individuals of similar age and self-reported activity levels.[9] This disparity is particularly pronounced in female patients, who show significantly lower odds of meeting MVPA recommendations compared to both healthy controls and male counterparts.[23] Objective measurements have identified consistent and clinically relevant deficits in both the volume and intensity of daily movement. Individuals following ACLR take significantly fewer steps than matched controls, with reported deficits of approximately 1,611 steps per day. In addition, patients accumulate around 65 fewer minutes of MVPA per week compared to uninjured peers.[9,11] On a daily level, ACLR patients achieve approximately 79 minutes of MVPA, whereas healthy controls reach around 93 minutes.[13] When expressed on a weekly basis, this corresponds to approximately 553 versus 651 minutes of MVPA per week, illustrating a cumulative deficit of nearly 100 minutes per week in individuals following ACL reconstruction. Beyond total activity volume, qualitative aspects of movement are also altered. Adults following ACLR spend approximately 42.7 fewer minutes per week in ambulatory activities performed at a cadence of ≥100 steps per minute, indicative of brisk walking.[11] Furthermore, alterations in gait mechanics have been observed, including a reduced ability to attenuate higher-frequency oscillations during walking, suggesting that the impact of ACL injury extends to whole-body movement control.[24]

Long-term data indicate that these deficits may persist over time. In cohorts assessed 32-37 years post-injury, approximately 71% of individuals meet the minimum recommended 150 minutes of MVPA per week; however, only 35% achieve higher recommended levels of 300 minutes per week.[20] Additionally, nearly one-third of individuals adopt a persistently inactive lifestyle regardless of treatment modality.[20] In older populations, mean daily step counts of approximately 5,415 steps further illustrate the long-term decline in total physical activity.[20]

A consistent finding across studies is the poor agreement between subjective and objective measures of physical activity. Commonly used scales, such as the Tegner Activity Scale and Marx Activity Rating Scale, demonstrate weak to non-significant correlations with objectively measured MVPA ($\rho \leq 0.31$).[14] Moreover, self-reported measures frequently overestimate activity levels by 36% to 173% compared to accelerometer-based data.[9] This discrepancy indicates that perceived activity levels or successful return to sport do not necessarily reflect a healthy habitual movement profile.

Evidence in Pediatric Population

Despite the rising incidence of ACL injuries in children and adolescents, no studies were identified that objectively quantified long-term habitual physical activity in strictly pediatric or skeletally immature patients following ACLR. Existing evidence is derived from mixed "youth and young adult" cohorts, including individuals up to 25 or 35 years of age, which limits the ability to draw conclusions specific to the pediatric population.

Only a limited number of studies have utilized accelerometry to evaluate physical activity (PA) in cohorts that include younger patients, and these are restricted to short-term or early medium-term outcomes. Ezzat et al.[10] assessed 51 female athletes aged 15-23 years at 1 to 2 years following ACLR and found no significant differences in daily MVPA compared to healthy controls. However, the ACLR group reported higher levels of knee pain, reduced quality of life, and poorer functional performance.

Similarly, Romero-Padron et al.[17] evaluated 61 individuals aged 13-35 years during early (10 weeks) and mid-phase (6 months) recovery, demonstrating that lower levels of daily step count and MVPA were associated with clinically significant weight gain following surgery. Wellsandt et al.[21] in a cohort of 30 participants (mean age 19.6 years), reported significant sex-based differences, with females demonstrating lower daily step counts (7,003 vs. 10,406) and reduced MVPA (31.3 vs. 54.9 minutes per day), corresponding to approximately 219 versus 384 minutes of MVPA per week at 6 months post-surgery. However, because physical activity was evaluated only at this early post-operative stage, these findings fail to reflect long-term activity trajectories or sustained behavioral deficits. A notable contribution is the study by Kuenze et al.,[12] which specifically analyzed adolescents (15.9±1.2 years) as a separate subgroup approximately 8 months following ACLR. The authors reported that only 9.1% of adolescents met recommended aerobic physical activity guidelines, compared to 83% of adults. However, the study compared adolescents to adult ACLR patients rather than to age-matched healthy controls. As a result, it remains unclear whether the observed differences reflect the impact of ACLR or are attributable to

