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# PERI-IMPLANTITIS: IDENTIFICATION OF RISK FACTORS AND TREATMENT PROTOCOLS – PART I

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## ABSTRACT

This article provides a comprehensive overview of peri-implantitis, a chronic inflammatory condition affecting the soft and hard tissues around stabilized dental implants. It discusses key risk factors, including systemic conditions, genetic predispositions, biomechanical and prosthetic factors, as well as the importance of implant surface morphology and roughness, and the presence of cement residues, emphasizes the importance of understanding the histopathological characteristics of peri-implantitis to develop targeted therapeutic protocols. Specific risk factors such as chronic periodontitis, repeated abutment disconnections, tobacco smoking, diabetes, and soft tissue characteristics, as well as implant positioning and prosthetic factors, are also analyzed. Genetic predisposition is also considered as a factor contributing to individual susceptibility to peri-implantitis. In conclusion, the article highlights the complexity of peri-implantitis and the need for a personalized diagnostic and therapeutic approach, based on concrete data and the assessment of predisposing factors. It emphasizes the importance of early diagnosis and effective preventive measures to preserve long-term peri-implant health and ensure patient satisfaction.

**KEYWORDS:** *Peri-implantitis, risk factors, treatment protocols, dental implants, inflammation*

## INTRODUCTION

Peri-implantitis is a chronic inflammatory condition that affects the soft and hard tissues surrounding previously stabilized implants, causing a progressive loss of bone support. It occurs following the accumulation of bacterial biofilm on the implant surface, which triggers a dysfunctional immune response in the host (1). Histologically, peri-implant lesions exhibit broader inflammatory infiltration and deeper bone destruction compared to periodontal lesions. Among the main risk factors are systemic conditions such as poorly controlled diabetes, smoking, periodontitis, genetic predispositions, and biomechanical or prosthetic factors (inadequate occlusion, unfavorable prosthetic emergence) that hinder hygiene or cause mechanical overload. Recent studies have shown that the morphology and roughness of the

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implant surface promote biofilm adhesion, while the presence of cement residues and poorly calibrated prosthetic components represent additional predisposing factors (2,3). The first step in the treatment of peri-implantitis involves non-surgical mechanical therapy, based on the debridement of implant surfaces using non-metallic instruments and irrigation, often supported by chlorhexidine, which allows for a significant reduction in biofilm and gingival inflammation (4). In case of resistance, it is possible to associate antibiotic therapy—local or systemic—generally with amoxicillin and metronidazole, which has been shown to improve probing depth in the short term, although the quality of the evidence is moderate and the risk of bacterial resistance requires caution (5). As an alternative or non-surgical aid, laser or photodynamic therapy (e.g., Er:YAG, Nd:YAG) can offer additional decontamination, with some studies showing supplementary clinical improvements, although not always superior to mechanical cleaning alone (6). When bone defects persist, surgical therapy is performed using a flap to expose the implant, thorough cleaning, and, in the presence of regenerable defects, guided bone regeneration (GBR), almost always resulting in a reduction of pocket depth and a gain in bone crest. (Give me the link to the citation for this as well (7). An emerging strategy is electrolytic cleaning, which uses low voltage and an electrolytic solution to disintegrate biofilms and promote re-osseointegration. Clinical studies demonstrate bone gains of approximately 2.7–2.8 mm and disease resolution rates exceeding 90% after 6–18 months, without altering the implant microstructure (8).

## EPIDEMIOLOGY AND DEFINITION

The probability of peri-implantitis onset increases over time, with prevalence rising after more than 10 years of function and represents a significant coefficient (0.044;  $p < 0.001$ ) (9). Peri-implantitis is a progressive inflammatory condition that affects the soft and hard tissues around dental implants. Clinically, it manifests with signs of inflammation such as bleeding and/or suppuration upon probing, accompanied by an increase in probing depth compared to baseline values and marginal bone loss visible radiographically, criteria consistent with those described in the 2017 international consensus. The presence of bleeding on probing (BoP) often represents the first indicator, allowing for the distinction between peri-implant mucositis and peri-implantitis, which includes progressive bone loss. Clinical studies show that BoP associated with bone loss  $> 1$  mm is highly predictive, with a prevalence of up to 45% in long-term studies (10). Regarding probing depth, the literature suggests that values  $\geq 6$  mm are highly indicative in the absence of baseline data, while intermediate measures (4–6 mm) may reflect early stages and  $> 8$  mm advanced forms – criteria widely reported in clinical consensus (11). In the case of radiographic bone loss, in the absence of a baseline, a threshold of  $\geq 3$  mm below the coronal portion is often adopted; some more conservative variants evaluate thresholds between 2 and 4 mm, also considering the proportion relative to the total length of the implant (12). When clinical and radiographic reference data are available, the diagnosis is based on the comparison between current and initial values of probing depth and bone. In the absence of baseline data, peri-implantitis is diagnosed only if the following are present simultaneously: inflammatory signs (BoP or suppuration), depth  $\geq 6$  mm, and bone loss  $\geq 3$  mm (10). The 2017 World Workshop guidelines recommend the use of flexible or plastic probes, applying a standardized pressure of around 0.25 N to avoid damaging the tissues and to obtain repeatable measurements. It is also essential to perform standard parallel radiographs to the baseline and regular monitoring to allow for timely diagnosis (13).

## HISTOPATHOLOGY

The peri-implant tissues, that is, the gingiva-bone interface around a dental implant, exhibit fundamental anatomical and biological characteristics that distinguish them from the periodontium of natural teeth, and that explain their particular vulnerability to inflammatory diseases. Unlike natural periodontium, implants lack periodontal ligament and collagen fibers inserted perpendicularly to the implant surface. In the natural periodontium, Sharpey's fibers firmly insert into the root cementum, creating a robust fibrous attachment that protects against bacterial penetration (14). Around the implants, however, the collagen fibers of the peri-implant mucosa run parallel to the titanium surface, without true insertion, making the tissue seal more fragile and easily compromised (15). This structure results in a deeper penetration of the periodontal probe next to the implants, due to the lack of a fixed ligamentous attachment; the seal is therefore mainly constituted by a junctional epithelium adhering through hemidesmosomes, a more delicate attachment vulnerable to inflammation or repeated mechanical trauma (16). Moreover, the limited vascular supply to the peri-implant tissues, dependent only on the periosteal and medullary vessels, reduces the capacity for local immune response and slows down the repair processes (17).

From a histopathological perspective, peri-implant disease manifests with an inflammatory picture characterized by an inflammatory infiltrate predominantly composed of T lymphocytes and macrophages, with a reduced presence of plasma cells compared to periodontitis (18). This difference indicates a different immunological dynamic in the response

to subgingival bacteria, with a more pronounced involvement of innate immunity in peri-implant lesions. In particular, the activation of mast cells by neuropeptides plays a central role in modulating the production of pro-inflammatory and anti-inflammatory cytokines, significantly influencing the course of local inflammation and its regulation (19). Peri-implant bone loss, a pathognomonic characteristic of peri-implantitis, is accompanied by a marked activation of osteoclasts, with an increased release of pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and RANKL, which promote bone resorption (2). The peri-implant attachment, in particular, is affected by the already described anatomical structure: the lack of inserted collagen fibers and limited vascularization create an environment where the inflammatory response can easily spread from the junctional epithelium to the underlying alveolar bone (17). This results in a faster and more severe progression of the disease compared to periodontitis, with lesions frequently exhibiting extensive tissue destruction and a lower capacity for spontaneous healing (18). The peri-implant soft tissues also show structural alterations at the histological level during the disease: an increase in edema, an increase in reactive vascularization, and a modification of the connective tissue, with a loss of the normal organization of collagen fibers and infiltration by inflammatory cells (7). These changes further reduce the effectiveness of the mucosal seal and facilitate bacterial penetration, triggering a vicious cycle of inflammation and bone loss (8). A detailed understanding of these histopathological characteristics is essential for comprehending the pathogenesis of peri-implantitis and developing targeted therapeutic protocols capable of modulating inflammation and promoting bone and tissue regeneration (9). Strategies such as minimizing mechanical trauma to soft tissues (for example, following the principle "one abutment, one time") and adopting targeted antimicrobial treatments arise precisely from this biological and histopathological awareness (2-20).

## RISK FACTORS

### *Chronic periodontitis*

Previous chronic periodontitis as a primary risk factor for the development of peri-implantitis. Numerous prospective studies and meta-analyses confirm that patients with a history of periodontitis have a significantly increased risk of peri-implant deterioration. A meta-analysis of 14 prospective studies has shown that, compared to periodontally healthy subjects, the risk of implant failure is 1.62 times higher within 5 years and 2.26 times higher after 5 years, with an increase also for peri-implantitis (RR  $\approx$  4.09) and an average bone loss of about 0.75 mm greater in subjects with a history of periodontitis. Subsequent meta-analyses report a risk ratio  $\geq$  1.6 at 5–10 years, up to RR  $\approx$  2.26 for follow-up > 5 years, reinforcing the association between previous periodontal disease and the development of peri-implantitis (21). The biological link between the two pathologies is primarily based on a dysfunctional immune response: Patients with periodontitis exhibit alterations in inflammatory regulation that can also manifest at the level of implant sites, exacerbating peri-implant inflammation. Moreover, the persistence of periodontal pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* in submucosal samples is well documented, which can colonize implant surfaces and compromise the mucosal seal, promoting disease progression (22). Finally, genetic factors, such as polymorphisms of pro-inflammatory cytokines (e.g., IL 1 $\alpha$ , IL 1 $\beta$ , IL 1RN), have been associated with a greater susceptibility to both periodontitis and peri-implantitis; a meta-analysis has indeed shown that IL 1 $\alpha$  C 889T and IL 1 $\beta$  +3954T variants increase the risk of peri-implant disease by 1.66–1.95 times (23). Some rare genetic conditions that affect bone development can impact overall oral health and the bone's ability to support dental implants. Specific genetic mutations can influence the development and function of bone, which could have implications for the long-term success of dental implants and susceptibility to peri-implantitis (24).

### *Repeated disconnections of the abutment*

The repeated removal and reapplication of prosthetic components, such as abutments or healing caps, during the implant restoration phase, is a known iatrogenic factor that compromises the biological stability of the peri-implant mucosal seal (25). Each disconnection results in the interruption of the maturing epithelial attachment and facilitates bacterial access to the implant-abutment interface, promoting microbial colonization of the internal structures of the implant (26). These repeated disturbances induce an apical reformation of the mucosal attachment, associated with progressive marginal bone loss. Such early remodeling of hard tissues, typically observable within the first 12 months, seems to constitute a biological prerequisite for the subsequent development of peri-implant inflammatory pathologies, especially in patients with poor tissue response or thin biotype. In this context, the 'one abutment–one time' prosthetic approach has been proposed as an effective strategy to reduce transmucosal manipulations, contributing to the maintenance of marginal tissue stability and the minimization of crestal bone loss. Recent digital developments, such as the use of virtual protocols with digital facebow (27), can also improve prosthetic accuracy and reduce the number of connections-disconnections, supporting a more conservative and biologically respectful clinical workflow (25). The

height of the stump, its geometry, the precision of the connection, and the ability to maintain a stable seal are crucial for preventing the apical migration of the epithelial attachment and the associated bone remodeling.

### *Tobacco smoke*

Tobacco smoke is widely recognized as a significant risk factor for peri-implant bone loss and the onset of peri-implantitis. Vasoconstriction induced by smoking compromises tissue healing and the local immune response in peri-oral tissues (28). Recent meta-analyses have shown that smokers have more than double the risk of early implant failure, with an odds ratio of up to 2.6 compared to non-smokers (29). A 2023 analysis highlighted a highly significant association between smoking and peri-implantitis, with a relative risk (RR) of approximately 2.07 (30), while longitudinal clinical studies indicate that the plateau of peri-implant anaerobic pathogens is higher in smokers, with a concomitant reduction in microbial diversity, a condition that favors the transition to chronic inflammatory states (28).

### *Diabetes*

Poorly controlled diabetes negatively affects the immune response, prolongs healing times, and is associated with higher rates of peri-implantitis and implant loss. The influence of diabetes mellitus on the development and progression of peri-implantitis is now supported by solid scientific evidence. The most recent meta-analyses indicate that diabetic patients have a significantly increased risk of developing peri-implantitis compared to non-diabetic subjects, with odds ratios ranging between 1.5 and 1.9 (31). In particular, glycosylated hemoglobin (HbA1c) levels above 8% have been associated with more pronounced marginal bone loss around implants, suggesting a clear link between poor glycemic control and worsening peri-implant clinical indices. A recent review study also identified diabetes as a "suggestive" risk factor for peri-implantitis, classifying it among the main systemic elements to consider in the implant decision-making process. At the biochemical level, chronic hyperglycemia compromises neutrophil function, increases the production of metalloproteinases (such as MMP-8), and hinders bone remodeling, making implant sites more susceptible to infection and progressive bone destruction (32). This pathogenetic framework supports the importance of accurate metabolic control (e.g., optimization of HbA1c) and rigorous monitoring of peri-implant clinical-radiographic parameters in diabetic patients, especially before and after implant placement. A systematic review published in 2024 indeed demonstrated that a 1% increase in HbA1c is associated with a significant increase in marginal bone loss (mean difference of +0.24 mm), explicitly emphasizing the need to determine the HbA1c value before implant placement and to constantly monitor it throughout the entire therapeutic course to ensure peri-implant health (33).

### *Soft tissues*

The quality and quantity of soft tissues around implants exert a decisive influence on peri-implant biological stability; in particular, the presence of a keratinized mucosa band  $\geq 2$  mm is associated with less inflammation and reduced marginal bone loss compared to sites with KMW  $< 2$  mm (34). Numerous cohort studies and meta-analyses indicate that implants with insufficient KMW show a significantly higher incidence of mucositis and peri-implantitis, reaching disease rates as high as 44%, compared to sites with an adequate amount of keratinized mucosa (5–8%) (35). An initial soft tissue thickness of less than 2 mm has been correlated with greater marginal bone loss in the first 12–14 months after implant placement, with an average difference of about 0.5 mm compared to sites with tissue  $\geq 2$  mm (36). The presence of thin, soft tissues ( $< 2$  mm) is also associated with a higher incidence of mucosal recession, resulting in exposure of the implant surface and greater plaque accumulation (37,38). Unlike KMW, vertical mucosal thickness (VMT) has shown less conclusive results: a two-year prospective study did not find significant differences in bone loss between groups with thicknesses above or below 2 mm, although plaque index and gingival index values were higher in thicker mucosae (37). Thanks to tissue grafting or expansion procedures during or immediately after implant placement, it is possible to increase both the thickness and the band of keratinized mucosa, improving the long-term prognosis of the implant (39–41). The healing of the soft tissues around implants can be influenced by the patient's age. Studies have shown that age can alter the cellular composition and regenerative capacity of tissues, which could impact the healing ability of peri-implant tissues and their response to stress (42).

### *Implant positioning*

The correct three-dimensional positioning of the implant plays a crucial role in the prevention of peri-implantitis. Implants positioned vestibularly, adjacent to a thin bone plate or soft tissue, are associated with increased bone remodeling and soft tissue recession, resulting in a thinner coverage that is more susceptible to inflammation (43). Similarly, insufficient bone volume around the implant, typical in non-regenerated thin ridges, can lead to the formation of fragile cortical bone, prone to resorption and unable to adequately support the surrounding soft tissues (44). In this context, it

has been demonstrated that the use of bone grafts in post-extraction sites can significantly improve the stability of peri-implant hard and soft tissues in the long term, reducing the risk of implant thread exposure and early bone resorption (45). In biological terms, this relates to the concept of biological width: the excessive proximity of the implant to the outer bone wall can stimulate pre-existing bone resorption, aimed at restoring the space necessary for the attachment of soft tissues, thus exposing the implant threads to a biologically unfavorable environment (44). Moreover, surgical traumas, such as bone overheating during implant site preparation, can cause early bone necrosis, compromising osseointegration and predisposing to local infections. The lack of primary stability or micromovements during the initial days of healing can also alter the physiological bone process, often leading to early implant failure rather than late peri-implantitis, but they still represent critical factors to consider (4). An analysis conducted on over 700 implants has shown that vertical deviations and the mandibular molar area represent high-risk factors ( $OR \approx 10$ ) for peri-implant bone loss, while moderate three-dimensional errors have a less significant impact. An incorrect position, combined with inappropriate surgical techniques, is therefore recognized as an iatrogenic factor for peri-implantitis, as it compromises tissue architecture and the correct remodeling pattern (44). Moreover, studies state that the design of the implant and the surface characteristics can influence the risk of peri-implantitis, so depending on the position of the implant, the structure of the implant itself is also fundamental (46). In this context, the adoption of innovative surgical protocols for implant site preparation, such as the Hybrid Funnel Technique, can help reduce the incidence of iatrogenic errors and optimize the three-dimensional alignment of the implant. This technique allows for selective and less traumatic modeling of the site, improving bone adaptation and reducing the risk of cortical microfractures and overheating, thereby promoting better primary stability and a favorable environment for biological healing (47).

#### *Prosthetic factor*

The design and precision of prosthetic fabrication significantly impact peri-implant health: the presence of microgap between the abutment and the implant favors bacterial colonization at the interface, contributing to the establishment of peri-implant inflammatory processes (48). Unstable connections, such as loose screws or external hex connections, allow micro-movements that facilitate "bacterial pumping," accelerating the contamination of the peri-implant sulcus and the progression towards peri-implantitis (49). Loose or damaged prosthetic components reduce the ease of oral hygiene management and cause irritation of the mucosal tissues, aggravating local inflammation (50). In the case of cemented crowns, the presence of residual cement is now recognized as a significant cause of peri-implantitis: the cement can act as a reservoir for biofilm, often leading to mucositis and subsequently to peri-implant bone lesions (51). Recent studies suggest that the selective use of screw-retained restorations or extremely precise cementations, with careful cement removal and radiographic verification, significantly reduces the biological risk in high-risk patients (52). The coronal profile of the prosthesis must be designed to facilitate hygiene: excessively rounded contours or oversized bridges can trap plaque and hinder cleaning, increasing local inflammation (49). On the contrary, prosthetic designs with smooth surfaces and optimized shapes, capable of facilitating the use of floss or interdental brushes, prove to be protective for peri-implant tissues (53). The materials used for the abutments are relevant: smooth titanium or zirconia surfaces, characterized by adequate biocompatibility properties and low bacterial retention index, promote better tissue attachment and reduce biofilm adhesion (54).

#### *Genetic predisposition*

Genetic predisposition Although the mechanisms are not yet fully understood, it is increasingly evident that genetic factors contribute to individual susceptibility to peri-implant diseases, similarly to what is observed in periodontitis (55). The variability in the immune-inflammatory response to bacterial insult seems to be partly determined by genetic polymorphisms, particularly in genes that encode pro-inflammatory cytokines such as interleukin 1 (IL 1), tumor necrosis factor alpha (TNF  $\alpha$ ), and interleukin 6 (IL 6), which can amplify inflammation and promote the destruction of peri-implant tissues. In fact, a 2021 meta-analysis showed that the polymorphisms IL 1 $\alpha$  C 889T, IL 1 $\beta$  C+3954T, and C 511T are significantly associated with the risk of peri-implant disease ( $OR \approx 1.7-1.95$ ) (23). A systematic analysis also highlighted a strong association between the IL 1 $\beta$  511 (TT) genotype and early marginal bone loss around implants, with high odds ratios (up to 5–10 times) (56). Some studies have reported that patients carrying specific gene variants, such as the IL 1 positive test genotype, show a greater predisposition to peri-implant bone loss compared to non-carriers. Despite some research not finding significant correlations for all variants (for example, TNF  $\alpha$  308 not always associated), a study in the Serbian population highlighted that the TNF  $\alpha$  308 GA/AA polymorphism carries an 8.9 times greater risk of peri-implantitis, regardless of smoking (57). This genetic component partially overlaps with the history of periodontitis—also hereditary—but represents an independent intrinsic risk, to be considered independently of the clinical history alone. The

genetic profile can indeed predispose one to a hyper-reactive immune response to the bacterial biofilm, making it more difficult to maintain peri-implant health even with proper hygiene and correct surgical-prosthetic technique.

## CONCLUSIONS

Peri-implantitis constitutes a complex and multifaceted issue in today's implantology. Its origin, which includes biological, mechanical, environmental, and genetic elements, requires both a diagnostic and therapeutic approach that is tailored and based on concrete data. Recognizing the predisposing factors, such as previous periodontitis, frequent abutment disconnections, smoking, uncontrolled diabetes, poor consistency of soft tissues, incorrect implant placement, prosthetic factors, and genetic predisposition, is of primary importance for identifying at-risk individuals and implementing effective preventive measures. Timely diagnosis, based on careful clinical and radiographic evaluation, is essential to identify the pathology at its onset and prevent its worsening. The recommendations from the 2017 World Workshop provide unique and uniform diagnostic parameters, including the examination of bleeding on probing, probing depth, and radiographic bone loss. In the last 10 years recent studies showed the potential role of cytokines (IL-33, IL-1 $\beta$ , etc.), mast cells and drugs in oral diseases, necrosis, allograft rejection and cancer development, and also the potential role of novel laser therapies in their treatment (14,58-65).

The therapeutic approach for peri-implantitis must be tailored according to the severity of the condition and the individual characteristics of the patient. Therapeutic alternatives range from non-surgical therapies, aimed at detoxifying the implant surface and regulating the inflammatory response, to surgical interventions of a resective, regenerative, or implantoplastic nature, depending on the structure of the bone defect and the need to restore long-term implant stability. Despite the significant progress made in understanding and treating peri-implantitis, further studies are necessary to refine therapeutic protocols, develop new technologies and biomaterials, and identify reliable prognostic indicators. The ultimate goal is to enhance clinical outcomes, preserve peri-implant health in the long term, and ensure full patient satisfaction.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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## PERI-IMPLANTITIS: IDENTIFICATION OF RISK FACTORS AND TREATMENT PROTOCOLS – PART II

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### ABSTRACT

This article delves into the surgical treatment strategies for peri-implantitis, an inflammatory condition affecting the tissues around dental implants. It emphasizes that while non-surgical therapy can be effective in the early stages, surgical intervention often becomes indispensable to halt the progression of the pathology. The article reviews various surgical approaches, including resective surgery, regenerative surgery, mechanical decontamination, laser treatments, antibiotic therapy, electrolytic cleaning, and implantoplasty. Resective surgery aims to reduce the depth of peri-implant pockets through resection of inflamed soft tissue and bone remodeling, while regenerative surgery aims to reconstruct lost bone tissue using bone biomaterials, barrier membranes, and biological factors. Mechanical decontamination involves removing biofilm and mineralized deposits from the implant surface, while laser treatments and electrolytic cleaning offer alternative methods for decontamination. Antibiotic therapy, both systemic and topical, is sometimes used as a support to mechanical decontamination. Finally, implantoplasty involves removing implant threads and smoothing the exposed surface to reduce biofilm accumulation. The article highlights the importance of appropriate selection of the surgical strategy based on the patient's characteristics, the severity of the bone damage, and the risk factors present. It further emphasizes the need for a multidisciplinary approach that integrates surgical therapies with non-surgical treatments and careful follow-up management to ensure the success of peri-implantitis treatment and the durability of dental implants. The article concludes by highlighting the need for further research to refine surgical techniques, develop new biomaterials, and evaluate the effectiveness of emerging therapies, with the aim of improving clinical outcomes and the quality of life of individuals affected by peri-implantitis.

**KEYWORDS:** *Peri-implantitis, surgical treatment, regenerative surgery, mechanical decontamination, laser therapy*

### INTRODUCTION

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Peri-implantitis is an inflammatory condition that affects the hard and soft tissues around dental implants. This condition, increasingly common in dentistry, can severely compromise the longevity of implants and the overall oral health of the patient (1). It manifests with loss of supporting bone, swelling, bleeding, and, sometimes, pus formation, making prompt and targeted therapeutic intervention essential (2). The etiology of peri-implantitis is multifactorial, with a primary role played by the accumulation of bacterial biofilm on the implant surface, which triggers a dysfunctional immune response in the host. Fundamental is also the role of mast cells and neuropeptides. The activation of mast cells by neuropeptides can influence the inflammatory microenvironment through the modulation of cytokines, and thus potentially contribute to the pathogenesis of peri-implantitis (3). Histologically, peri-implant lesions are distinguished by a more extensive inflammatory infiltration and deeper bone destruction compared to periodontal lesions. Risk factors such as poorly controlled diabetes, smoking, previous periodontitis, genetic predispositions, and biomechanical or prosthetic factors—such as inadequate occlusions and unfavorable prosthetic emergencies—significantly contribute to the onset and progression of the disease (4). The management of peri-implantitis is complex and must be personalized based on the severity of the disease, the characteristics of the patient, and specific risk factors. A correct diagnosis and evaluation of the patient are essential for planning an effective treatment of peri-implantitis and minimizing risks. This process must include a comprehensive medical history, not only of local and environmental risk factors but also of the patient's medical and family conditions. Although rare, some genetic conditions that affect bone development, such as cleidocranial dysplasia associated with mutations in the *CBFA1/RUNX2* gene, can impact oral health and the bone's ability to support dental implants. Therefore, including a detailed family and medical history can help identify at-risk patients and customize the treatment plan to maximize long-term success (5). Treatment options range from non-surgical therapies, focused on the mechanical and chemical decontamination of the implant surface, to surgical interventions. The latter include resective, regenerative approaches, and implantoplasty (6). This article aims to explore in detail the various surgical treatment strategies for peri-implantitis, analyzing the indications, techniques, and clinical outcomes associated with each method. Through an in-depth analysis of the most recent scientific literature and clinical guidelines, this work aims to provide a comprehensive and up-to-date overview of the surgical options available for the management of peri-implantitis. The aim is to provide clinicians with evidence-based decision support to improve therapeutic outcomes and long-term prognosis for their patients.

## SURGICAL THERAPY

Although non-surgical therapy can be effective in the early stages of the disease (mild peri-implantitis), surgical treatment often proves indispensable to halt the progression of the pathology and promote the recovery of peri-implant tissues (7). The reasons for this necessity are manifold: the morphological complexity of peri-implant pockets, the difficulty of access for cleaning, the particular nature of the implant surface that promotes bacterial adhesion, and the presence of deeper bone defects (8). Surgical treatment allows direct access to the implant surface to remove inflammatory tissues and bacterial contamination, modify the bone morphology to facilitate home hygiene, and, in selected cases, regenerate lost bone tissue (9). The scientific literature of the last 10 years has consolidated two fundamental surgical approaches: resective surgery and regenerative surgery, the choice of which depends on the type and severity of the bone defect, as well as local and systemic factors that can influence the prognosis (10).

### *Resective Surgery*

Resective surgery aims to reduce the depth of peri-implant pockets through the resection of inflamed soft tissue and the remodeling of peri-implant bone, with the goal of facilitating plaque removal and maintaining a more favorable biological environment (8). This technique is particularly indicated for bone defects with unfavorable geometry, such as horizontal or saucer-shaped defects, where bone regeneration is unpredictable or impossible (11). Numerous clinical studies have reported encouraging data: in a systematic review of 12 studies with follow-up from 1 to 5 years, resective surgery showed an average reduction in probing depths of 3.1 mm, a decrease in bleeding on probing (BOP) of over 70%, and stability in bone loss in over 80% of cases (12). A randomized trial involving 58 patients showed a significant improvement in probing depth from 6.4 mm to 3.2 mm at 12 months, accompanied by an improvement in peri-implant soft tissue (13). The decontamination of the implant surface is a crucial step in this protocol. It has been demonstrated that mechanical decontamination alone is not always sufficient: therefore, multiple methods are combined, including ultrasonic scalers with titanium tips, Er:YAG or CO<sub>2</sub> lasers, and chemical agents such as sodium hypochlorite, chlorhexidine, and hydrogen peroxide (14). Recent studies indicate that the use of the Er:YAG laser, in conjunction with resective surgery, significantly improves the reduction of bacterial load and promotes better clinical stability. The EFP 2022 guidelines suggest resective surgery as the treatment of choice for shallow (<3 mm) and horizontal bone defects, especially in the presence of an adequate amount of keratinized soft tissue (15). However, it is essential to consider the

aesthetic limitations of this technique, especially in anterior sectors, where the reduction of soft tissue can lead to mucosal recessions and aesthetic alterations (12). The management of soft tissue is crucial, with techniques to increase the volume of keratinized mucosa to improve site stability and prevent recurrences (16,17). Moreover, smoking patients or those with poor oral hygiene present a higher risk of long-term failure.

### *Regenerative Surgery*

Regenerative surgery aims to reconstruct lost bone tissue through the use of bone biomaterials, barrier membranes, and biological factors that stimulate tissue regeneration (18). It is indicated for contained bone defects, such as those with three or four walls or deep vertical defects ( $\geq 4$  mm), where the morphology allows for the containment of the graft material and the formation of a stable clot (10). Clinical evidence supports a significant improvement in clinical and radiographic parameters with regenerative surgery. A meta-analysis of 14 clinical studies found an average reduction in probing depth of 3.8 mm and a radiographic bone gain between 2.5 and 4.2 mm at 12-24 months, with an improvement in BOP of over 60% (14). More recent studies have also highlighted how the addition of platelet-derived growth factors (PRF, PRP) enhances bone regeneration and clinical stability over time (19). The therapeutic protocol involves the complete removal of infected tissue, decontamination of the implant surface, placement of autologous, allogeneic, or synthetic bone grafts, and the use of resorbable or non-resorbable membranes to guide regeneration (20). The management of soft tissue is crucial, with techniques to increase the volume of keratinized mucosa to improve site stability and prevent recurrences

(12). A large multicenter study on 85 implants treated with regenerative surgery showed clinical success (pockets  $\leq 4$  mm and absence of BOP) in 82% of cases at 2 years, compared to 58% in the group treated with resective surgery (19). These data confirm the effectiveness of regenerative surgery in selected patients and underscore the importance of proper clinical indication. The EFP 2022 guidelines recommend regenerative surgery for deep defects ( $\geq 4$  mm) with adequate presence of keratinized soft tissue, while emphasizing the need for long-term monitoring and careful management of systemic risk factors (smoking, diabetes) to prevent recurrences (15).

## **MECHANICAL TREATMENT OF PERI-IMPLANTITIS**

### *Scaling and Mechanical Decontamination*

Scaling and mechanical decontamination represent the first recommended therapeutic approach in the management of peri-implantitis, especially in the early stages or as a stabilization treatment in advanced clinical cases. The objective of this intervention is the effective removal of biofilm and mineralized deposits present on the implant surface, responsible for chronic inflammation and progressive bone loss (21). According to the guidelines of the European Federation of Periodontology (EFP), professional scaling performed with mechanical instruments is indicated as a first-line treatment in all diagnosed cases of mucositis and mild-moderate peri-implantitis (22). The most commonly used instruments include curettes made of reinforced plastic or titanium, sonic or ultrasonic inserts with coated tips, and rotary brushes, which allow access to the rough surfaces of implants without damaging them (23). The effectiveness of these instruments has been evaluated in numerous controlled clinical studies: For example, a randomized study conducted by Louropoulou (24) demonstrated that the removal of biofilm with titanium curettes allows for a significant reduction in probing depth (from 5.4 mm to 3.9 mm on average) and bleeding on probing (from 84% to 36%) after 3 months of treatment. Recent *in vitro* analyses have confirmed the effectiveness of ultrasonic scaling techniques and air-abrasive powders on different surfaces of implants and prosthetic components, highlighting significant differences in decontamination capacity depending on the material and surface topography (25). Implants with a rough surface present greater difficulties in the complete removal of biofilm due to increased bacterial adhesion. Despite this, an *in vivo* study conducted by Toma et al. showed that the repeated use of mechanical decontamination in a 6-month follow-up maintains a significant reduction in peri-implant inflammation when associated with regular maintenance recalls (26). In terms of clinical outcomes, mechanical debridement alone has been shown to achieve an average reduction in pocket depth ranging from 0.5 mm to 1.3 mm, with significant improvements in bleeding and plaque (27). However, the long-term success rate varies significantly depending on patient compliance and the frequency of professional recalls: a 3-year longitudinal study conducted by Carcuac et al. found that only 39% of sites treated exclusively with mechanical decontamination maintained clinical stability without further bone loss, highlighting the need for intensive monitoring (28). In this context, the integration of biocompatible regenerative approaches, such as the use of Platelet-Rich Fibrin (PRF), can represent a valuable support in the management of inflamed soft tissues, promoting tissue healing and reducing symptoms, as demonstrated in the treatment of oral mucositis in oncological patients (29). Finally, it should be emphasized that mechanical scaling, although less invasive than surgical treatments, requires precision, repetition, and appropriate instrumentation to be effective. Its effectiveness is greatly enhanced by the patient's motivation and strict adherence to personalized hygienic-professional

maintenance protocols. It thus represents an essential pillar in the management of peri-implant diseases, both as an initial treatment and as long-term supportive therapy.

## TREATMENT OF PERI-IMPLANTITIS USING LASER TECHNIQUES

The use of lasers in the treatment of peri-implantitis has received increasing attention in recent years, thanks to their ability to deeply decontaminate the implant surface, reduce inflammation, and promote tissue healing, all with a minimally invasive approach (30). The main devices used in clinical settings include Nd:YAG, Er:YAG, CO<sub>2</sub>, and diode lasers, each with specific absorption and penetration characteristics in soft and hard tissues (31). One of the main advantages of lasers is their ability to eliminate biofilm and granulation tissue without causing permanent microstructural alterations to the implant surface (32). According to a randomized controlled trial by Schwarz et al, the use of the Er:YAG laser in open surgery resulted in an average reduction of pocket depth by 2.4 mm and a radiographic bone gain of 1.2 mm after 6 months, results comparable to or superior to those obtained with conventional mechanical decontamination (33). Moreover, laser treatment has proven effective in significantly reducing probing bleeding and inflammatory infiltrate, without the need for direct contact with the implant surface. Another systematic review conducted by Panda et al. analyzed 12 randomized clinical studies and highlighted that the use of lasers, particularly Er:YAG and Nd:YAG, significantly improves periodontal indices compared to mechanical treatment alone (34). However, the authors emphasize that effectiveness is highly dependent on the operational parameters used, such as wavelength, power, and duration of exposure, as well as the type of laser employed. An important aspect to consider concerns post-treatment biocompatibility: An *in vitro* study conducted by Aoki et al. demonstrated that irradiation with Er:YAG laser, set to clinically acceptable parameters, does not compromise the adhesion of osteoblastic cells to the implant surface, but rather promotes their recolonization (35). Even the diode laser, although less powerful in ablative terms, has proven useful as an adjunct for controlling infection and bacterial load in deep pockets, as evidenced by Ramanauskaite et al. in a clinical trial conducted on 36 patients. (36). Finally, recent guidelines published by the European Association for Osseointegration (EAO) recommend the use of lasers as an adjunctive therapeutic option in the early or moderate stages of peri-implantitis, especially when there are contraindications to surgery. However, it is specified that the effectiveness of the laser, although supported by encouraging data, does not yet have sufficient evidence to completely replace surgical protocols in advanced cases (37).