age-related factors. Crucially, in a broader historical cohort of youth and young adults evaluated 3 to 12 years following a sport-related knee injury sustained during childhood (<18 years), Toomey et al.[25] demonstrated that previously injured individuals spent 13.5 fewer minutes per day in MVPA (~94.5 minutes per week fewer) compared to matched uninjured controls. Interestingly, injured youth substituted this lost MVPA time with light-intensity physical activity (+29.4 adjusted min/day), while sedentary time remained unchanged. Furthermore, lower MVPA participation was directly associated with worse self-reported knee function during sport and recreation. However, it is critical to emphasize that Toomey et al.[25] evaluated a heterogeneous sample encompassing all types of intra-articular knee injuries broadly, rather than an isolated, homogeneous ACLR cohort. Consequently, although informative, these findings cannot be directly extrapolated to children and adolescents undergoing ACL reconstruction.

The interpretation of these findings is limited by several methodological weaknesses. A primary concern is age heterogeneity, as most studies combine skeletally immature adolescents with adults, potentially masking age-specific biological and behavioral responses to ACLR.[1,8] Furthermore, objective data are largely restricted to short-term follow-up periods (6-12 months), providing only a snapshot of early recovery and preventing assessment of long-term behavioral adaptations after ACLR.[9,15] This limitation is particularly relevant because adult studies suggest that reductions in habitual physical activity may persist for decades after injury and reconstruction.[20] Consequently, the period during which long-term behavioral adaptations, sustained reductions in activity levels, and early risk factors for post-traumatic osteoarthritis may emerge remains largely unexplored in children and adolescents.

Additional methodological concerns include small sample sizes, potential selection bias toward higher-functioning individuals, lack of pre-injury physical activity data, and absence of assessor blinding in functional testing. Moreover, many commonly used functional tests and subjective outcome measures have been developed for adult populations and are not fully validated for pediatric patients.[26] A notable discrepancy also exists between RTS clearance and actual physical activity behavior. Although a high proportion of pediatric patients are cleared for RTS, only a subset return to their pre-injury level, and many fail to meet recommended levels of daily physical activity.[4] This indicates that successful RTS does not necessarily reflect restoration of a healthy habitual activity profile.

Overall, while preliminary evidence suggests that adolescents may be at increased risk of reduced physical activity following ACLR, current literature remains insufficient to fully characterize habitual movement patterns in this population. Consequently, the long-term influence of ACLR on physical activity trajectories from adolescence into adulthood remains unclear, with important implications for joint health and the prevention of early-onset osteoarthritis.

This gap highlights a critical need for longitudinal studies focusing exclusively on pediatric populations, incorporating objective monitoring of physical activity beyond the early postoperative period. Addressing these limitations will be essential for developing evidence-based strategies to optimize long-term recovery and physical activity levels in this high-risk population.

Clinical Implications

The findings of current research highlight the need to reconsider how recovery is evaluated following ACLR, particularly in pediatric and adolescent populations. Rather than focusing solely on RTS, greater emphasis should be placed on long-term functional recovery and habitual physical activity behavior.

Pediatric and adolescent patients face a markedly elevated risk of secondary ACL injuries, with reinjury rates ranging from 17% to 30%.[4] A substantial proportion of these injuries occur shortly after RTS, indicating that traditional clearance criteria may not adequately reflect true recovery status.[7] Furthermore, a history of ACLR significantly increases the likelihood of subsequent injury within the first two years after return to activity.[6] An important clinical consideration is that participation in sport does not necessarily indicate sufficient overall physical activity. Objective data demonstrate that many individuals fail to achieve recommended activity levels despite returning to sport participation.[9,11] This has important implications for long-term joint and general health. The absence of long-term objective monitoring data in pediatric populations further limits the ability to determine whether activity levels are successfully maintained into adulthood or progressively decline over time. Such information is essential for identifying patients at risk of inactivity, weight gain, recurrent injury, and the development of post-traumatic osteoarthritis.

Current RTS decision-making is further limited by a lack of standardized, validated criteria for pediatric populations. Time-based benchmarks (e.g., 6-9 months) are still widely used despite poor correlation with functional recovery.[27] Similarly, reliance on limb symmetry indices (LSI), often derived from adult populations, may be misleading in adolescents. Functional decline in the contralateral limb following injury may result in overestimation of recovery when using LSI thresholds.[5,28] In addition, psychological readiness-an important determinant of both RTS success and reinjury risk-is assessed in only a small proportion of pediatric studies (approximately 6%-8%).[29]

These limitations support a shift toward continuous monitoring of recovery. The integration of objective physical activity assessment using wearable technology may provide valuable insight into real-world movement patterns.