## ANTIBIOTIC THERAPY

The use of antibiotics, both systemic and topical, represents a consolidated and often used strategy as support for mechanical decontamination in cases of peri-implantitis with acute infections or deep pockets (>5 mm). However, isolated systemic antibiotic therapy is not recommended, as emphasized by the guidelines of the European Federation of Periodontology (EFP, 2022). In a randomized controlled study involving 37 patients who received amoxicillin (375 mg) in combination with metronidazole (250 mg) for 7 days, combined with mechanical decontamination, the mean probing depth decreased by 2.28 mm compared to 1.47 mm in the group receiving only mechanical therapy. However, the bleeding on probing rate remained high (≈81%), suggesting a partially limited clinical benefit over time (38). A similar study conducted by De Waal et al. on 62 patients showed that the systemic addition of amoxicillin/metronidazole did not bring about significant clinical or microbiological improvements compared to mechanical decontamination alone at 3 months, indicating the need to reduce the use of systemic antibiotics as a therapeutic adjunct (39). Conversely, studies on topical antibiotics have reported more encouraging results. A multicenter clinical trial evaluated the local application of 2% minocycline gel, administered weekly for 4 weeks in addition to mechanical debridement. After 6 months, a significant reduction in probing depth (−1.8 mm) and a decrease in bleeding on probing (−47%) were recorded compared to the control group (40). Another study by Carcuac et al. confirmed that topical minocycline administered during the surgical phase led to clinical improvement and radiographic stabilization in 66.7% of cases, compared to 36.3% in the group without local antibiotic (41). In this context, the use of anti-inflammatory drugs could also play an important role. Studies have explored the incorporation of anti-inflammatory drugs into polymeric nanohybrids for localized controlled release. This approach could allow for targeted drug release, potentially reducing systemic side effects and maximizing local efficacy in modulating inflammation and promoting the healing of peri-implant tissues. Further research is necessary to evaluate the clinical efficacy of these strategies (42).

Finally, a meta-analysis of 5 randomized studies has shown that the systemic use of amoxicillin with metronidazole does not result in significant differences in probing depth at 3 and 6 months but shows a significant improvement in bleeding on probing and bone level at 12 months (43). Systemic antibiotic therapy may offer a modest and short-term clinical benefit and should be used with caution due to the risk of bacterial resistance. Topical therapy, particularly with

minocycline gel, seems to offer more stable and specific results in managing bacterial load and peri-implant inflammation. However, the support of mechanical decontamination remains fundamental and indispensable.

## ELECTROLYTIC CLEANING

Electrolytic cleaning is an emerging technique that presents itself as a minimally invasive and highly effective method for the decontamination of implant surfaces in cases of peri-implantitis. This technology, based on the application of low-intensity electric current in the presence of an electrolyte, promotes the selective removal of the bacterial biofilm without altering the microtopography of the implant (44,45) thereby preserving the macro- and nanostructural features (46). *In vitro* study has demonstrated that applying  $\pm 3$  V for 5 minutes on contaminated implants results in a reduction of bacterial load from approximately  $3.15 \times 10^6$  to  $2.9 \times 10^4$  CFU/mL, showing superiority over lower voltages (44). This suggests a significant clinical potential in biofilm removal. In a 24-month randomized clinical trial, electrolytic cleaning (EC) was compared with a combined approach of air-water abrasion + electrolysis (PEC) in surgical contexts. After 6 months, both modalities showed similar bone gain (EC: 2.7 mm; PEC: 2.8 mm), with a peri-implant healing rate of 91% in the EC group, demonstrating the clinical applicability of electrolytic cleaning alone (47). The 18-month follow-up data conducted by the same group showed that approximately 50% of the implants subjected to electrolytic cleaning exhibited complete bone reintegration, without the need for further invasive procedures (48). Finally, a pilot *in vitro* study compared electrolytic cleaning with mechanical methods (toothbrushes and erythritol jets), showing similar efficacy in decontamination but a notable advantage in preserving the implant microstructure, a crucial aspect for long-term osseointegration (45). Several studies have demonstrated the crucial role of mast cells (3), cytokines (IL-33, IL-1 $\beta$ , etc.) (49), and drugs (50) in oral and intestinal inflammation (51), soft and hard tissue necrosis (50,51), allograft rejection (52,53) and cancer development (53), and the potential role of laser technology in their therapy (54). In summary, electrolytic cleaning proves to be a promising methodology for halting the progression of peri-implantitis, with bone gains between 2.7–2.8 mm in trials and a high healing rate (>90%). These results, combined with the preservation of implant microtopography, make it an effective and safe option: further clinical studies are still necessary to consolidate its routine use.

## IMPLANTOPLASTY

Implantoplasty is a surgical procedure aimed at removing implant threads and smoothing the exposed surface to reduce biofilm accumulation and facilitate post-treatment cleaning. A systematic review conducted by Esteves Lima et al. reported that implantoplasty, integrated into surgical treatment protocols, allows for an implant survival rate of 94–97% at one or more years, with significant clinical improvements in terms of probing depth (PD) and bleeding on probing (BOP) (55). A randomized prospective clinical study on 33 implants compared implantoplasty plus mechanical debridement vs. debridement alone. While observing temporal improvements in both groups, no statistically significant difference was found in the PD, PI, and BOP parameters at 24 months, suggesting that the additional effectiveness of implantoplasty might be modest (56). From a biomechanical perspective, an *in vitro* study with finite element analysis has shown that implantoplasty reduces the fracture resistance of implants with 5 mm of bone loss, while implants with only 3 mm of bone loss did not show significant variations (57). This indicates that the procedure can alter structural integrity when the supporting bone is already compromised. In an *in situ* clinical trial, a significant reduction in biofilm accumulation was observed on surfaces treated with implantoplasty, decreasing from 65% biofilm coverage to 16% compared to untreated implants, confirming the utility of polishing in controlling recolonization (58). A 2022 meta-analysis compared implants subjected to implantoplasty in regenerative vs non-regenerative contexts, finding better bone gains when the procedure was integrated into regenerative protocols, although no significant differences were noted in PD or BOP parameters between groups (59). Implantoplasty improves the manageability of the implant and reduces bacterial accumulation, with proven effectiveness in clinical stabilization: The data indicate high survival rates (>94%) and greater bone gains in regenerative approaches. However, it is essential to carefully assess the decrease in structural strength, particularly in cases with advanced bone loss (>5 mm) (60,61). This procedure can be particularly advantageous in immediate post-extraction implants to ensure healing and long-term maintenance (62).

## CONCLUSIONS

Peri-implantitis remains a significant issue in contemporary dentistry, necessitating an integrated and personalized therapeutic approach. Although non-surgical strategies are a cornerstone in the initial phase and long-term maintenance, surgical procedures prove essential for addressing advanced bone lesions and restoring the health of peri-implant tissues. Furthermore, in the future, better understanding of how age-related changes influence tissue response to peri-implantitis

could lead to more personalized treatments. In this perspective, the study of age-related molecular alterations in tissues can provide valuable insights into the biology of ageing and its influence on the host's response to peri-implantitis (63), highlighting the importance of interdisciplinary research and the application of molecular biology techniques in the study and treatment of this pathology (64). The selection of the most appropriate surgical strategy must be

based on a careful analysis of the patient's characteristics, the severity of the bone damage, and the present risk factors. A multidisciplinary approach, which integrates surgical therapies with non-surgical ones and careful follow-up management, is essential to ensure the success of peri-implantitis treatment and the durability of dental implants. Further investigations are desirable to refine surgical techniques, develop new biomaterials, and evaluate the effectiveness of emerging therapies, with the aim of improving clinical outcomes and the quality of life for individuals affected by peri-implantitis.

#### Conflict of interest

The authors declare that they have no conflict of interest.

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# PATIENT ON DUAL ANTIPLATELET THERAPY: ASSESSMENT OF BLEEDING RISK AND ITS MANAGEMENT IN MINOR ORAL SURGERY WITH A FOCUS ON EXTRACTION SURGERY

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## ABSTRACT

**Background:** Antiplatelet drugs are widely used to prevent and treat ischemic cardio-cerebrovascular conditions by inhibiting platelet aggregation and reducing thrombotic events. However, their use poses significant challenges in dental procedures due to the increased risk of bleeding. **Materials and Methods:** This study evaluates the safety of dental extractions in patients on dual antiplatelet therapy (DAPT) through clinical and statistical analysis of 48 patients undergoing 71 tooth extractions. Appropriate local hemostatic measures were employed to manage bleeding risks. **Results:** The results indicate that, with appropriate local hemostatic measures, dental extractions can be safely performed without significant hemorrhagic complications. The study highlights the importance of personalized patient management, especially in the presence of periodontal inflammation, to minimize bleeding risks. **Conclusions:** The findings support the continuation of antiplatelet therapy during minor oral surgeries, emphasizing the need for careful planning and collaboration with cardiologists to balance bleeding risks and thrombotic prevention.

**KEYWORDS:** *Antiplatelet drugs, dual antiplatelet therapy, dental extractions, bleeding risk, hemostatic measures, periodontal inflammation, patient management*

## INTRODUCTION

Antiplatelet drugs are increasingly used to prevent and treat ischemic cardio-cerebrovascular conditions (1). These drugs work by preventing blood platelets from aggregating and forming clots, thereby reducing the risk of thrombotic events such as heart attacks and strokes (2). From a dental perspective, the use of antiplatelet agents presents specific challenges, particularly due to the risk of bleeding during and after dental procedures (3). Despite the significant benefits of these drugs in preventing thrombotic events, they can increase the risk of intraoperative and postoperative bleeding

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(4). Therefore, their management in the dental field requires attention and planning to minimize bleeding risks and ensure patient safety (5). The optimal management of patients on long-term dual antiplatelet therapy (DAPT) is not defined by appropriate approved guidelines (6). DAPT involves the use of two antiplatelet drugs taken simultaneously, typically acetylsalicylic acid (ASA) and a P2Y<sub>12</sub> inhibitor (7). Discontinuing therapy could elevate the risk of thrombotic complications, while continuing treatment could increase the risk of bleeding following extraction surgery and minor oral surgery (8). From the existing data, it appears that there is an increase in the incidence of minor immediate postoperative bleeding, but not a clinically significant increase in intra or postoperative hemorrhagic complications. For immediate postoperative bleeding, or in the rare case of prolonged bleeding, local hemostatic measures are generally sufficient (9). The results of Joel J. Napeñas literature review suggest that it is not necessary to modify or discontinue antiplatelet therapy before invasive dental procedures, as local hemostatic measures are effective in managing the rare case of postoperative bleeding (3).

The aim of this study is to demonstrate, based on clinical and statistical evidence from the treatment of 48 patients and a total of 71 tooth extractions, that these surgical procedures can be performed safely for both the patient and the operator. Despite antiplatelet therapy, tooth extractions can be carried out without a significant increase in the risk of hemorrhagic complications. It is important to note that, in some cases, local hemostatic measures were necessary to facilitate the coagulation process and accelerate the formation of the platelet thrombus. These measures include the use of sutures, local compression, and local hemostatic agents, and have proven effective in controlling postoperative bleeding. Additionally, the adoption of these techniques has reduced the risk of prolonged bleeding, ensuring safe healing for patients. This study is of crucial importance, as optimal postoperative hemostasis is essential for proper bone healing. This aspect is extremely relevant in the context of implant rehabilitations, where new bone formation is critical for optimal planning and implant placement. In this context, implant surface engineering has also been shown to influence bone healing dynamics and improve the predictability of osseointegration (10). Effective hemostasis, therefore, represents a fundamental prerequisite for the long-term success of implant-prosthetic procedures (11-16). The study also examined the local conditions of periodontal tissues, noting that in some situations these can increase the hemorrhagic risk in patients on DAPT. In particular, the presence of periodontal inflammation can further compromise coagulation ability, necessitating more careful and personalized patient management. This approach minimizes the risks of hemorrhagic complications and ensures the safety and well-being of both the patient and the operator during and after the surgical procedure.

## MATERIALS AND METHODS

### *Patient selection: population*

#### *i. Inclusion Criteria*

The study was conducted on a total of 48 patients: 16 of whom were not on any antiplatelet therapy, 16 on single antiplatelet therapy, and 16 on dual antiplatelet therapy.

#### *ii. Exclusion Criteria*

The study excluded all patients who might have conditions that could alter the hemostasis process due to factors independent of antiplatelet therapy: cancer patients, patients on anticoagulant therapy, patients with hemophilia, patients with Von Willebrand disease, patients with liver disease, patients with thrombocytopenia, and patients with uncontrolled diabetes.

#### *iii. Other Clinical Evaluations*

The periodontal status of the patient was also considered because there is an increased risk of bleeding complications in patients on DAPT who have local factors such as periodontal or periapical disease.

### *Surgical Protocol*

Anesthesia: Articaine 4% with a concentration of adrenaline 1:100000 was used (17). In dentistry, local anesthetics are often used in conjunction with vasoconstrictors like adrenaline. This is because vasoconstrictors counteract the blood vessel dilation caused by anesthetics, slowing their absorption into the cardiovascular system (18). This prolongs the effect of the anesthesia, reduces the risk of toxicity, and helps control bleeding during surgical procedures. Additionally, it improves intraoperative visibility due to its vasoconstrictive effect. However, it also stimulates  $\beta_1$  receptors, increasing heart rate and blood pressure, which can be problematic for patients with heart conditions. Adrenaline must be

administered in limited quantities to avoid cardiovascular complications, especially in patients with pre-existing heart diseases (19).

The sutures used were 3-0 silk threads. Silk was chosen for its superior handling properties and its ability to maintain stable clot formation. The diameter was also selected for similar reasons, including good mechanical strength (20,21).

A tapercut needle was used, which has excellent cutting ability and minimal tissue trauma (22). The gauze used was sterile, 100% pure cotton, and therefore hydrophilic (23). The chosen size was 10 x 10 cm. Sterile Saline Solution was pre-cooled and brought to a temperature of approximately 5°C.

Gelatin-based hemostatic agents were used in the form of sponges. These materials are saturated with thrombin, which promotes clot formation and also acts mechanically through an expansion process. Initially, these materials undergo liquefaction within about a week and are completely resorbed within another 4-5 weeks (24).

Tranexamic acid (TXA): The antifibrinolytic drug TXA is widely recognized for its ability to effectively reduce blood loss during surgical procedures (25). In particular, tranexamic acid was used at a concentration of 500mg/5ml (26).

Oxidized regenerated cellulose (ORC): The specific size used in this case was 5cm x 7.5cm. Once fully saturated with blood, ORC transforms into a black or brown gelatinous mass, which promotes clot formation and helps stop local bleeding (27).

### *Hemostasis Evaluation*

Extractions were performed following the evaluation of radiographic exams, orthopantomography, and periapical intraoral X-rays. The former was used for a macroscopic assessment, while the latter was used to specifically evaluate the conditions of the periodontium and periapex. Subsequently, the patient was asked to rinse with 0.2% chlorhexidine for approximately 60 seconds (28). A local infiltration with 4% articaine with a concentration of adrenaline of 1:100,000 was then administered for extractions in the upper arch and the anterior sectors of the lower arch. For the posterior sectors, anesthesia involved an inferior alveolar nerve block with a vial of 3% mepivacaine without a vasoconstrictor. Once the anesthetic effect was achieved, surgical procedures were carried out with the utmost respect for both soft and hard tissues. After the extraction, 3-0 silk sutures were placed using the back-and-forth technique. A sterile gauze moistened with saline solution, pre-cooled to 5°C, was applied to the surgical site to facilitate the formation of the platelet clot. The patient was then asked to apply instant ice to the area affected by the surgical procedure. These measures related to low temperatures were employed to maximize the vasoconstrictive effect produced by the cold (29). In the postoperative phases, various instructions were provided to patients to follow in the 72 hours following the procedure. Patients were advised to avoid hot foods and prefer foods with a particularly soft consistency, avoid physical exertion, and prolonged sun exposure, especially if temperatures were particularly high. Patients were instructed to intermittently apply ice during the first 24 hours and were provided with sterile gauze in case of minor bleeding. They were also given a phone number to contact in case of any doubts or other needs. The use of medications that could interact with antiplatelet drugs, such as ibuprofen, was also discouraged. Patients were evaluated one week later to assess healing, and sutures were removed where deemed appropriate; otherwise, another appointment was scheduled for an additional 7 days later. To better analyze hemostasis after surgery, we empirically evaluated clinical parameters. Specifically, we estimated the time and additional hemostatic measures required to stop the bleeding. The bleeding was assessed in various grades:

*Grade 1:* If it stops within 15 minutes of placing the sutures.

*Grade 2:* If it stops within 30 minutes of placing the sutures, with hemostasis facilitated by the placement of a compression gauze previously moistened with sterile saline solution.

*Grade 3:* If it stops within 60 minutes of placing the sutures, with hemostasis facilitated by the placement of a compression gauze moistened with tranexamic acid.

*Grade 4:* If it stops within 24 hours of placing the sutures, with hemostasis facilitated by the placement of oxidized cellulose gauze over the surgical site, stabilized with 3-0 silk sutures.

These evaluation parameters were decided upon following the scheme used in the publication by Archana Shenoy et al. (30).

## **RESULTS**

Below are the tables related to the three pharmacological groups analyzed: Control, single antiplatelet therapy (SAPT), and DAPT (Table I,II,III). The tables include data on the 48 patients studied, of whom 28 were male and 20 were female. The average age of the patients is 77.91 years, and a total of 71 extractions were performed. Each patient underwent at least one extraction, with a maximum of four extractions, which were not all performed in the same operative session. An

important aspect to note is that only one patient experienced grade 4 bleeding, and all treatments were performed with hemostasis control within two hours. Two qualitative independent variables were evaluated: Therapies (with three categories: Control, SAPT, DAPT), and bleeding on probing (BOP) or Periodontal Lesion (with two categories: yes or no), and one discrete quantitative dependent variable, Grade (with four categories: 1, 2, 3, 4). This is reported in Table I, Table II, and Table III.

**Table I.** *Control Patients Table.*

| PZ | N.S. | Age | Sex M/W | Therapy | Treatment | BOP o<br>Periodontal<br>Lesion | Grade |
|----|------|-----|---------|---------|-----------|--------------------------------|-------|
| 1  | T.F. | 67  | M       | Control | Ext 2.6   | No                             | 1     |
| 2  | R.C. | 72  | M       | Control | Ext 3.5   | Yes                            | 1     |
| 3  | A.V. | 81  | W       | Control | Ext 1.3   | Yes                            | 1     |
| 4  | R.L. | 65  | W       | Control | Ext 4.2   | No                             | 1     |
| 5  | E.D. | 74  | M       | Control | Ext 3.4   | Yes                            | 1     |
|    |      |     |         | Control | Ext 3.5   | Yes                            | 1     |
| 6  | D.B. | 59  | W       | Control | Ext 2.6   | No                             | 1     |
| 7  | S.B. | 77  | M       | Control | Ext 1.8   | No                             | 1     |
| 8  | P.F. | 68  | M       | Control | Ext 2.7   | Yes                            | 1     |
| 9  | C.N. | 69  | W       | Control | Ext 2.7   | No                             | 1     |
| 10 | P.O. | 73  | M       | Control | Ext 1.2   | Yes                            | 1     |
|    |      |     |         | Control | Ext 1.3   | Yes                            | 2     |
|    |      |     |         | Control | Ext 1.4   | Yes                            | 2     |
| 11 | N.F. | 68  | W       | Control | Ext 3.2   | Yes                            | 1     |
| 12 | A.V. | 86  | M       | Control | Ext 4.2   | No                             | 1     |
| 13 | N.P. | 74  | W       | Control | Ext 2.2   | No                             | 1     |
|    |      |     |         | Control | Ext 2.4   | No                             | 1     |
| 14 | L.P. | 78  | M       | Control | Ext 1.1   | No                             | 1     |
| 15 | M.R. | 82  | M       | Control | Ext 2.6   | No                             | 1     |
|    |      |     |         | Control | Ext 1.7   | No                             | 1     |
| 16 | F.L. | 58  | W       | Control | Ext 4.4   | No                             | 1     |

**Table II.** *Single antiplatelet therapy (SAPT) Table.*

| PZ | N.S. | Age | Sex M/W | Therapy | Treatment | BOP o<br>Periodontal<br>Lesion | Grade |
|----|------|-----|---------|---------|-----------|--------------------------------|-------|
| 17 | F.G. | 63  | M       | SAPT    | Ext 1.3   | No                             | 1     |
|    |      |     |         | SAPT    | Ext 1.4   | No                             | 1     |
| 18 | A.A. | 60  | W       | SAPT    | Ext 3.6   | Yes                            | 1     |
| 19 | G.V. | 83  | M       | SAPT    | Ext 1.7   | Yes                            | 3     |
| 20 | M.P. | 78  | W       | SAPT    | Ext 3.1   | Yes                            | 1     |
|    |      |     |         | SAPT    | Ext 4.1   | Yes                            | 1     |
|    |      |     |         | SAPT    | Ext 4.2   | No                             | 1     |
| 21 | G.P. | 77  | W       | SAPT    | Ext 4.2   | No                             | 1     |
|    |      |     |         | SAPT    | Ext 4.3   | No                             | 1     |
| 22 | F.C. | 79  | W       | SAPT    | Ext 3.4   | Yes                            | 1     |
| 23 | G.A. | 80  | M       | SAPT    | Ext 4.6   | Yes                            | 1     |
| 24 | S.B. | 74  | M       | SAPT    | Ext 4.2   | No                             | 1     |
| 25 | C.O. | 82  | W       | SAPT    | Ext 3.6   | Yes                            | 2     |
| 26 | P.F. | 80  | M       | SAPT    | Ext 3.2   | Yes                            | 1     |
|    |      |     |         | SAPT    | Ext 3.3   | Yes                            | 1     |
| 27 | I.T. | 64  | W       | SAPT    | Ext 1.5   | No                             | 1     |
| 28 | G.B. | 72  | M       | SAPT    | Ext 1.1   | Yes                            | 2     |
|    |      |     |         | SAPT    | Ext 1.2   | Yes                            | 1     |
| 29 | F.C. | 79  | W       | SAPT    | Ext 2.3   | No                             | 1     |
| 30 | G.L. | 82  | W       | SAPT    | Ext 4.7   | Yes                            | 1     |
| 31 | T.S. | 87  | M       | SAPT    | Ext 1.4   | No                             | 1     |
|    |      |     |         | SAPT    | Ext 1.5   | No                             | 1     |
| 32 | P.S. | 59  | M       | SAPT    | Ext 2.4   | No                             | 1     |

**Table III.** *Dual antiplatelet therapy (DAPT) Table.*

| PZ | N.S.   | Age | Sex M/W | Therapy | Treatment | BOP o<br>Periodontal<br>Lesion | Grade |
|----|--------|-----|---------|---------|-----------|--------------------------------|-------|
| 33 | V.V.   | 83  | M       | DAPT    | Ext 3.3   | No                             | 1     |
|    |        |     |         |         | Ext 3.4   | No                             | 1     |
| 34 | D.C.   | 82  | M       | DAPT    | Ext 1.6   | Yes                            | 4     |
|    |        |     |         |         | Ext 1.7   | Yes                            | 4     |
|    |        |     |         |         | Ext 3.6   | No                             | 2     |
| 35 | A.C.   | 73  | W       | DAPT    | Ext 1.7   | No                             | 1     |
| 36 | A.P.   | 86  | M       | DAPT    | Ext 3.4   | No                             | 1     |
| 37 | R.R.   | 61  | M       | DAPT    | Ext 4.4   | No                             | 2     |
|    |        |     |         |         | Ext 4.5   | No                             | 1     |
| 38 | P.P.   | 65  | M       | DAPT    | Ext 4.8   | Yes                            | 1     |
|    |        |     |         |         | Ext 1.6   | No                             | 2     |
| 39 | D.F.   | 73  | M       | DAPT    | Ext 2.2   | No                             | 1     |
| 40 | S.D.P. | 60  | M       | DAPT    | Ext 2.4   | No                             | 2     |
|    |        |     |         |         | Ext 2.7   | Yes                            | 2     |
| 41 | A.B.   | 67  | M       | DAPT    | Ext 3.2   | Yes                            | 2     |
| 42 | V.M.   | 84  | M       | DAPT    | Ext 4.7   | No                             | 1     |
|    |        |     |         |         | Ext 4.8   | No                             | 1     |
| 43 | T.P.   | 91  | W       | DAPT    | Ext 2.5   | Yes                            | 2     |
| 44 | G.P    | 83  | M       | DAPT    | Ext 3.5   | No                             | 2     |
| 45 | D.A.   | 65  | M       | DAPT    | Ext 4.5   | No                             | 1     |
|    |        |     |         |         | Ext 4.7   | No                             | 1     |
| 46 | M.R.   | 68  | M       | DAPT    | Ext 4.6   | No                             | 1     |
| 47 | M.C.   | 72  | M       | DAPT    | Ext 2.4   | No                             | 1     |
|    |        |     |         |         | Ext 1.3   | No                             | 3     |
|    |        |     |         |         | Ext 1.4   | No                             | 3     |
|    |        |     |         |         | Ext 4.3   | Yes                            | 2     |
| 48 | M.V.   | 81  | W       | DAPT    | Ext 1.3   | No                             | 2     |

## STATISTICAL ANALYSIS

### *Grade-Therapy*

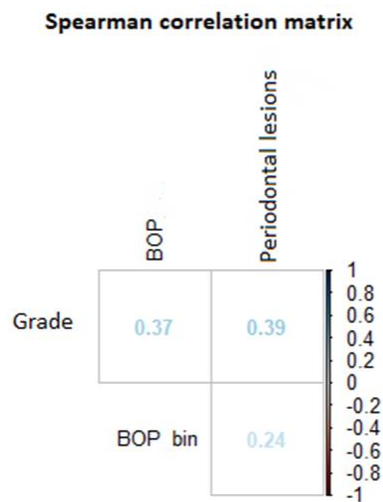
To investigate whether there is an association between therapy (Control, SAPT, DAPT) and the degree of bleeding, that is, whether therapy influences the level of bleeding in any way, a non-parametric test was chosen (Fig.1). Given the nature of the collected data, it is not possible to assume they come from a normal distribution. Therefore, a test that does not require assumptions about the data distribution was selected. The Kruskal-Wallis test, proposed in 1952 by W.H. Kruskal and W.A. Wallis, known as the “Kruskal-Wallis One-Way ANOVA by Ranks” or simply the “Kruskal-Wallis test,” was used. The test performed on the observed sample data shows sufficient statistical evidence to reject the null hypothesis of the test, which states that all groups of interest have the same median ( $p$ -value < 0.05). Thus, there is a statistically significant difference between Therapy and the Degree of bleeding.



**Fig. 1.** Average grade between types of therapy.

#### Grade – BOP – Periodontal Lesion

To perform this analysis, the correlation between the two variables under examination was calculated. Since the original dataset had BOP and Periodontal Lesions as dichotomous qualitative variables (Yes/No), they were converted into binary numerical variables (0-1), where 1 represents “Yes” and 0 represents “No”. This transformation allowed for the calculation of Spearman’s correlation. Spearman’s correlation is a non-parametric measure of the correlation (statistical dependence) between two variables. It is used to assess the monotonic relationship between two sets of ordinals, continuous, or a combination of both types of data. Spearman’s correlation does not assume that the data are normally distributed and can handle variables that do not follow a linear relationship (Fig.2). The results show a modest positive correlation between BOP and the degree of bleeding (0.37) and between periodontal lesions and the degree of bleeding (0.39) in both cases. Additionally, the test also reports the significance of the correlation, with a p-value much lower than 0.05 in both cases. This indicates that the correlation is not due to chance but that there is a significant association between the variables. Therefore, in general, as the correlation increases, the degree of bleeding will also increase, and vice versa. The same applies to lesions.



**Fig. 2.** Spearman correlation matrix.

## DISCUSSION

In their studies, a higher frequency of postoperative bleeding was observed when dental procedures were performed. Therefore, it was decided to analyze the presence of these two parameters (31):

- Presence of bleeding on probing (BOP): This aspect was chosen for analysis because an element that already shows an inflammatory state and BOP is a candidate for a suboptimal hemostasis process. Periodontitis is associated with a higher tendency for bleeding complications. Inflammation, associated with an increase in inflammatory mediators such as IL-1, IL-6, TNF- $\alpha$ , and metalloproteinases in the affected area, along with increased local blood flow, increased vascular permeability, and possible vascular fragility, can lead to excessive bleeding after tooth extraction (32). As highlighted in the study by Tettamanti et al. (2018), inflammation mediated by mediators such as IL-33 can contribute to mast cell activation and influence the inflammatory response,

demonstrating how cytokines also play a crucial role in local inflammatory responses and potentially in excessive bleeding in inflammatory conditions (33). The presence of periodontitis and other periodontal diseases increases the risk of bleeding in patients undergoing dental therapies (34). Recent findings suggest that mast cells play a pivotal role in mucosal inflammation and that their activity may be modulated by anti-inflammatory cytokines such as IL-37 (35).

- Radiographic Presence of Periodontal Lesion: Periapical disease manifests with local inflammation, causing the destruction of bone and surrounding tissues, and areas of radiolucency (36). This condition is also associated with inflammation, which can lead to excessive bleeding (37,38).

Another aspect to consider, which was not directly addressed, is the number of dental elements extracted simultaneously. Often, a particularly cautious approach was chosen, and single extractions were frequently performed. The literature agrees that extracting multiple dental elements in a single operative session is necessarily associated with a higher risk of bleeding episodes (39). Several studies have demonstrated the crucial role of mast cells (40), cytokines (IL-33, IL-1b, etc.) (41), and genes (42,43) in oral and intestinal inflammation (40) and cancer development (44) and also in soft and hard tissue necrosis (45), allograft rejection (46), bleeding risk in oral surgery, implant osseointegration procedures (10) with an important capacity of drugs and novel laser technologies in their treatments (47,48). In addition to these considerations, recent studies have highlighted innovative surgical techniques for alveolar ridge preservation, which may be critical in minimizing bleeding complications and optimizing outcomes in dental procedures, particularly when immediate dental implant placement is involved (49). Recent evidence suggests that the use of biomaterials in immediate post-extractive implant procedures may enhance aesthetic outcomes, even if it does not significantly affect bone loss or probing depth (50).

## CONCLUSIONS

The results obtained from this study clearly indicate a significant correlation in the degree of bleeding between the control group and the group on DAPT. This correlation is statistically significant. Additionally, a similarly significant correlation was observed between the degree of bleeding in patients with BOP or periodontal lesions compared to those with healthy periodontium. This finding underscores the importance of a careful and personalized evaluation of each clinical case, which should not be limited solely to local aspects of the oral cavity.

For patients on DAPT, it is advisable to plan particularly atraumatic operative sessions. This approach minimizes the risk of hemorrhagic complications during and after the procedure. Additionally, it is prudent to foresee a longer postoperative observation period compared to patients to monitor for any complications and ensure safe healing.

In this study, a specific protocol for hemostasis management was adopted, which involves the consecutive use of various hemostatic measures. In clinical practice, these measures could be used simultaneously to further accelerate the hemostasis process and reduce the risk of postoperative bleeding.

Despite the necessary precautions for major procedures, minor oral surgery, such as simple tooth extractions, can be safely performed even in patients on continuous DAPT. This is possible thanks to the adoption of adequate hemostatic measures and careful planning of the procedure. Emerging evidence highlights the role of neuropeptides in mast cell-mediated inflammation and suggests that anti-inflammatory cytokines such as IL-37 and IL-38 may offer novel therapeutic avenues (40).

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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# CLINICAL AND FUNCTIONAL COMPARISON OF BONE–PATELLAR TENDON–BONE AND HAMSTRING TENDON AUTOGRAFTS IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION: A RANDOMIZED CONTROLLED TRIAL

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## ABSTRACT

The purpose of this study was to compare the clinical and functional outcomes of anterior cruciate ligament reconstruction (ACLR) using hamstring tendon (HT) and bone–patellar tendon–bone (BTB) autografts through a prospective randomized trial. Thirty-eight patients with isolated ACL injuries were randomized to undergo ACLR using either HT (n = 19) or BTB (n = 19) autografts. All procedures were performed using an anatomic single-bundle arthroscopic technique. Patients were evaluated preoperatively and at 12 months postoperatively using the IKDC score, rolimeter testing, Lachman and pivot shift tests, hop test, and range of motion. Both groups showed significant improvement in all parameters. The mean IKDC score was  $82.6 \pm 6.3$  in the HT group and  $83.2 \pm 5.9$  in the BTB group. No significant differences were found in knee stability, hop test results, or return-to-sport rates. No complications or graft failures occurred. ACLR using either autograft type yielded comparable outcomes. Graft choice should be individualized based on patient characteristics and surgeon preference.

**KEYWORDS:** *ACL reconstruction, hamstring tendon, patellar tendon, autograft comparison, functional outcome, graft choice*

## INTRODUCTION

Anterior cruciate ligament (ACL) injury is one of the most common and functionally disabling knee injuries encountered in orthopaedic practice, particularly among young and physically active individuals (1,2). The ACL plays a vital role in maintaining knee stability by resisting anterior tibial translation and providing rotational control (3). Untreated ACL injuries are strongly associated with functional instability, meniscal tears, chondral damage, and the development of early post-traumatic osteoarthritis (4,5).

Surgical reconstruction is the gold standard treatment for symptomatic ACL deficiency in active patients. The primary goal of anterior cruciate ligament reconstruction (ACLR) is to restore knee kinematics, allow safe return to sports, and prevent further intra-articular damage (6).

Among various graft choices for ACLR, the two most commonly used autografts are the bone–patellar tendon–bone (BTB) and the hamstring tendon (HT) grafts. Each graft has distinct biomechanical and clinical characteristics that influence the surgeon preference, selection and patient outcomes (7,8).

The BTB autograft type is often considered the “gold standard” because of its rigid bone-to-bone fixation and faster healing at the tunnel interfaces. Several biomechanical studies have confirmed its superior initial stiffness and load to failure (9,10). However, this type of graft also associated with significant donor site morbidity including anterior knee pain, patellar tendinopathy, kneeling discomfort, and rare but serious complications like patellar fractures or tendon rupture (11,12).

On the other hand, the HT autograft type, typically harvested from the semitendinosus and gracilis tendons, which offers the advantage of lower donor site morbidity and reduced anterior knee pain. The graft is flexible also, which allows for smaller incisions, and may be biomechanically adequate when prepared as a quadrupled construct (13,14). However, some studies reported increased postoperative laxity, slower graft incorporation due to soft-tissue-to-bone healing, and higher re-tear rates in certain athletic populations (15-17).

Numerous systematic reviews, including Cochrane and registry-based studies, have shown no definitive superiority of one graft type over the other with regard to patient-reported outcomes, knee laxity, or return to sports (17-19). However, the major challenges in interpreting the literature stems from variations in surgical technique, rehabilitation protocols, and patient demographics.

In light of the ongoing debate and the absence of a clear consensus, this randomized controlled trial was designed to compare clinical and functional outcomes of ACL reconstruction using hamstring tendon versus bone–patellar tendon–bone autografts. Our hypothesis was that both grafts would yield equivalent stability and functional outcomes at one year follow up, which allowing for an evidence-based approach to personalized graft selection.

## MATERIALS AND METHODS

### *Study Design and Setting*

This study was a prospective, randomized controlled trial conducted at Kasr Al-Ainy Medical School Hospital, Cairo University, Egypt between February 2020 and March 2022. The study was approved by the institutional review board, and a written informed consent was obtained from all patients prior to participation in the study. The trial also adhered to the ethical standards of the Declaration of Helsinki and CONSORT guidelines for randomized trials (1).

### *Patient Selection*

A total of 40 patients presenting with isolated ACL rupture were assessed for eligibility. After applying inclusion and exclusion criteria, 38 patients were enrolled to the study and randomized equally into two groups: 19 patients underwent ACL reconstruction using HT autografts, and 19 patients received BTB autografts.

### *Inclusion Criteria:*

Our inclusion criteria were, patient age between 18 and 55 years, symptomatic, MRI-confirmed complete ACL tear, no radiological evidence of osteoarthritis > grade II (Kellgren-Lawrence), normal contralateral knee, and lastly patient willingness and ability to comply with rehabilitation and follow-up.

### *Exclusion Criteria:*

Our exclusion criteria were, patients with multiligamentous knee injury, Previous surgery on the affected knee, contralateral knee pathology, systemic disease affecting healing (e.g., diabetes, rheumatoid arthritis), and active infection or open wounds.