In addition, more comprehensive evaluation frameworks that include functional, behavioral, and psychological components may improve clinical decision-making and support the development of more effective, individualized rehabilitation strategies.

Future Directions

Future research should focus on addressing the limited availability of data on objectively measured physical activity following ACL reconstruction in pediatric populations. There is a need for well-designed prospective studies involving clearly defined pediatric cohorts, with follow-up extending beyond the early postoperative period in order

to capture long-term changes in habitual physical activity. Standardization of objective measurement approaches, including device selection and age-specific thresholds, is necessary to improve comparability across studies.

In addition, integrating objective monitoring with functional and patient-reported outcomes may provide a more comprehensive understanding of recovery. The use of wearable technologies offers an opportunity for continuous monitoring of real-world activity patterns and may support more individualized rehabilitation strategies.

Finally, establishing clinically meaningful thresholds for physical activity in pediatric patients following ACLR remains an important objective for future research.

CONCLUSION

Current evidence demonstrates that, despite successful return to sport, adults following anterior cruciate ligament reconstruction frequently exhibit lower levels of objectively measured physical activity than healthy individuals. Research-grade accelerometry has revealed deficits in both total activity volume and moderate-to-vigorous physical activity that are not adequately captured by traditional subjective assessment tools. In contrast, evidence in pediatric populations remains extremely limited. No studies have objectively evaluated long-term habitual physical activity specifically following ACL reconstruction in strictly pediatric cohorts, and available data are largely derived from mixed-age populations with substantial methodological heterogeneity. The absence of long-term objective monitoring data represents a major gap in the literature and limits understanding of how ACL reconstruction influences physical activity trajectories from adolescence into adulthood. Future prospective studies incorporating standardized objective monitoring and age-matched control groups are needed to optimize rehabilitation strategies and improve long-term joint health outcomes in young patients.

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

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Review

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Gene therapy: molecular foundations, therapeutic strategies, and emerging applications in dentistry and orthodontics

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ABSTRACT

Gene therapy has emerged as a transformative therapeutic strategy that addresses diseases at their genetic origin by replacing, repairing, silencing, or editing defective genes. Recent advances in gene-editing technologies, particularly CRISPR/Cas systems, together with improvements in viral and non-viral gene delivery platforms, have significantly enhanced the precision, safety, and clinical applicability of gene therapy. This review provides a comprehensive overview of the molecular foundations of gene therapy, including its historical evolution, classification, mechanisms of action, and gene delivery systems. Particular emphasis is placed on its emerging applications in dentistry and orthodontics, where gene therapy has demonstrated promising potential in periodontal and craniofacial regeneration, bone repair, salivary gland dysfunction, tooth regeneration, management of head and neck carcinomas, and modulation of orthodontic tooth movement through targeted regulation of the RANK-RANKL-OPG signalling pathway. The review also discusses the integration of gene therapy with tissue engineering and regenerative medicine to facilitate biologically driven and personalized treatment approaches. Current challenges, including delivery efficiency, safety concerns, immune responses, ethical considerations, and limited long-term clinical evidence, are critically evaluated. Despite these limitations, continued advances in vector technology, genome editing, and translational research are expected to accelerate the clinical implementation of gene therapy. Overall, gene therapy holds considerable promise for transforming future dental and orthodontic practice by enabling precision therapeutics, enhancing tissue regeneration, and improving long-term patient outcomes.

Keywords: Gene therapy, CRISPR/Cas9, viral vectors, non-viral vectors, regenerative dentistry, orthodontics

INTRODUCTION

All living organisms are composed of cells, the basic structural and functional units of life. Within the nucleus of each cell are chromosomes composed of deoxyribonucleic acid (DNA), the hereditary material that carries the genetic information required for normal growth, development, differentiation, and cellular function. Genes, the fundamental units of heredity, are specific DNA sequences that direct protein synthesis through transcription and translation, thereby regulating a wide range of biological processes. Alterations or mutations in these genes can disrupt normal cellular homeostasis, resulting in inherited or acquired disorders.[1-3]

Gene therapy has emerged as a transformative therapeutic strategy that addresses diseases at their genetic origin by replacing, repairing, silencing, or modifying defective genes rather than merely alleviating clinical symptoms.[1,4] Recent advances in gene-editing technologies, particularly the CRISPR/Cas system, together with improvements in viral and non-viral gene delivery platforms, have significantly enhanced the precision, efficiency, and safety of targeted genetic interventions, expanding their therapeutic potential across numerous medical specialties.[4-6]

Beyond systemic diseases, gene therapy has gained considerable attention in dentistry and orthodontics owing to its potential to promote tissue regeneration, modulate bone remodeling, enhance craniofacial development, and facilitate personalized treatment approaches. A deeper understanding of the genetic basis of dentofacial abnormalities, combined with emerging genome-editing technologies, has opened new possibilities for managing craniofacial disorders, accelerating orthodontic tooth movement, improving periodontal regeneration, and advancing precision orthodontics (**Figure 1, 2**).[2,3,7]

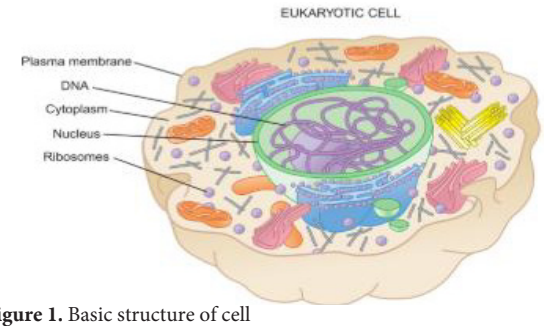

Figure 1. Basic structure of cell

Clark DP, Pazdernik NJ. Molecular Biology. 2nd ed. Elsevier; 2012.

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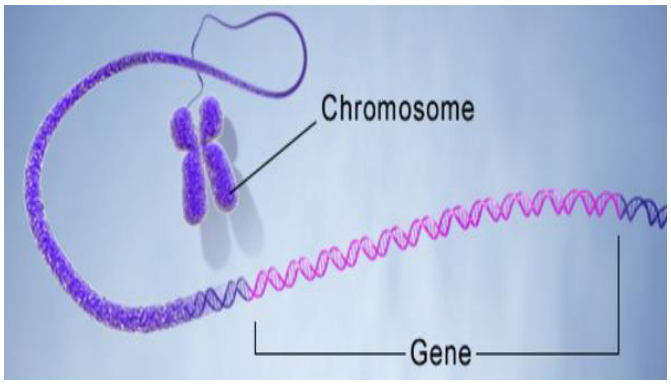

Figure 2. Gene and DNA

DNA: Deoxyribonucleic acid

Cummings S, Dobrea LF. Fundamentals of genetics and genomics in oncology nursing practice and navigation. *J Oncol Navig Surviv.* 2019;10(10):388-397.

MOLECULAR BASIS OF GENE THERAPY

Gene therapy involves the delivery of therapeutic DNA or RNA sequences into target cells or tissues to correct or modulate gene expression.[8-11] The therapeutic gene is introduced using vectors that facilitate cellular uptake and expression.[8,12] Once delivered, the gene may function by adding a normal gene copy, correcting a defective sequence, or silencing a harmful gene.[8]

The success of gene therapy depends on efficient gene delivery, sustained gene expression, minimal immunogenicity, and accurate targeting of specific tissues or cells.[8,12]

HISTORY OF GENE THERAPY

The concept of gene therapy originated in the mid-20th century with the understanding of DNA as the genetic blueprint of life.[13,14] The first approved clinical gene therapy trials in the 1990s targeted severe combined immunodeficiency (SCID)[15] Since then, advances in recombinant DNA technology, viral vector engineering, and gene-editing tools have accelerated research and clinical translation. Today, over a thousand clinical trials are underway worldwide, many focusing on cancer and genetic disorders.[16]

CLASSIFICATION OF GENE THERAPY

Based on Target Cells

Somatic gene therapy: Somatic gene therapy involves genetic modification of non-reproductive cells. The changes are not heritable and are confined to the treated individual. Most current clinical applications, including CAR-T cell therapy for leukaemia, fall under this category (**Figure 3**).[16]

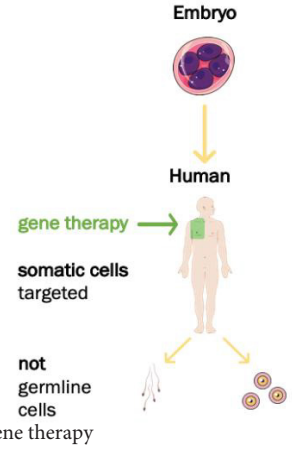

Figure 3. Somatic gene therapy

Frazier S. Embryo Gene Editing: Changing Life As We Know It. 2019.