Randomization was performed using a sealed-envelope technique immediately prior to surgery. Group allocation was blinded from both patient and outcome assessor.

### *Surgical Techniques*

All procedures were performed arthroscopically under spinal or general anesthesia by senior orthopedic consultants trained in sports surgery. Standard diagnostic arthroscopy was first conducted to confirm ACL rupture and rule out any additional intra-articular injuries (Table I).

**Table I.** *Surgical Technique and Graft Fixation Characteristics.*

| <b>Surgical Parameter</b> | <b>HT Group</b>   | <b>BTB Group</b>   |
|---------------------------|---|--|
| Graft Type                | Semitendinosus and gracilis tendons (quadrupled)            | Central third of patellar tendon with tibial and patellar bone plugs |
| Harvest Site              | Medial tibia (oblique incision over pes anserinus)          | Anterior knee (longitudinal incision over patellar tendon)           |
| Tunnel Drilling Technique | Anteromedial portal with knee at 120° flexion               | Same as HT group   |
| Femoral Tunnel Fixation   | Bioabsorbable interference screw (average diameter: 7–8 mm) | Bioabsorbable interference screw (average diameter: 9 mm)            |
| Tibial Tunnel Fixation    | Bioabsorbable interference screw                            | Bioabsorbable interference screw                                     |
| Graft Tensioning          | Manual pre-tensioning to eliminate creep                    | Manual pre-tensioning to eliminate creep                             |
| Fixation Angle            | Tibial fixation at ~10° flexion                             | Tibial fixation at ~10° flexion                                      |
| Notchplasty Performed?    | Yes   | Yes  |
| Arthroscopic Approach     | Standard anteromedial and anterolateral portals             | Same   |

*Hamstring Tendon Group (HT):*

The semitendinosus and gracilis tendons were harvested through a small oblique incision over the pes anserinus. After tendons debridement and preparation, tendons were quadrupled and secured using whipstitch sutures. Anatomic single-bundle ACL reconstruction was performed. The femoral tunnel was drilled through the anteromedial portal with the knee in deep flexion (120°). Both femoral and tibial fixation were achieved using bioabsorbable interference screws.

*Patellar Tendon Group (BTB):*

A central-third BTB graft measuring approximately 10 mm wide and 25 mm long, with tibial and patellar bone plugs, was harvested through a longitudinal midline incision. Bone ends were shaped into trapezoids for anatomical fit. Tunnel placement was done similar to the HT group. Bone-to-bone fixation was achieved using biodegradable interference screws of appropriate diameter. Special care was taken to minimize donor site morbidity.

All patients underwent the same arthroscopic technique for femoral and tibial tunnel preparation, graft passage, and tensioning.

*Postoperative Rehabilitation*

A standardized rehabilitation protocol was followed in both groups, designed in accordance with current evidence-based guidelines (2,3): Day 1–7: Isometric quadriceps activation, cryotherapy, and passive ROM 0–90°, week 2–6: Progressive weight bearing with crutches; closed-chain exercises; proprioception training, month 3: Jogging and low-impact sports-specific drills if quadriceps strength  $\geq$  80% of contralateral limb, month 6–8: Return to full sport allowed if hop test and strength assessments  $\geq$  90% symmetric.

Patients were reviewed at 1, 3, 6, and 12 months postoperatively. Primary and secondary outcomes were recorded at baseline and final 12-month follow-up for analysis.

**STATISTICAL ANALYSIS AND DATA INTERPRETATION***Sample size*

Sample size was calculated using Power Analysis and Sample Size software program (PASS) version 15.0.5 for windows (2017) using the results published by Baur et al (2015) with the postoperative clinical and functional outcome assessed by Tegner activity scales the primary outcome. Patients will be allocated into two groups; Group I: BTB group, Group II: HT group. The null hypothesis was considered as the presence of difference between both treatment modalities regarding the total post-operative Tegner activity scale (non-inferiority study). A sample size of 15 patients in each group is needed to achieve 90% power ( $1-\beta$  or the probability of rejecting the null hypothesis when it is false) in the proposed study using a one-sided two sample unequal-variance t test with margin of non-inferiority 1.0 and significance level ( $\alpha$  or the probability of rejecting the null hypothesis when it is true) of 5% 4 Patients drop-out is expected, so 19 patients will be enrolled to each group.

### Data analysis

Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for Windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non- normally distributed data and mean± Standard deviation for normally distributed data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the ( $\leq 0.05$ ) level.

- Chi-Square, Fischer exact test was used to compare qualitative data between groups as appropriate
- Mann Whitney U test was used to compare between 2 studied groups for non-normally distributed data.
- Student t test was used to compare 2 independent groups for normally distributed data.
- Paired t test was used to compare 2 paired readings for normally distributed data.

### Results

In our study, the mean age was 31.14±2.41 in hamstring tendon group and 31.10±2.53 in bone patellar tendon bone (BTB) group. The two groups were analyzed and showed no statistical significance difference ( $P=0.8$ ). Additionally, there were no statistically significant difference between weight of the patients in both groups ( $p$ -value-0.9) and duration of symptoms till time of surgery ( $p$ -value =0.07). Both groups were comparable in these parameters

#### Primary Outcomes:

The primary outcomes were, Anterior tibial translation using a rolimeter (measured in mm), Lachman and, pivot shift tests (graded 0–2), and Single-leg hop distance test (in cm).

#### Secondary Outcomes:

The secondary outcomes were, Subjective IKDC score (validated Arabic version), Range of motion (ROM) measured with a goniometer, Return to sport activity level, Postoperative complications (e.g., infection, graft failure, anterior knee pain). All clinical evaluations were performed by a blinded senior physiotherapist trained in orthopaedic outcome measurement.

### Statistical Analysis

Sample size was calculated using PASS software based on a minimum clinically important difference (MCID) of 10 points in the IKDC score, with a power of 90% and alpha of 0.05. A minimum of 17 patients per group was required; 19 were recruited to allow for potential dropout.

Data were analyzed using SPSS version 25.0 (IBM Corp, Armonk, NY). Normality was tested using the Kolmogorov–Smirnov test. Continuous variables were compared using Student’s t-test or Mann–Whitney U test as appropriate. Categorical data were analyzed using chi-square or Fisher’s exact test. Statistical significance was set at  $p < 0.05$ .

## RESULTS

### 1. Patient Demographics and Baseline Characteristics

A total of 38 patients (19 in the HT group and 19 in the BTB group) were included in the final analysis. No statistically significant differences were observed between groups in terms of demographic data or symptom duration (Table II). These comparable baseline characteristics support the internal validity of the trial.

**Table II.** Patient Demographics and Baseline Characteristics.

| Variable                  | HT Group (Mean ± SD) | BTB Group (Mean ± SD) | p-value |
|---------------------------|----------------------|-----------------------|---------|
| Age (years)               | 31.15 ± 2.43         | 31.10 ± 2.53          | 0.800   |
| Body weight (kg)          | 74.42 ± 5.08         | 74.47 ± 4.73          | 0.900   |
| Symptom duration (months) | 12.42 ± 10.34        | 7.94 ± 4.09           | 0.070   |

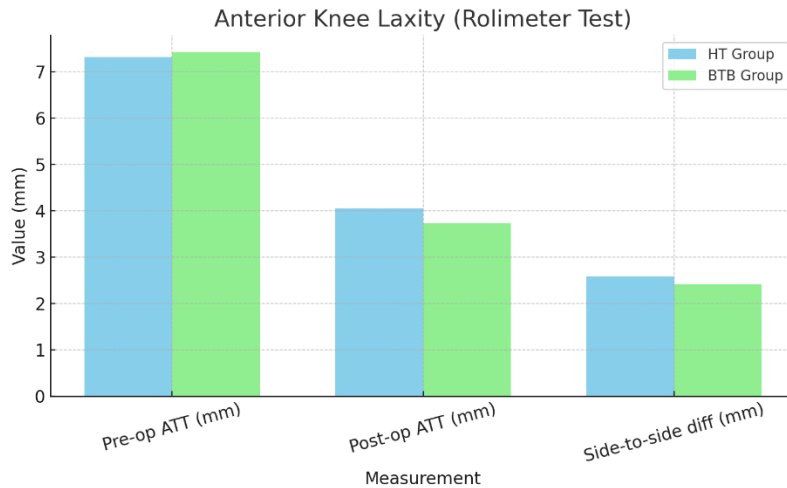
### 2. Anterior Knee Laxity – Rolimeter Test

Both groups showed statistically significant improvements in anterior tibial translation (ATT) from preoperative to postoperative evaluations. Preoperative ATT (injured knee): HT group: 7.31 ± 1.94 mm, BTB group: 7.42 ± 2.24 mm,  $p$  value = 0.8. Postoperative ATT at 12 months: HT group: 4.05 ± 1.08 mm, BTB group: 3.73 ± 0.99 mm,  $p$  value = 0.3. Side-to-side difference (post-op): HT: 2.58 ± 0.77 mm, BTB: 2.42 ± 0.69 mm,  $P$  value = 0.5 (Table III).

**Table III.** Anterior Knee Laxity by Rolimeter Test.

| Measurement                         | HT Group (Mean ± SD) | BTB Group (Mean ± SD) | p-value |
|-------------------------------------|----------------------|-----------------------|---------|
| Preoperative ATT (injured knee, mm) | 7.31 ± 1.94          | 7.42 ± 2.24           | 0.800   |
| Postoperative ATT at 12 months (mm) | 4.05 ± 1.08          | 3.73 ± 0.99           | 0.300   |
| Side-to-side difference (mm)        | 2.58 ± 0.77          | 2.42 ± 0.69           | 0.500   |

Although the BTB group had slightly less residual laxity, the difference was not statistically or clinically significant. These values are within acceptable thresholds reported in comparative studies (6,8,13) (Fig.1).



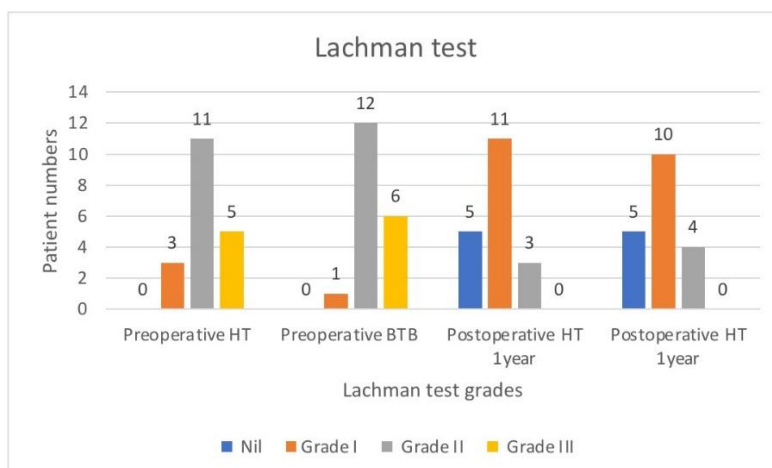
**Fig. 1.** Anterior Knee Laxity by Rolimeter Test at 12 Months Post-Operative. Bar chart comparing anterior tibial translation (ATT) measurements between the hamstring tendon (HT) and bone–patellar tendon–bone (BTB) groups. Data include preoperative ATT, postoperative ATT at 12 months, and side-to-side difference. Both groups demonstrated significant improvement postoperatively with no statistically significant differences between them.

**3. Clinical Stability – Lachman and Pivot Shift Tests**

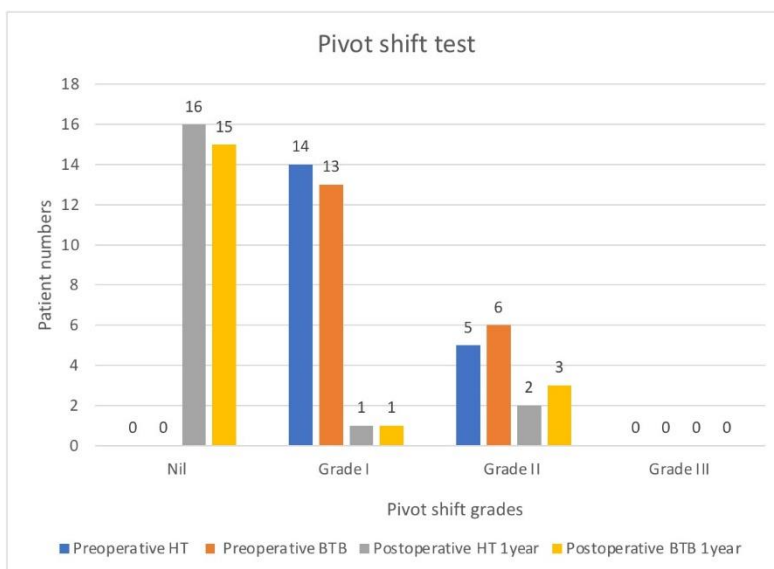
Lachman test (12 months): Grade 0 (firm endpoint): HT = 26%, BTB = 26%, Grade I: HT = 58%, BTB = 53%, Grade II: HT = 16%, BTB = 21%, p value = 0.6. Pivot Shift test (Grade 0/1): Negative/trace pivot shift: HT = 89%, BTB = 95%, P value = 0.3 (Table IV). These results demonstrate equivalent graft stability at one-year follow-up (Fig.2,3).

**Table IV.** Clinical Stability – Lachman Test (12 Months).

| Lachman Grade | HT Group (n, %) | BTB Group (n, %) | p-value |
|---------------|-----------------|------------------|---------|
| Grade 0       | 5 (26%)         | 5 (26%)          | 0.600   |
| Grade I       | 11 (58%)        | 10 (53%)         |         |
| Grade II      | 3 (16%)         | 4 (21%)          |         |



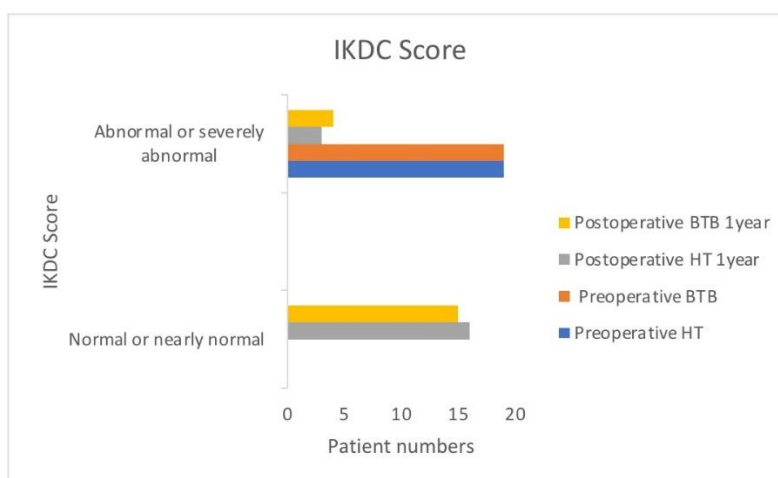
**Fig. 2.** Bar graph illustrating the preoperative and postoperative assessment of Lachman test in both groups.



**Fig. 3.** Bar graph illustrating the preoperative and postoperative assessment of pivot shift test in both groups.

**4. Functional Outcome – IKDC Subjective Score**

The IKDC subjective score improved significantly in both groups from baseline to final follow-up. Preoperative IKDC: HT:  $53.4 \pm 8.2$ , BTB:  $54.1 \pm 7.9$ , p value = 0.7. Postoperative, IKDC (12 months);, HT:  $82.6 \pm 6.3$ , BTB:  $83.2 \pm 5.9$ , p value = 0.8 (Table IV). The improvements were clinically significant and mirror those observed in high-volume registry-based trials (15,16) (Fig.4).



**Fig. 4.** Functional Outcomes – IKDC Subjective Scores and Single-Leg Hop Test. Bar graph illustrating the preoperative and postoperative IKDC scores and single-leg hop distances in both HT and BTB groups. Postoperative values showed significant improvements in both groups. Differences between groups were minimal and not statistically significant.

**5. Range of Motion (ROM)**

Extension: Full extension ( $0^\circ$ ) was achieved by all patients except one in the HT group who had a persistent  $5^\circ$  lag. Flexion: Mean flexion  $>130^\circ$  in both groups at 12 months. P value = 0.9 for ROM between groups. ROM recovery was excellent overall and comparable to previous studies (5,14).

**6. Single-Leg Hop Test**

Preoperative hop distance: HT:  $56.2 \pm 4.9$  cm, BTB:  $57.4 \pm 5.1$  cm, p value = 0.6. Postoperative hop distance (12 months): HT:  $88.4 \pm 6.2$  cm, BTB:  $89.7 \pm 5.7$  cm p value = 0.5 (Table IV). This test reflects successful restoration of dynamic knee function in both groups.

### 7. Return to Sport and Complications

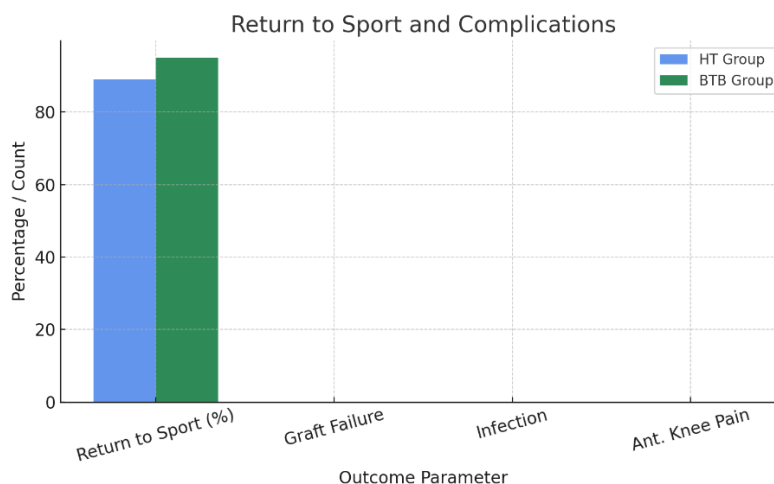
Return to previous sport level: HT: 89%, BTB: 95%, p value= 0.3 (Table V). No graft failures, infections, DVTs, or neurovascular injuries reported in either group. No donor site complications requiring reoperation (Table VI). These results are consistent with reports from large ACL registries and confirm the safety and efficacy of both grafts when used with proper technique (15) (Fig.5).