Germline gene therapy: Germline gene therapy alters genes in sperm or egg cells, making changes heritable. Although it holds potential for preventing inherited diseases such as cystic fibrosis and sickle cell anaemia, it is ethically controversial and prohibited in humans in most countries (**Figure 4**).[11]

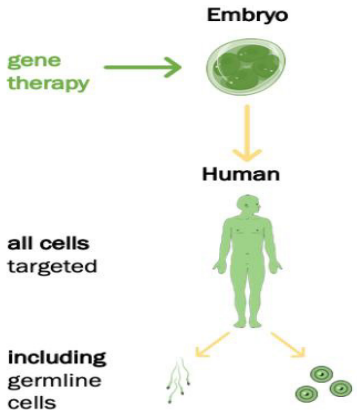

Figure 4. Germline gene therapy

Frazier S. Embryo Gene Editing: Changing Life As We Know It. 2019.

Based on Method of Gene Delivery

In vivo gene therapy: In vivo gene therapy involves direct introduction of the gene-vector complex into the patient's body. It is suitable for diseases affecting internal organs or widespread tissues. Common routes include intravenous, intramuscular, intrathecal, subretinal, and inhalation delivery (**Figure 5**).[8,12]

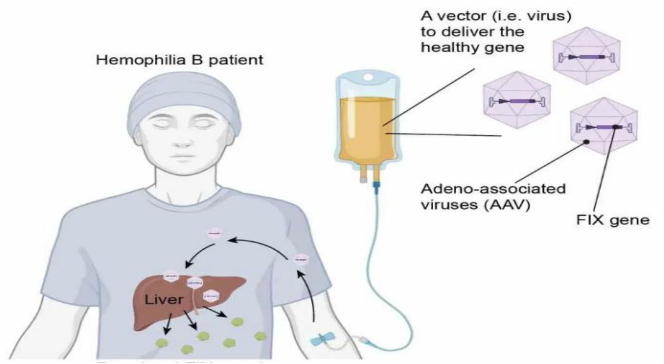

Figure 5. In vivo gene therapy

Rachael. Gene therapy: a promising biotechnology for the treatment of genetic diseases and cancers-basic introduction.

Ex vivo gene therapy: In this approach, patient cells are harvested, genetically modified outside the body, expanded in culture, and reintroduced. This method offers better control over gene transfer and is widely used in stem cell and immunotherapy applications (**Figure 6**).[16,17]

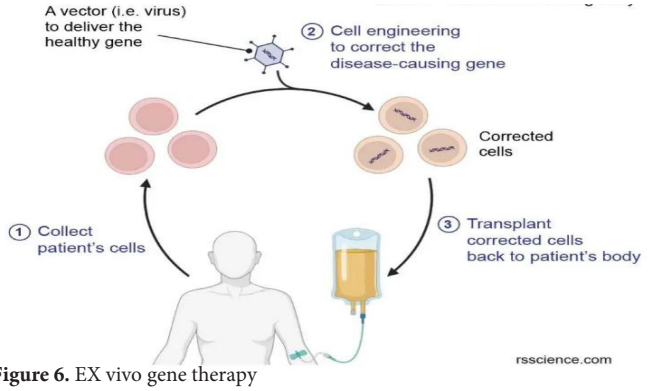

Figure 6. EX vivo gene therapy

Rachael. Gene therapy: a promising biotechnology for the treatment of genetic diseases and cancers-basic introduction.