**Table V.** Functional Outcomes – IKDC and Hop Test.

| Outcome                        | HT Group (Mean ± SD) | BTB Group (Mean ± SD) | p-value |
|--------------------------------|----------------------|-----------------------|---------|
| Preoperative IKDC              | 53.4 ± 8.2           | 54.1 ± 7.9            | 0.700   |
| Postoperative IKDC (12 months) | 82.6 ± 6.3           | 83.2 ± 5.9            | 0.800   |
| Preoperative Hop Test (cm)     | 56.2 ± 4.9           | 57.4 ± 5.1            | 0.600   |
| Postoperative Hop Test (cm)    | 88.4 ± 6.2           | 89.7 ± 5.7            | 0.500   |

**Table VI.** Return to Sport and Complications.

| Parameter                                 | HT Group | BTB Group | p-value |
|---|----------|-----------|---------|
| Return to pre-injury activity             | 17 (89%) | 18 (95%)  | 0.300   |
| Graft failure                             | 0        | 0         | –       |
| Infection                                 | 0        | 0         | –       |
| Anterior knee pain requiring intervention | 0        | 0         | –       |



**Fig. 5.** Return to Sport and Postoperative Complication Rates. Comparison of return-to-sport rates and complication incidences (graft failure, infection, and anterior knee pain requiring intervention) between the two groups. Both graft types had excellent safety profiles, and return-to-sport rates were slightly higher in the BTB group (95% vs. 89%), but without statistical significance.

## DISCUSSION

This randomized controlled trial provides additional evidence that both HT and BTB autografts achieve comparable outcomes one year after anterior cruciate ligament reconstruction ACLR. Both groups in our study demonstrated statistically significant improvements in knee stability, subjective knee function, and functional hop performance, with no significant differences between them.

These findings are consistent with a Cochrane systematic review by Mohtadi et al. (7), which included 17 randomized controlled trials (RCTs) and concluded that both grafts offer similar outcomes in terms of stability and patient-reported function, although BTB grafts were associated with higher rates of anterior knee pain and kneeling discomfort. Similarly, a large-scale meta-analysis by Xie et al. (8) analyzing 47 studies found that BTB grafts provided slightly better stability but worse donor-site morbidity, reinforcing the concept that both grafts are clinically effective.

Although no anterior knee pain requiring intervention was observed in our series, long-term studies have reported persistent kneeling discomfort in up to 50% of BTB graft recipients (20). A 5-year follow-up RCT by Sajovic et al. (6) reported that both HT and BTB grafts led to excellent knee function, but BTB patients had higher rates of anterior knee

pain and pain during kneeling (29% vs. 7%). Our study aligns with their short-term data and confirms the absence of superiority regarding stability or IKDC scores at 12 months.

Another long-term RCT by Pinczewski et al. (13), with a 10-year follow-up, showed that HT grafts had lower rates of kneeling pain and similar rates of graft failure and return to sport compared to BTB. However, they did observe slightly increased pivot shift positivity in the HT group — an effect not confirmed in our study, likely due to improvements in fixation methods such as suspensory devices and tunnel drilling techniques.

Adjunctive procedures, such as lateral extra-articular tenodesis, have recently gained attention for reducing residual pivot shift in high-demand patients, as demonstrated in the stability trial (21).

Our results also parallel those of the Multicenter Orthopaedic Outcomes Network (MOON) cohort (16), where no clinically significant difference was found between HT and BTB grafts in over 2000 patients. Notably, their study emphasized that surgeon experience and patient rehabilitation adherence had more influence on outcome than graft choice itself.

Return-to-sport rates were slightly higher in the BTB group (95% vs. 89%), though not statistically significant. Similar findings were reported by Ibrahim et al. (22) and Feller & Webster (23), who demonstrated no significant difference in activity resumption at mid-term follow-up. The importance of concomitant meniscal status on final outcomes was highlighted by the MARS Group (24).

In addition, rehabilitation strategies and neuromuscular training programs have been shown to play a crucial role in restoring functional performance and minimizing re-injury risk (25, 26). Anterior knee pain following BTB autograft harvest has been identified as a potential risk factor for delayed return to full athletic participation (27).

Recent literature also emphasizes the role of psychological readiness and fear-avoidance behaviors as critical factors affecting successful return to sport, beyond purely physical rehabilitation metrics (28). A major strength of our study is the uniformity in surgical technique and rehabilitation protocol. Unlike some prior RCTs that included multiple surgeons or varied rehab programs, our study eliminated these confounders. Moreover, we used validated functional tests such as the single-leg hop test and the IKDC subjective knee score, improving the reliability of our comparisons.

Study limitations must be acknowledged. The sample size is relatively small, limiting the power to detect rare complications or subtle differences. Furthermore, the follow-up duration was limited to 12 months; therefore, conclusions regarding long-term graft integrity, osteoarthritis development, or re-injury rates cannot be made. Additionally, donor-site morbidity was not quantitatively measured using VAS or anterior knee pain scales, which might have revealed functional trade-offs between graft types.

### *Clinical Interpretation*

This study confirms that ACLR with either HT or BTB autografts can yield excellent short-term outcomes. Given the comparable clinical performance, the choice of graft should be tailored to the patient's lifestyle, professional demands (e.g., occupations requiring kneeling), and preference—an approach supported by systematic reviews and multicenter databases (6-10,15-16,19).

## **CONCLUSIONS**

Both hamstring tendon and patellar tendon autografts offer reliable results at one year after ACL reconstruction. Given the comparable clinical performance, the choice of graft should be tailored to the patient's lifestyle, occupational demands (particularly activities involving kneeling), cosmetic concerns, and personal preference.

Our findings reinforce the concept that there is no absolute “gold standard” graft and that individualized decision-making should be emphasized.

Future research should aim to include large, multicenter randomized controlled trials with standardized surgical techniques and rehabilitation protocols, longer follow-up periods to evaluate graft survival and osteoarthritis progression, and more comprehensive assessment of donor-site morbidity and patient-reported outcomes. Such studies would provide higher-level evidence to guide graft selection and optimize long-term outcomes for diverse patient populations.

### *Ethics approval and consent to participate*

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University. Written informed consent was obtained from all participants prior to their inclusion in the study.

### Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Funding

Not applicable

### Authors' contributions

AME conceived the study, participated in its design and coordination, and helped draft the manuscript. WR contributed to data collection and surgical procedures. AMG participated in data analysis and interpretation. AES contributed to literature review and manuscript editing. All authors read and approved the final manuscript.

### Conflict of interest

The authors declares that they have no conflict of interest.

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# ARTHROSCOPY FOR RESISTANT TENNIS ELBOW

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## ABSTRACT

**Background:** Tennis elbow (TE) is frequently identified in patients presenting with pain localized to the elbow lateral aspect, exacerbated by excessive or repetitive wrist movements while the elbow is extended. **Aim:** to assess arthroscopic intervention efficacy as a minimally invasive approach for managing resistant tennis elbow (RTE) cases that do not respond to conventional treatments. **Patients and methods:** This prospective study involved 30 RTE patients. All participants underwent elbow arthroscopy. This research was conducted from January 2016 to April 2017 at Cairo University Hospital as well as other hospitals. **Results:** In terms of complications, 26 cases (86.7%) experienced no complications, while 4 cases (13.3%) reported complications. In terms of patient satisfaction, nine individuals (30.0%) reported being not satisfied, while 21 (70.0%) reported being satisfied. The relationship between DASH levels at each follow-up interval demonstrated statistically as well as clinically significant differences, reflecting clinical improvement as measured by DASH levels throughout the patients' follow-up periods. **Conclusions:** Significant complications encompass permanent nerve injury as well as tourniquet-associated complications. In this study, one patient developed permanent median nerve palsy. Most complications can be avoided through surgical experience, understanding of anatomy, and appropriate surgical indications.

**KEYWORDS:** Tennis elbow, arthroscopic intervention, DASH score, hospital, anesthesia

## INTRODUCTION

Tennis elbow (TE) is frequently identified in patients presenting with pain localized to the lateral elbow region, which is exacerbated by excessive or repetitive wrist movements while the elbow is extended. Pain is located over the lateral epicondyle, and resisted wrist extension exacerbates the sensation of pain. TE is most commonly observed in individuals during their fourth and fifth decades of life, exhibiting no gender bias, and impacts the dominant elbow in 70% of cases (1).

The proposed pathology is angiofibroblastic hyperplasia of the common extensor origin, particularly affecting the tendon of the extensor carpi radialis brevis (ECRB), consistent with the other overuse tendinopathies (2).

TE diagnosis is primarily clinical, utilizing imaging modalities like ultrasound and MRI solely for confirmatory rather than diagnostic purposes (3).

The literature outlines a spectrum of treatment modalities for lateral epicondylitis TE, ranging from relative rest to surgical interventions. However, consensus regarding the optimal therapeutic approach remains controversial. Initial management prioritizes conservative strategies, including activity modification, rest, non-steroidal anti-inflammatory drugs (NSAIDs), forearm bracing, local corticosteroid injections, and physiotherapy (4). These measures lead to a

transient remission in nearly 90% of patients, while 3-8% of those that are refractory to treatment may require surgical intervention (5). Conservative treatment yields favorable outcomes; however, surgical intervention is considered when conservative measures fail after 3 to 6 months and in about 12 percent of refractory chronic cases. Recent overviews of arthroscopic treatment highlight its benefits, including direct visualization of concomitant intra-articular pathology, shorter rehabilitation periods, preservation of the extensor aponeurosis, and diminished complication rates (6).

The objective of this study was to assess arthroscopic intervention efficacy as a minimally invasive procedure for managing resistant tennis elbow (RTE) cases refractory to conventional treatments. This evaluation focused on clinical outcomes, elbow arthroscopy technique, and the safety and potential complications associated with its usage.

## PATIENTS AND METHODS

The current prospective study recruited 30 RTE patients undergoing elbow arthroscopy. The study procedures were performed in the interval between January 2016 and April 2017 at Cairo University Hospital and other hospitals.

### *Inclusion criteria*

RTE patients for whom conservative treatment (physiotherapy, analgesics,  $\geq 2$  steroid injections, or anti-inflammatory agents) had failed over  $\geq 3$ –6 months, regardless of sex or age.

### *Exclusion criteria*

Prior ipsilateral elbow surgery or fracture; concomitant disorders including rheumatological diseases, joint instability, lateral compartment arthrosis, capitellar osteochondritis dissecans, or posterior interosseous syndrome.

## METHODOLOGY

### *Preoperative evaluation*

All study subjects underwent radiological evaluation, routine investigations, and clinical evaluation.

### *Operative Technique*

**Instruments:** Arthroscopic instrumentation comprised the following: Light source, videoscope camera, 4 mm and/or 2.7 mm 30° lens (with a dual-port sheath), monitor, manual instruments (graspers, baskets, and probes), radiofrequency vapor probe, switching stick, motorized abradar/shaver, and irrigation system or arthroscopic pump. Non-arthroscopic instruments included a mosquito hemostat, a No. 11 scalpel blade, a 20 mL syringe, and tourniquets.

Other non-arthroscopic instruments included a Mosquito hemostat, No.11 scalpel blade, 20 ml syringe, and Tourniquets.

**Anesthesia:** All patients received general anesthesia.

**Prophylactic antibiotics:** Broad-spectrum parenteral antibiotics (first-generation cephalosporin) were administered during anesthesia induction prior to tourniquet application, continued for 24 hours postoperatively, and followed by a 5-day oral course.

**Examination under anesthesia:** Post-anesthesia assessment included evaluation of passive range of motion (flexion/extension, pronation/supination) and joint stability. No substantial differences were identified between preoperative baseline measurements and EUA findings.

**Patient positioning:** All procedures were conducted with patients positioned in the lateral decubitus orientation. The affected arm was positioned with elevation, the shoulder flexed forward at 90°, internally rotated, and the elbow flexed at 90° over a padded bolster.

**Marking the bony landmarks:** Key anatomical structures, including the ulnar nerve, the medial epicondyle, the radial head, the olecranon tip, and the lateral epicondyle, were palpated and delineated with a non-sterile surgical pen prior to draping.

**Draping:** The elbow was sterilized from the tourniquet to the fingertips, with the elbow positioned at 90° flexion and the antecubital fossa unobstructed by the bolster. A non-sterile tourniquet was applied to the proximal upper arm.

**Arthroscopic procedure (for lateral epicondylitis):** Following identifying and marking anatomical landmarks, the limb underwent exsanguination, followed by the inflation of a tourniquet to 250 mmHg. An 18-gauge needle was inserted into the lateral soft spot, situated within the triangular area defined by the olecranon, lateral epicondyle, and palpable radial head. A saline injection of approximately 20–30 mL was administered into the joint to achieve distention, thereby anteriorly displacing neurovascular structures and reducing the risk of iatrogenic injury. Correct intra-articular needle placement was confirmed through the observation of free fluid backflow.

The proximal anteromedial portal, serving as the viewing portal, was positioned 2 cm proximal to the medial epicondyle and anterior to the medial intermuscular septum. A nick-and-spread technique was utilized, involving an incision of the skin followed by blunt subcutaneous dissection utilizing a mosquito hemostat to protect sensory nerves. A blunt trocar was advanced along the anterior humeral cortex toward the joint center, with entry confirmed by fluid egress through the cannula.

A 4.0 mm or 2.7 mm 30° arthroscope was introduced, allowing for the visualization of the lateral capsule and radiocapitellar articulation. The systematic examination involved the assessment of the coronoid process, capitellum, coronoid fossa, anterolateral capsule, and radial head. The integrity of the radiocapitellar joint was assessed via forearm pronation and supination, and the capsule was examined for signs of inflammation, scarring, and thickening.

The proximal anterolateral portal (working portal) was established 2 cm proximal and 1 cm anterior to the lateral epicondyle. A skin incision was made with a No. 11 blade, followed by blunt fascial dissection utilizing a mosquito hemostat directed toward the joint center, thereby reducing the risk to radial nerves and cutaneous. The portal enabled the examination of the coronoid process, trochlea, and medial capsule.

Access to the posterior compartment was obtained through a proximal posterolateral portal with the elbow positioned at a 45° flexion. The entry site, located 2 cm proximal to the olecranon tip along the lateral border of the triceps, facilitated blunt trocar insertion into the olecranon fossa. The 30° arthroscope provided visualization of the posterior radiocapitellar joint, lateral and medial gutters, olecranon fossa, and the olecranon tip. Mid-lateral portal placement improved the visualization of the ulnohumeral articulation, capitellum, and posterior radial head.

Diagnostic arthroscopy confirmed lateral pathology, leading to the identification and resection of the ECRB lesion from the anterior aspect of the lateral epicondyle. A capsular window established via the anterolateral portal facilitated retractor positioning to enhance visualization and safeguard the radial nerve. Motorized shaver debridement of the lateral capsule revealed the CEO.

Following diagnostic arthroscopy confirming lateral pathology, the ECRB lesion was identified and resected from the lateral epicondyle's anterior aspect. A capsular window created through the anterolateral portal allowed retractor placement to optimize visualization and protect the radial nerve. The CEO was exposed utilizing motorized shaver debridement of the lateral capsule. A monopolar radiofrequency probe replaced the shaver to complete ECRB release and ablate tendinopathic tissue until a healthy tendon or the ECRL was visualized. Selective anterior epicondyle decortication was performed in select cases. Posterior release boundaries were maintained anteriorly to a radial head bisecting line to preserve lateral ligaments, with distal extension limited to prevent PIN injury. Closure involved simple sutures at portal sites followed by sterile dressing application.

### *Postoperative Management*

Neurovascular examinations were repeated in the recovery area following the patient's alertness and orientation to exclude iatrogenic complications. The affected arm was immobilized in a broad arm sling for a duration of 24 to 36 hours, accompanied by the application of lateral elbow ice packs. Analgesic, anti-inflammatory medications were administered during this period to manage edema and pain. The sling was removed after 36 hours, followed by the initiation of active and active-assisted range of motion (ROM) exercises. Patients were generally discharged on the same day following a day-case surgery protocol. A 5-day course of oral antibiotics was prescribed postoperatively.

A structured workout regimen focusing on active and active-assisted ROM (supination, pronation, extension, and flexion) was presented to the patient and was to be continued at home. Light-duty activities were allowed following swelling and pain resolution, generally occurring 3 to 4 weeks after surgery. Resumption of occupations necessitating extensive upper extremity utilization was postponed for 6–8 weeks or until the attainment of pain-free functional capacity.

### *Follow up*

Patients underwent systematic outpatient evaluations at Cairo University Hospital and affiliated centers at 2 weeks, 6 weeks, and 6 months postoperatively. All previously referenced clinical scores (Nirschl staging, DASH, MEPS) were rigorously documented at each interval.

## **RESULTS**

Table I displays the outlines cohort demographics, demonstrating a significant correlation between limb dominance and the affected side ( $p < 0.05$ ) (Table I). Higher disease prevalence was observed in non-working individuals (primarily housewives) and the heavy worker populations.

**Table I.** Demographic data of the studied patients.

|                      |               | Patients         |      |
|----------------------|---------------|------------------|------|
|                      |               | No. (30)         | %    |
| Sex                  | Male          | 13               | 43.3 |
|                      | Female        | 17               | 56.7 |
| Age (ys)             | Range         | 36-58            |      |
|                      | Mean $\pm$ SD | 45.57 $\pm$ 6.66 |      |
| Dominant side        | Right         | 25               | 83.3 |
|                      | Left          | 5                | 16.7 |
| Affected side        | Right         | 22               | 73.3 |
|                      | Left          | 8                | 26.7 |
| Number of injections | Range         | 2-5              |      |
|                      | Mean $\pm$ SD | 2.83 $\pm$ 0.874 |      |
| Occupation           | Not working   | 14               | 46.7 |
|                      | Heavy worker  | 13               | 43.3 |
|                      | Doctor        | 1                | 3.3  |
|                      | Nurse         | 1                | 3.3  |
|                      | Accountant    | 1                | 3.3  |

Table II illustrates the relationship between the level of MEPS at each follow-up time interval, demonstrating statistically and clinically significant differences in clinical improvement as indicated by the MEPS levels during patient follow-up (Table II).

**Table II.** Correlation of MEPS Levels.

|                                   | MEPS     |         |       |       | P. value |
|-----------------------------------|----------|---------|-------|-------|----------|
|                                   | Minimum  | Maximum | Mean  | SD    |          |
| preop                             | 55       | 85      | 70.43 | 7.564 | .000     |
| postop                            | 50       | 72      | 61.83 | 5.837 |          |
| 2 weeks                           | 68       | 90      | 80.50 | 6.415 |          |
| 6 weeks                           | 72       | 94      | 84.63 | 5.828 |          |
| 6 months                          | 70       | 100     | 92.43 | 6.468 |          |
| <b>Multiple comparison (MEPS)</b> |          |         |       |       |          |
| Preop                             | postop   |         |       |       | .000     |
|                                   | 2 weeks  |         |       |       | .000     |
|                                   | 6 weeks  |         |       |       | .000     |
|                                   | 6 months |         |       |       | .000     |
| postop                            | 2 weeks  |         |       |       | .000     |
|                                   | 6 weeks  |         |       |       | .000     |
|                                   | 6 months |         |       |       | .000     |
| 2 weeks                           | 6 weeks  |         |       |       | .000     |
|                                   | 6 months |         |       |       | .000     |
| 6 weeks                           | 6 months |         |       |       | .000     |

Table III illustrates the relationship between DASH levels at each follow-up time interval, demonstrating statistically and clinically significant differences indicative of clinical improvement as reflected by DASH levels throughout the patients' follow-up period (Table III).

**Table III.** *The relation between the levels of DASH score.*

|                                   | DASH     |         |       |       | P. value |
|-----------------------------------|----------|---------|-------|-------|----------|
|                                   | Minimum  | Maximum | Mean  | SD    |          |
| preop                             | 12       | 38      | 27.33 | 7.317 | .000     |
| postop                            | 26       | 45      | 35.93 | 5.489 |          |
| 2 weeks                           | 10       | 24      | 15.57 | 3.636 |          |
| 6 weeks                           | 2        | 20      | 10.93 | 4.828 |          |
| 6 months                          | 0        | 12      | 3.60  | 3.180 |          |
| <b>Multiple comparison (DASH)</b> |          |         |       |       |          |
| preop                             | postop   |         |       |       | .000     |
|                                   | 2 weeks  |         |       |       | .000     |
|                                   | 6 weeks  |         |       |       | .000     |
|                                   | 6 months |         |       |       | .000     |
| postop                            | 2 weeks  |         |       |       | .000     |
|                                   | 6 weeks  |         |       |       | .000     |
|                                   | 6 months |         |       |       | .000     |
| 2 weeks                           | 6 weeks  |         |       |       | .000     |
|                                   | 6 months |         |       |       | .000     |
| 6 weeks                           | 6 months |         |       |       | .000     |

Table IV depicts the relationship between Nirschl staging scores at each follow-up interval, demonstrating statistically and clinically significant differences in clinical improvement as indicated by the Nirschl staging scores over time for the patients (IV).

**Table IV.** *The relation between the levels of Nirschl staging score.*

|                                      | Nirschl  |         |      |       | P. value |
|--------------------------------------|----------|---------|------|-------|----------|
|                                      | Minimum  | Maximum | Mean | SD    |          |
| preop                                | 1        | 7       | 4.13 | 1.697 | .000     |
| postop                               | 2        | 7       | 5.30 | 1.343 |          |
| 2 weeks                              | 1        | 5       | 2.80 | .887  |          |
| 6 weeks                              | 1        | 4       | 2.20 | .961  |          |
| 6 months                             | 1        | 5       | 1.73 | 1.081 |          |
| <b>Multiple comparison (Nirschl)</b> |          |         |      |       |          |
| preop                                | postop   |         |      |       | .001     |
|                                      | 2 weeks  |         |      |       | .000     |
|                                      | 6 weeks  |         |      |       | .000     |
|                                      | 6 months |         |      |       | .000     |
| postop                               | 2 weeks  |         |      |       | .000     |
|                                      | 6 weeks  |         |      |       | .000     |
|                                      | 6 months |         |      |       | .000     |
| 2 weeks                              | 6 weeks  |         |      |       | .048     |
|                                      | 6 months |         |      |       | .000     |
| 6 weeks                              | 6 months |         |      |       | .070     |

No complications were observed in 26 cases (86.7%), while complications occurred in 4 cases (13.3%), as demonstrated in Table V (Table V).

**Table V.** Frequency and percentage of complications.

|               |                  | No. | (%)  |
|---------------|------------------|-----|------|
| Complications | No complications | 26  | 86.7 |
|               | complications    | 4   | 13.3 |

In terms of patient satisfaction, 9 (30.0%) reported being not satisfied, while 21 (70.0%) reported being satisfied (Table VI).

**Table VI.** Patient satisfaction.

|                      |               | No. | (%)  |
|----------------------|---------------|-----|------|
| Patient satisfaction | Not satisfied | 9   | 30.0 |
|                      | satisfied     | 21  | 70.0 |

## DISCUSSION

The age distribution in this cohort ranged from 36 to 58 years (mean:  $45.57 \pm 6.2$  years). Comparatively, Elfeddali et al. reported a slightly higher mean age of 50 years (range: 37–77). Occupational analysis revealed that 43.3% of patients were manual laborers, 46.7% engaged in repetitive tasks (primarily housewives), and 3.3% held sedentary professions (e.g., accountants and healthcare workers). These findings align with Lattermann et al.'s findings, where 66% of participants performed heavy manual labor (8).

A strong association was observed between limb dominance and pathology, with 83.3% of cases affecting the right side (dominant limb: 73.3%). The results exceed the 58% dominant-side prevalence documented by Zingg et al. (9).

The current study involved patients receiving conservative treatment comprising NSAIDs and corticosteroids with local anesthetic injections. The mean number of injections administered was 2.83, with a range of 2 to 5 injections. Similar findings were observed in other series by Lattermann et al., with a mean injection of 2.5 comparable results showed; mean injection 2.5 (8).

The mean overall MEPS in the present study increased from 70.43 points preoperatively (range: 55 - 85 points) to 92.43 points at six months postoperatively (range: 70 - 100 points). Jerosch and Schunck (10) demonstrated that the mean MEPS postoperatively was 93.6 points (range: 67-100) and 89 points (range: 65-100), respectively.

The Nirschl staging score in our study demonstrated an improvement from a mean of 4.13 points preoperatively (range 1 - 7 points) to a mean of 1.73 points at six months postoperatively (range 1 - 5 points).

The DASH score measures upper extremity pain and disability (on a scale from 0 to 100), indicating reduced symptomatology. The lower DASH scores represent less pain and disability. A study on a non-clinical population by Jester et al. (11) conducted a study on a non-clinical population, revealing that the DASH score among healthy employed adults is  $13 \pm 15$ . In this study, a DASH score of  $< 14$  points was deemed a favorable outcome. In our study, the DASH score improved from a mean of 27.33 points preoperatively to 3.60 points at six months postoperatively. This result is favorable when compared to other studies. Wada et al. (12) reported that the mean postoperative DASH score was 10.6 points, with a range of 0 to 50.

The current study indicates that the mean VAS improved from 5.27 points preoperatively (range: 3 to 8) to 1.47 at six months postoperatively (range: 0 to 5).

Owens et al. (13) conducted a retrospective review of 16 lateral epicondylitis patients who underwent arthroscopic ECRB release (between January 1995 and November 1998), with a minimum follow-up of one year. They reported a mean postoperative VAS of 0.58 (range: 0-3).

The average satisfaction in the current study, measured by VAS, was 21 out of 30. Nine patients expressed dissatisfaction, representing approximately 30%, while the remaining 70% reported satisfaction. Beker et al. (14) stated that the overall results of their clinical series were promising, with 95% of patients indicating they were "much better" or "better" following arthroscopic release.

Four complications were reported: four patients had nerve injury; three ulnar nerve injuries and one had median nerve injury. Concerning the three patients with ulnar nerve injury, two patient (sensory) after one-month follow-up after surgery, sensory function was partially restored. And at the fourth month follow-up, the patients' sensory function had fully recovered with just supportive medical treatment while the third one (sensory and motor) still not recovered with

hypothenar wasting and some trophic changes and undergone exploration in which only neurolysis has been done and the nerve was found intact.

The reported incidence of neurologic injuries after elbow arthroscopy is 0% to 14% (15). Injury to the radial nerve during an arthroscopic procedure of the elbow is a rare complication with very few reported cases (15,16). Neurologic injury after elbow arthroscopy may be caused by direct injury at a portal entry site, overly aggressive distension of the joint, compression of the nerve during arthroscopic manipulation, extravasation of local anesthetics (15).

In 2013, Solheim et al (17), reported that the poor outcome was found after the primary operation in 16 patients (7%) in the arthroscopic group and 3 patients (4%) in the open group, and they were re-operated on by the same technique. These cases were recorded as failures. The failure rate in the 2 groups was not statistically different ( $P = 0.285$ ).

The current study had some limitations. In the study group, there was no control group to compare the results of arthroscopic release with open or other methods. The observational nature of the study and the corresponding lack of a control group preclude a definitive conclusion regarding the benefits of this surgical intervention. Further study is required, including a prospective controlled study comparing functional outcomes of both arthroscopic and non-arthroscopic treatment modalities.

## CONCLUSIONS

Pain relief and early restoration of elbow function can be reliably achieved with minimal morbidity and high rate of patient satisfaction after arthroscopic release of ECRB for lateral epicondylitis. Minor complications of elbow arthroscopy include transient nerve palsies as the most common occurrence, followed by prolonged portal site drainage and superficial wound infection. In this study, there were two transient ulnar nerve palsies; one permanent ulnar nerve.

Major complications include permanent nerve injury and tourniquet related complications. In the current study, there was one patient with permanent median nerve palsy. Most elbow arthroscopy complications can be avoided with careful patient selection, proper surgical indications, thorough understanding of the anatomy, and experience.

### *Ethics approval and consent to participate*

All participants obtained written information and informed consent was obtained. The study was approved by the Ethics Committee of Cairo University Hospital, and the investigation conforms to the principles outlined in the 1964 Declaration of Helsinki and its later amendments.

### *Data availability*

Data is provided within the manuscript.

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No funding was received for this study.

### *Author Contributions:*

AMA, ANM, MMA, and MAI: contributed equally to this article as follows conception, design of the work, analysis, method and statistical analysis, interpretation of data, have drafted the work and substantively revised it. All authors reviewed the manuscript.

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### *Conflict of interest*

The authors declare that they have no conflict of interest.

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# ADAPTIVE NEUROMODULATION AND BIO-PHYSICO-METRIC APPROACH IN THE MANAGEMENT OF CERVICOGENIC HEADACHE: A SINGLE-ARM PILOT OBSERVATIONAL STUDY

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## ABSTRACT

Headache is a disorder affecting roughly 47% of population worldwide, which is also usually underestimated in its severity and spread due to its complexity. Indeed, it still remains insufficiently diagnosed and treated today. This single-arm pilot study aims to evaluate the effectiveness of a Bio-Physico-Metric (BPM) approach, based on organized and systematic assessment and stimulation of Myofascial Trigger Points at a global musculoskeletal level, in the treatment of Cervicogenic Headache (CH). A group of 10 CH patients was enrolled after medical examination and observed while undergoing treatment with Adaptive Neuromodulation (ANM) applied following the BPM approach. Patients received BPM-ANM treatments 2 times a week every 48/72 hours, for eight weeks in total, with each treatment session lasting 20 minutes. They were evaluated before the start of the protocol (T0) and after the end of it (T1) through the Neck Disability Index, pressure-based Muscle Strength Analysis and Digitized Bio-Metric Assessment. Statistical analysis showed an overall improvement in values between T0 and T1, which was not statistically significant but was characterized by a generally good effect size. The BPM-ANM approach might be a safe and valid therapeutic option for CH patients but further studies are necessary to clarify the validity of the approach.

**KEYWORDS:** *Cervicogenic headache, transcutaneous electrical stimulation, physical therapy, rehabilitation*

## INTRODUCTION

Headache is a disorder that affects 47% of population around the world, being among the ten most disabling condition for both sexes and the five most disabling for women, according to the classification of causes of disability made by the World Health Organization (1). In spite of the complexity of headache disorders, they are underestimated in their severity and spread, still remaining insufficiently diagnosed and treated today (1). In particular, Cervicogenic Headache (CH) is a chronic pain syndrome belonging to the class of secondary headaches. Its origin depends on dysfunctions of the joints, bones or soft tissues of the cervical compartment, that cause painful symptoms referred in the head and neck region, up to the ocular, temporal and occipital areas. Bogduk, to describe areas and characteristics of the condition, defined CH as

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a "pain perceived in any region of the head, caused by a primary nociceptive source in the musculoskeletal tissues innervated by the cervical nerves" (2). The prevalence of CH is more than 53% in patients with whiplash cervical spine injury (3-5), and it differs depending on the clinical and diagnostic criteria considered. When clinical criteria are used, the prevalence of CH is estimated at 1%, 2-5% or 4-10% in the general population and up to 17-25% among patients with severe CH (5).

Headache from cervicogenic origin could cause also other disorders in the cervical structures. The correlation between head and neck dysfunctions and headache is attributable to the relationship between nerve roots of the upper cervical vertebrae and trigeminal sensory fibers (6). This somatic dysfunction can be traced back to the presence of Myofascial Trigger Points (MTrPs) in the region affected by the pathology, which could generate altered proprioceptive and exteroceptive feedback, resulting in pain and other neurovegetative symptoms (7). The alteration of these nervous feedback mechanisms attributed to the presence of MTrPs can over time lead to the genesis of somatosensory alterations even at a distance from the primarily symptomatic area, especially in the presence of chronic pathologies such as CH (8). The state of perpetual contraction and dysfunction of some muscular areas affected by the presence of active MTrPs leads to the genesis of pain, other biomechanical-postural alterations and symptoms that are reflected at a visceral level (9). Therefore, it is possible that the treatment of MTrPs could determine a modification of the spinal and cortical afferents, resulting in a resolution of the various hierarchically established dysfunctions starting from the presence of Key MTrPs.

The Key MTrPs are the primary objective of the Bio-Physico-Metric (BPM) approach, which is based on the direct identification and treatment of these dysfunctional points through various types of assessments and therapeutic methods (10). One of the therapeutic approaches that can be used in this regard is Adaptive Neuromodulation (ANM) (11).

The aim of this study is to preliminarily investigate the short-term efficacy and safety of a BPM-ANM therapy in the treatment of CH.

## MATERIALS AND METHODS

This research is a single-arm pilot retrospective analytical observational study carried out under the organization of the Center for Physiotherapy Rehabilitation and Re-Education (Ce.Fi.R.R.) of Chieti (Italy), from June to September 2021.

All the procedures applied complied with the Italian safety regulations and the protocol was open for anyone who did not highlight specific contraindications during the initial medical evaluation. The main major contraindications to access the protocol were acute infectious disease, cancer disease, neurological disease, sleep disorders, gastrointestinal disorders, bruxism, emotional stress and a feeling of instability or dizziness, pregnancy, epilepsy, electrical implants, and tuberculosis. The protocol was not an experimental practice, since it applied the same procedures used at the study facility for all patients who did not present the above-mentioned contraindications. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained at enrolment from participants who were willing and able. Furthermore, the Ce.Fi.R.R. owns the ISO 9001:2015 certification for the realization of "Clinical observational studies in the rehabilitation field" (Certificate from the Italian Accreditation Body "Accredia" n. IT15/0304). Due to these considerations and the lack of incontrovertible national legislation regarding the need for the submission of retrospective and/or non-pharmacological observational studies to an ethics committee, normal ethics committee clearance was not required (12,13).

We have recovered the data of 10 patients (2 males and 8 females, mean age  $38 \pm 22$  years) affected by CH, who, during the reference period, referred to the study center for their condition, receiving an initial medical evaluation, a treatment protocol, and a subsequent re-evaluation at the end of the therapeutic cycle. Based on the first medical evaluation, all patients were diagnosed with CH as defined by ICHD 3 criteria (14).

To assess the musculoskeletal health status of patients before (T0) and after (T1) the therapeutic protocol, a routine evaluation of the patients was carried out using the following diagnostic tools:

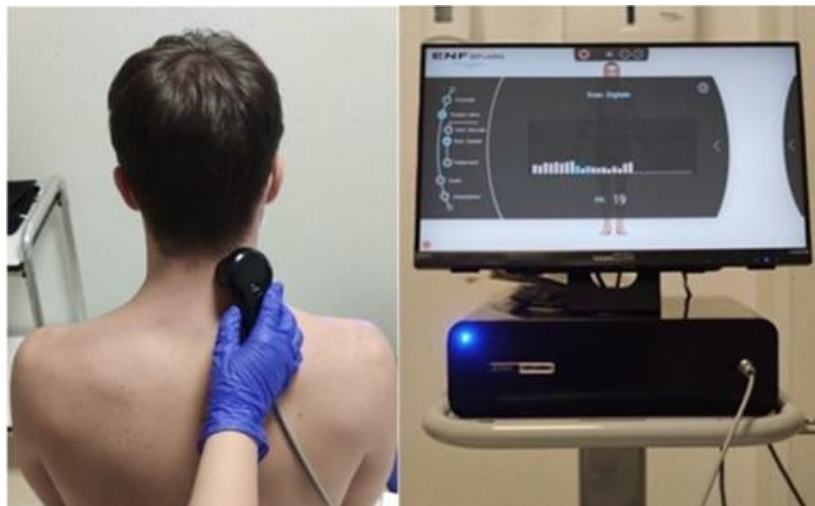
- Neck Disability Index (NDI): a questionnaire used to assess different problems such as neck pain, chronic pain in patients with whiplash cervical spine injury or cervical radiculopathy and cervicogenic headache. It showed good factorial structure and psychometric properties which replicated results of other versions (15-17);
- Muscle Strength Analysis (MSA): assessed with the Stabilizer Pressure Biofeedback (Chattanooga Group Inc., Vaudreuil, Canada). It is an inflatable cushion connected to a pressure gauge, which allows to monitor the pressure applied by specific body parts on the cushion itself (18). Specifically, the cranio-cervical flexion test was performed by having the patient lie supine on a rigid examination table and placing the cushion, inflated to a base pressure of 20 mmHg, in the hollow space at the nape of the neck. The patient was then asked to assume a chin tuck position, applying pressure with the occiput on the pillow, while the therapist recorded the instant maximal pressure developed by the patient (MSA-MAX) and the maximum pressure reached in a 10-second isometric hold

(MSA-ISO), both expressed in mmHg. Pressure values detected in the range of 20-24 mmHg were considered a symptom of muscle weakness, while values above 25 mmHg were considered a sign of adequate muscle strength.