Based on Therapeutic Approach

Gene augmentation therapy: Addition of a functional gene copy to compensate for a defective gene (Figure 7).[8]

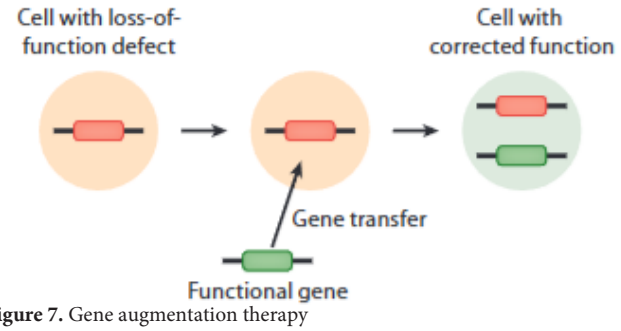

Figure 7. Gene augmentation therapy

Anguela XM, High KA. Entering the modern era of gene therapy. *Annu Rev Med.* 2019;70:273-288. doi:10.1146/annurev-med-012017-043332

Gene inhibition therapy: Silencing of harmful or overexpressed genes (Figure 8).[8]

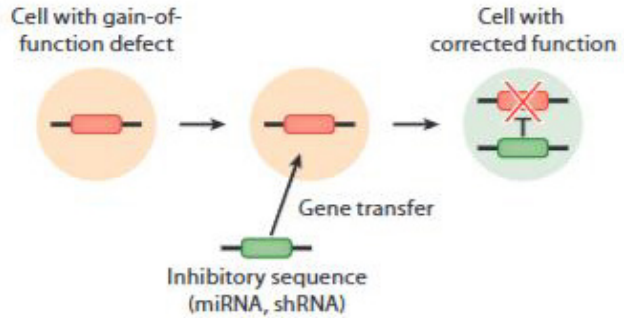

Figure 8. Gene inhibition therapy

miRNA: Micro ribonucleic acid, shRNA: Short hairpin ribonucleic acid

Anguela XM, High KA. Entering the modern era of gene therapy. *Annu Rev Med.* 2019;70:273-288. doi:10.1146/annurev-med-012017-043332

Gene editing therapy: Direct modification of DNA sequences for permanent correction.[12,18]

Suicide gene therapy: Introduction of genes that convert non-toxic prodrugs into toxic compounds within cancer cells.[12,18]

VECTORS AND GENE DELIVERY SYSTEMS

Viral Vectors

Modified viruses serve as efficient gene carriers due to their natural ability to enter cells. Common viral vectors include adenoviruses, retroviruses, lentiviruses, adeno-associated viruses (AAV), and herpes simplex viruses. These vectors are engineered to be replication-defective to enhance safety.[8,12]

Non-Viral Vectors

Non-viral vectors include liposomes, nanoparticles, electroporation, gene guns, microinjection, and calcium phosphate precipitation. Although safer and less immunogenic, they are generally less efficient than viral vectors.[8,19]

MECHANISMS OF GENE THERAPY

Gene therapy operates through three principal mechanisms:

Gene addition: Introduction of a functional gene to restore protein synthesis.[8,10]

Gene correction: Precise repair of mutated DNA sequences using gene-editing tools.[8,17]

Gene silencing: Suppression of harmful gene expression by targeting mRNA.[8,10]

APPLICATIONS OF GENE THERAPY IN DENTISTRY

Orofacial Pain

Gene therapy offers a novel approach to managing chronic orofacial pain by enabling continuous production of anti-nociceptive proteins. Viral or plasmid delivery near the spinal dorsal horn and herpes virus-mediated gene transfer to dorsal root ganglia have shown promising results (Figure 9 and Table).[12,20]

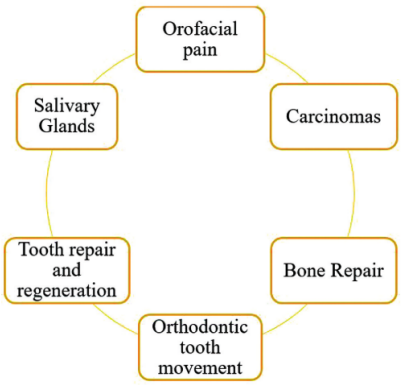

Figure 9. Application of gene therapy in dentistry

Karthika N, Bhat AR. Applications of gene therapy in dentistry: a review article. *J Health Allied SciNU.* 2023;13(4):445-452. doi:10.1055/s-0042-1759711

Table. Applications of gene therapy in dentistry and orthodontics

Application	Therapeutic strategy	Clinical benefit
Bone repair and regeneration	Delivery of osteogenic genes (BMP-2, BMP-4, BMP-7, PDGF)	Enhances osteogenesis, bone regeneration, and craniofacial reconstruction
Salivary gland dysfunction	AQP1 gene transfer	Restores salivary secretion in radiation-induced xerostomia
Tooth repair and regeneration	Gene-modified dental stem cells combined with tissue engineering	Regeneration of dentin, pulp, periodontal tissues, and biological tooth replacement
Orthodontic tooth movement	Modulation of the RANK-RANKL-OPG pathway and growth factor expression (VEGF, PDGF)	Accelerates tooth movement, improves anchorage control, and enhances periodontal healing
Root resorption	Regulation of osteoclast and odontoclast activity through RANK-RANKL-OPG signalling	Reduces orthodontically induced root resorption while maintaining effective tooth movement
Head and neck carcinoma	Tumour suppressor gene replacement, oncogene silencing, and suicide gene therapy	Targeted tumour destruction with reduced systemic toxicity
Orofacial pain	Viral or plasmid-mediated delivery of anti-nociceptive genes	Long-term management of chronic orofacial pain
Cleft lip and palate	BMP-mediated gene delivery for bone regeneration	Improves bone formation in craniofacial defects and supports reconstructive treatment

BMP: Bone morphogenetic protein, PDGF: Platelet-derived growth factor, AQP1: Aquaporin-1, RANK: Receptor activator of nuclear factor kappa B, RANKL: Receptor activator of nuclear factor kappa B ligand, OPG: Osteoprotegerin

Head and Neck Carcinomas

Squamous cell carcinoma of the head and neck is among the most common cancers globally. Gene therapy strategies include tumor suppressor gene replacement (p53), oncogene silencing, and suicide gene therapy. Localized gene delivery minimizes systemic toxicity and enhances therapeutic efficacy.[18,20]

Bone Repair and Regeneration

Gene therapy has emerged as a promising strategy for enhancing bone repair by delivering genes encoding osteogenic growth factors directly to target tissues. Genes encoding bone morphogenetic proteins (BMP-2, BMP-4, and BMP-7) and platelet-derived growth factor (PDGF) stimulate osteoblast differentiation, promote angiogenesis, and accelerate bone formation, thereby improving the quality and rate of osseous regeneration. When combined with stem cell-based tissue engineering approaches, gene delivery provides sustained local expression of regenerative molecules, overcoming the limitations associated with repeated protein administration. These strategies have shown encouraging potential for alveolar bone regeneration, craniofacial reconstruction, and periodontal tissue engineering, highlighting their future role in regenerative dentistry.[11,12,21]

Salivary Gland Dysfunction

Gene therapy using aquaporin-1 (AQP1) has shown success in restoring salivary flow in radiation-induced xerostomia. Salivary glands are ideal targets due to their encapsulated structure and protein secretion efficiency.[20]

Root Resorption

Orthodontically induced root resorption is associated with inflammatory mediators and senescent periodontal ligament cells expressing RANKL, which stimulate osteoclast and odontoclast activity. Targeted gene therapy aimed at modulating the RANK-RANKL-OPG signalling pathway may offer future strategies for minimizing root resorption while maintaining effective orthodontic tooth movement.[10,21]

Tooth Repair and Regeneration

Gene therapy combined with tissue engineering offers a biologically based approach for regenerating dental tissues rather than merely replacing lost structures. Genetically modified dental pulp stem cells and mesenchymal stem cells can enhance the regeneration of dentin, pulp, periodontal ligament, and alveolar bone through sustained expression of regenerative growth factors. These approaches may facilitate the development of bioengineered teeth and improve healing following dental trauma or disease. Although most evidence remains preclinical, continued advances in gene delivery systems are expected to accelerate the clinical translation of regenerative dental therapies.[11,12,21]

Cleft Lip and Palate

BMP-2 and BMP-7 gene delivery has shown improved bone regeneration in cleft defects. Although still experimental, prenatal gene therapy holds promise for preventing craniofacial anomalies.[21]

GENE THERAPY IN ORTHODONTICS

Orthodontic tooth movement involves controlled bone remodeling mediated by cytokines, chemokines, and growth factors. The RANK-RANKL-OPG pathway plays a pivotal role in osteoclast regulation.[10,21]

- RANKL gene delivery accelerates tooth movement.
- OPG gene delivery suppresses bone resorption and preserves anchorage.
- VEGF and PDGF gene overexpression enhances angiogenesis and periodontal healing.