- Digitized Biometric Assessment (DBA): assessed through a high-resolution 2D platform that captures plantar pressure distribution changes with 4 sensors per cm<sup>2</sup> (Diasu Health Technologies, Rome, Italy) (19). It is a non-invasive investigation to provide quantitative and qualitative values about the posture and balance of a patient. The evaluation made for the study included the record of the Static Pressure Test (SPT), equivalent to the percentage difference in load between the right and left foot, and the Sway Path Length (SPL), corresponding to the sway path of the center of pressure of the foot in a time of 30 seconds, expressed in mm.

Furthermore, patients were instructed to report verbally or in writing to the study center staff any adverse reactions or side effects they experienced during individual treatment sessions and for up to 48 hours afterward.

The observed patients underwent BPM-ANM treatment sessions lasting 20 minutes, twice a week for 8 weeks, with an interval of 48/72 hours between sessions. The treatment was carried out in standard environmental conditions by instructed physical therapists, using the ENF Studio device (Fast Therapies Srl, Carpenedolo, Italy). The device exploits low-grade electrical biphasic, sinusoidal, damped impulses, applied by a bipolar electrode on the skin surface (Pulse frequency between 15 and 354 Hz, pulse duration between 3 and 483 ms, pulse voltage between 20 and 450 V, maximum current intensity of 20mA). It records the impedance of the skin and creates an operative feedback alternating skin resistance input and therapeutic response current output, constantly adjusting the emitted current to the skin conductivity, to avoid nervous adaptation processes. The device detects a First Reaction (FR) value, which is a dimensionless parameter expressing the conductivity of the skin in the assessed point. According to the BPM approach, muscles showing the greater  $\Delta$ FR between the right and left side are considered the ones presenting dysfunctional Key MTrPs. In the patients studied, the  $\Delta$ FR assessment was performed in every session bilaterally on 17 muscles (Pectoralis Major, Rectus Abdominis, Rectus Femoris, Adductor Magnus, Tibialis Anterior, Quadratus Plantae, Abductor Hallucis, Abductor Digiti Minimi, Splenius Cervici, Upper Trapezius, Lower Trapezius, Paraspinal-Longissimus Dorsi, Gluteus Maximus, Hamstrings, Gastrocnemius, Soleus, Quadratus Lumborum). In each session, the 4 muscle districts with the most unbalanced FR values were recorded, identifying the 4 Key MTrPs to be treated in the session on the side characterized by the highest FR value in that asymmetric district. The Current Intensity (CI) to perform the scan was set at a standard value of 30%. The device application is shown in Figure 1 (Fig.1).



**Fig. 1.** Example of application of the ENF Studio device. On the left, the application of the handpiece equipped with a detection and treatment electrode on the skin of the target points (in this case on the Upper Trapezius) is shown. On the right, the device screen is shown during the detection phase, highlighting the First Reaction (FR) values detected in sequence at various points, also representing them graphically with vertical bars.

The 4 Key MTrPs identified for each session were then treated using the same instrumentation, applied for 5 minutes on each point (CI = 30%), using the "Automatic Rebalancing" mode, that is automatically started by the device when the handpiece electrode is left in contact with a scanned area for approximately 3 seconds. The selected treatment mode determines the establishment of a self-managed bioelectrical exchange between skin impedance input and current response output, with parameters varying within the operating ranges of the device. This exchange of currents aims to normalize the resistance to current flow offered by the target area. As a result, the BPM-ANM treatment was personalized

not only from one patient to another, but also within the same patient between sessions, focusing the treatment not only on the cervical area but also on areas located at a great anatomical distance from it.

Given the relatively small size of the observed group of patients, the data collected at time T0 and T1 were processed through the application of a non-parametric Wilcoxon signed-rank test. Data analysis was performed through the Statistics Kingdom open online calculator software (<https://www.statskingdom.com>, Melbourne, Australia). The observed changes were considered significant for  $p$  values  $< 0.05$ . Effect size ( $r$ ) was also calculated.

## RESULTS

Statistical analysis highlighted non-significant variations in the data considered, although effect sizes ranging from medium to very large were observed for most of the variations, with the exception of the SPT value which had a very small effect size. The results of the data analysis have been reported in detail in Table I (Table I).

**Table I.** Results of the data analysis.

| Variable     | Count | Mean $\pm$ SD        | $p$  | $r$   | % variation |
|--------------|-------|----------------------|------|-------|-------------|
| NDI (T0)     | 10    | 24.8 $\pm$ 12.4      | n.s. | -0.23 | -11.3%      |
| NDI (T1)     | 10    | 22.0 $\pm$ 14.9      |      |       |             |
| MSA-MAX (T0) | 10    | 24.8 $\pm$ 3.3 mmHg  | n.s. | 0.52  | +8.5%       |
| MSA-MAX (T1) | 10    | 26.9 $\pm$ 3.9 mmHg  |      |       |             |
| MSA-ISO (T0) | 10    | 24.2 $\pm$ 3.4 mmHg  | n.s. | 0.64  | +7.0%       |
| MSA-ISO (T1) | 10    | 25.9 $\pm$ 3.8 mmHg  |      |       |             |
| SPT (T0)     | 10    | 2.6 $\pm$ 1.3 %      | n.s. | 0.09  | +4.6%       |
| SPT (T1)     | 10    | 2.7 $\pm$ 1.5 %      |      |       |             |
| SPL (T0)     | 10    | 422.3 $\pm$ 414.8 mm | n.s. | -0.41 | -37.2%      |
| SPL (T1)     | 10    | 265.3 $\pm$ 212.1 mm |      |       |             |

No reports of adverse events or side effects were recorded in any of the treatment sessions of each patient.

## DISCUSSION

The present study highlighted a relationship between the implementation of a BPM-ANM protocol and the changes in biometric parameters and perceived disability in CH patients. Although the observed changes were not statistically significant, all data, except for SPT, improved, with a moderate to large effect size, indicating good clinical relevance of the treatment-associated effects. Furthermore, the treatment appears to be characterized by a high level of short-term safety, as confirmed by the absence of reports of adverse reactions and/or side effects during or after the treatment sessions.

It is possible that the localization and the treatment of Key MTrPs according to the BPM approach generated a reduction of aberrant stimulation and increased positive feedback and adaptations in the musculoskeletal system. Several therapeutic approaches dedicated to the treatment of MTrPs in cervical pathologies have shown an improvement in the disability perceived by patients, as measured by NDI, without any specific approach proving superior to others (20). It follows that, probably, to improve the symptomatology of musculoskeletal patients, the correct identification of MTrPs associated with a specific pathological condition is more important than the therapeutic modality applied to resolve MTrPs. The assessment phase is core part of the BPM approach that was observed, which could significantly contribute to correctly targeting therapeutic stimulation of MTrPs, which proved to be a valid strategy also for the management of CH (21).

Not surprisingly, the BPM-ANM treatment applied in the present study was also associated with slight improvements in cervical muscle strength, measured by MSA tests, and in overall body stability of patients, as indicated by SPL values, with the distribution of the foot load remaining substantially unchanged. It is believed that the presence of MTrPs in the musculoskeletal system can determine deficits in strength and muscle recruitment of various kinetic chains, so much so that the treatment of these MTrPs could restore strength to the pathological districts, although it is still unclear to what extent and in what timeframe (22,23). Even in the field of stabilometry and plantar pressure, the treatment of MTrPs is associated with variable modifications in the postural alignment of patients, making it necessary to investigate new

evaluative and therapeutic approaches to contextualize the role of MTrPs in these adaptation reactions of the human body (24,25).

Some studies have already highlighted how the distribution of MTrPs in the musculoskeletal system follows a hierarchical pattern, the logical reconstruction of which allows for the deactivation of Satellite MTrPs by stimulating Key MTrPs (26,27). Typically, this tracking of MTrPs distribution is performed fairly effectively through a manual evaluation, although this leads to some variability in assessment consistency between different practitioners (28). It follows that a structured and instrumentally supported assessment and treatment approach, such as the BPM-ANM observed in this study, could contribute to more precise identification of Key MTrPs and their treatment.

Indeed, musculoskeletal dysfunction could be related to problems from different systems of the body, for instance somatic, autonomic or neurodegenerative systems. In detail, dysfunctions of somatic or visceral systems could produce discordant impulses afferent to the posterior horn of the spinal cord that excites the same somatic segments (29). When the activation threshold of spinal interneurons is lowered, pain perception could increase, causing a reflex increase in muscle tone (30). This muscle contraction state could produce a palpable modification of the tissue texture, resulting in the presence of MTrPs. Consequently, the tension produced by MTrPs could reduce the range of motion of related joints (31). Considering that various forms of electrotherapies have been shown to be systematically effective in the treatment of MTrPs (32), ANM applied according to the BPM scheme could represent a non-invasive, rapid, efficient and safe strategy for a condition strongly associated with muscular tension states such as CH. Considering that phenomena such as headaches and migraines are characterized by a strong neuromuscular component, especially of the oculomotor, trigeminal and occipital type (33), electrical neuromodulation, in the form of ANM, could be even more suitable for CH, given its nature of stimulation dedicated to neuromuscular structures. Furthermore, the fact that the observed treatment apparently also had effects on the postural stability of patients is significant, since it is well known that CH is also associated with stability disorders due to altered cervical proprioception and sensorimotor dysfunction (34). In particular, CH could determine a reduced efficiency of the vestibulo-ocular reflex and sensory fibers in the neck muscles, especially in the deeper parts of the suboccipital muscles, which make central and automatic links to the systems that control balance, vision, and posture (34).

Nevertheless, the present study is characterized by a series of important limitations that prevent from making clear generalizations of the results. First, the observed sample is very small. Second, the observational single-arm nature of the study limited the possibility of making a comparison between the observed sample and a sample of subjects undergoing sham treatment or no treatment. Finally, the assessments, being based on routine, rapid, and minimally invasive methods, were probably not sufficiently thorough. Therefore, more in-depth studies on the topic should consider larger and better stratified samples, combined with the presence of a control group and the use of additional assessment systems, such as thermographic and sonographic analyses of MTrPs, myometric assessments of muscle tone, and assessments of the pressure threshold of pain.

## CONCLUSIONS

The observed BPM-ANM treatment appears to produce positive effects in CH patients, maintaining an excellent short-term safety profile. Given the non-invasive nature of the treatment, its rapid application, and the reduced fatigue it entails for the therapist, it would be appropriate to continue investigating the efficacy of the method in larger and better structured studies to better define its advantages and limitations in the clinical context.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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# PSYCHOPHARMACOLOGICAL OPTIMIZATION IN DRUG-RESISTANT MOOD DISORDERS AND MUSCLE METABOLISM

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## ABSTRACT

Skeletal muscle has a significant impact on drug distribution and can influence pharmacokinetics and drug resistance due to myokines that are produced during muscular activity. The activity of muscle interacts with the central nervous system (CNS), influencing metabolism and modulating drug-resistant mood disorders by affecting neuroendocrine signaling. Antidepressant medications have often proven treatment-resistant in patients with mood and anxiety disorders. Optimal clinical psychopharmacological therapy can achieve maximum efficacy with minimal side effects. Individualized therapy can produce rapid and effective antidepressant effects in patients with mood and anxiety disorders, where some medications have often proven treatment-resistant. It can be concluded that both psychopharmacological therapy and the application of strategies that include dosage optimization, the study of pharmacokinetic factors, and individualized treatment with personalized clinical practice can improve various pathologies, including those of the CNS.

**KEYWORDS:** *Muscle metabolism, depression, drug-resistance, mood disorder, pharmacokinetic*

## INTRODUCTION

The role of muscle in drug resistance has been little discussed in the biomedical literature (1). The link between skeletal muscle, muscle mass, metabolism, and drug-resistant mood disorders, such as drug-resistant depression, is an important, recent topic (2). Skeletal muscle can influence pharmacokinetics and therefore, drug resistance (3). Muscles represent approximately 45% of human body weight and have a significant impact on drug distribution, metabolism, and clearance.

## DISCUSSION

Muscle is an endocrine organ that secretes cytokines and myokines, molecules with systemic effects on various organs including the central nervous system (CNS) (4). Muscle can intervene in the local perfusion, absorption, metabolism, distribution, and elimination of ingested drugs (5). Muscle mass and blood flow are important because they can affect the effective drug concentration and pharmacokinetic resistance (6).

The myokines released by muscle during its activity include interleukin (IL)-6, IL-1, irisin (which derives from FNDC5), and cathepsin. IL-6 improves glucose and lipid metabolism, IL-1 causes inflammation, and irisin promotes neurogenesis, while cathepsin B promotes the formation of new neurons (7). Aerobic exercise increases brain-derived neurotrophic factor (BDNF), which enhances the antidepressant effect, induces neurogenesis and the production of

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serotonin and dopamine, and regulates the hypothalamic-pituitary-adrenal (HPA) axis, reducing hypercortisolemia (4). Muscle cross-talks with the CNS, and muscle activity and metabolism modulate drug-resistant depression by acting on inflammation, neuroplasticity, and neuroendocrine signaling (8).

In patients with drug-resistant depression, the psychiatric history can be supplemented with parameters such as muscle strength and muscle metabolism (9). In clinical practice, psychopharmacological optimization can achieve maximum therapeutic efficacy with minimal side effects (10). This treatment may reduce therapeutic doses of drugs, and therapy is also individualized (11). Drugs that produce rapid and robust antidepressant effects in patients with mood and anxiety disorders have often proven resistant to treatment (12,13). At times, treatment ineffectiveness and the lack of long-term efficacy data have led to an increase in the use of unapproved off-label medications (14,15).

The goal of personalized pharmacological treatment is to tailor therapy to the biological, genetic, and clinical characteristics of each individual, as occurs in precision psychiatry. Pharmacogenomics and pharmacogenetics are involved in drug metabolism, identifying metabolizers, which are elements necessary to predict drug efficacy and toxicity. Personalized clinical treatment must take into account certain patient characteristics, such as age, weight, medical and psychiatric comorbidities, gender, patient preferences, and previous response to medications. The choice of antidepressants should be based on the CYP enzyme profile, and the dosage of antipsychotics should be personalized based on plasma levels.

While certain medications may be beneficial for some patients with mood disorders, it is important to consider the potential risks associated with the drug when considering treatment (16). Clinicians should recommend evidence-based use of the drug to ensure patient safety. The goals are to improve symptoms, reduce side effects, facilitate individual therapy, prevent relapse, and integrate treatment with psychological therapies (17). To achieve these goals, specific strategies must be implemented for each individual being treated. Each patient requires dose adjustment based on the response, tolerability, and kinetics of the drug being used (18). Flexibility in using a different drug that targets different receptors is essential, as is the use of multiple drugs with complementary mechanisms.

The most important strategies to implement must involve reducing or discontinuing unnecessary or harmful medications (19). Several factors must be considered, such as the precise diagnosis, significant symptoms and organic and psychiatric comorbidities, metabolism, such as CYP450 variants, and drug interactions (20). The patient's age, gender, and lifestyle, the use of clinical scales, regular interviews, and dosages must also be considered. In these cases, useful tools to consider are international guidelines (APA, NICE, CANMAT, WPA), personalized therapies based on "precision psychiatry", and pharmacogenetics such as CYP2D6 and CYP2C19.

The American Psychiatric Association (APA) guidelines (USA) refer to APA Practice Guidelines, which focus primarily on the diagnosis and treatment of mental disorders (21). Their key features are evidence-based. They are a systematic framework with recommendations for diagnosis, pharmacological treatment, and psychotherapeutic interventions. They also place great emphasis on personalized treatment, comorbidity, and continuity of care.

The National Institute for Health and Care Excellence (NICE) guidelines (UK) focus primarily on integrated clinical treatment (medication, psychotherapy, and social support) (22). These treatments include extremely detailed guidelines geared toward daily clinical practice, and consider not only efficacy, but also cost-effectiveness, social impact, and quality of life.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines primarily address mood and anxiety disorders, which are widely used in psychiatry for the management of major depressive disorder and bipolar disorder (23).

The World Psychiatric Association (WPA) Practice Guidelines & Position Statements focus primarily on global standards of psychiatric care, adaptable to different cultural and resource contexts, promoting international harmonization of psychiatric practice and paying attention to cultural, ethical, and human rights factors (24). The guidelines are often developed in collaboration with the World Health Organization (WHO) (25).

## CONCLUSIONS

In summary, psychopharmacological optimization should improve symptoms, reduce side effects, facilitate therapeutic adherence, prevent relapse, and integrate psychotherapeutic interventions. A systematic approach including dosage optimization, switching, augmentation, and therapeutic combinations, leads to the identification and discontinuation of medications and targeted prescription, personalized clinical practice, pharmacokinetic factors, and patient characteristics.

*Conflict of interest*

The authors declare that they have no conflict of interest.

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