Gene therapy enables spatial and temporal control of tooth movement, reducing treatment duration while avoiding systemic side effects.[10]

In addition to accelerating tooth movement, gene therapy has potential applications in anchorage preservation, periodontal regeneration, and prevention of orthodontically induced root resorption. Targeted modulation of the RANK-RANKL-OPG pathway may allow precise control of osteoclast activity, thereby facilitate desired tooth movement while minimize unwanted bone resorption. Furthermore, localized delivery of growth factors such as BMPs, PDGF, and VEGF may enhance alveolar bone remodelling, angiogenesis, and periodontal healing during orthodontic treatment. These emerging strategies highlight the potential of gene therapy to support more efficient, biologically guided, and patient-specific orthodontic care (**Figure 10**).[10,21]

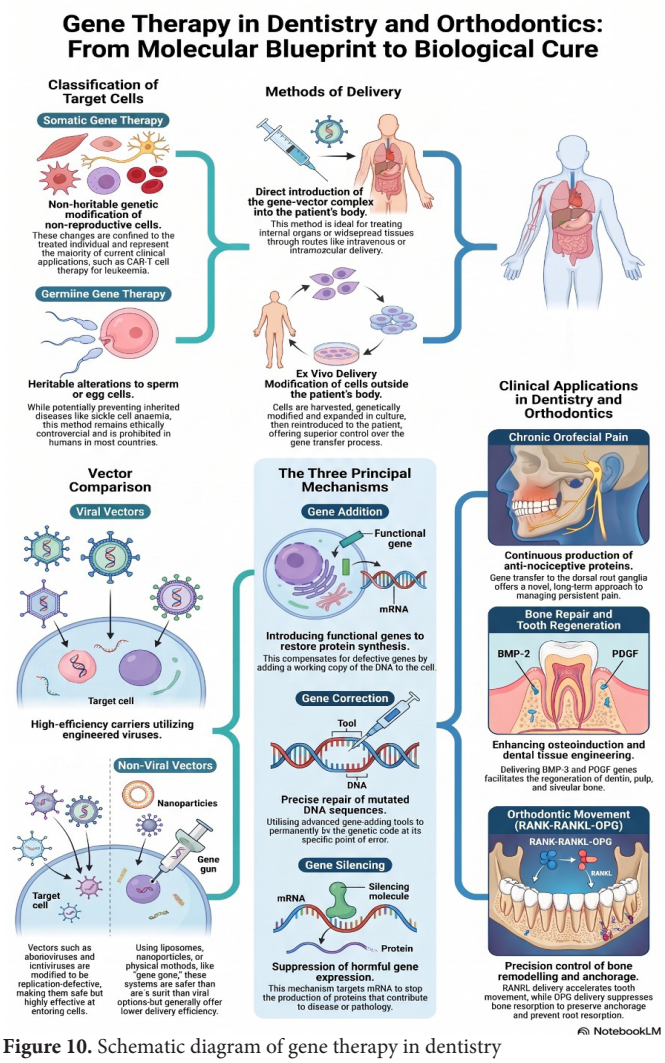

Figure 10. Schematic diagram of gene therapy in dentistry

FUTURE PERSPECTIVES

Future developments in gene therapy are expected to transform dental and orthodontic practice by integrating gene editing, tissue engineering, and regenerative medicine into routine clinical care. Advances in vector technology and targeted gene delivery may enable personalized treatment strategies for periodontal regeneration, craniofacial reconstruction, biological tooth repair, and controlled orthodontic tooth movement. As the safety and efficiency of gene delivery systems continue to improve, gene therapy has the potential to shift orthodontic treatment from purely mechanical approaches toward biologically guided therapies that optimize tissue remodeling and improve long-term treatment outcomes.[11,12,14,21]

Limitations

Despite its promise, gene therapy faces challenges including inefficient delivery, immune reactions, short-lived gene expression, insertional mutagenesis, high costs, ethical concerns, and limited long-term clinical data.

CONCLUSION

Gene therapy represents a transformative approach in modern medicine and dentistry by addressing diseases at their genetic basis. Continued advances in gene editing, vector technology, and tissue engineering are expected to accelerate its translation into routine clinical practice. In dentistry and orthodontics, gene therapy holds significant promise for periodontal and craniofacial regeneration, biological tooth repair, controlled orthodontic tooth movement, and personalized treatment strategies. Although challenges related to safety, delivery efficiency, long-term outcomes, and ethical considerations remain, ongoing research and well-designed clinical trials are likely to establish gene therapy as an integral component of future precision dental care.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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