Volume 14, no.3, September-December 2025

ISSN 2038-4106

European Journal of Musculoskeletal Diseases

Leonardo da Vinci. Saint Jerome in the Wilderness (circa 1480)

Published by
Biolife

www.biolife-publisher.it

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

European Journal of Musculoskeletal Diseases

14(3) September-December 2025

CONTENTS

EFFECTS AND CLINICAL IMPLICATIONS OF SERIAL EXTRACTIONS IN ORTHODONTICS: A LITERATURE REVIEW. A. Manti, A. Torraco, C. Maspero and L. Giannini …….. 105-110

OSTEONECROSIS OF THE JAWS. ANALYSIS OF RISK FACTORS AND DENTAL MANAGEMENT STRATEGIES- PART I. M. Scarpati Cioffari di Castiglione, S. Lauri, I. Mastrorilli, A. Bonomo, F. Ferrantini, L.M. Laudiero, G.M. Granata and A. Della Corte ……... 111-118

OSTEONECROSIS OF THE JAWS. ANALYSIS OF RISK FACTORS AND DENTAL MANAGEMENT STRATEGIES- PART II. M. Scarpati Cioffari di Castiglione, S. Lauri, C. Moscetta, F. Ferrantini, L.M. Laudiero, G.M. Granata, V.M. Spadoni and I. Mastrorilli 119-127

IMPLANT SURFACES IN ORAL IMPLANTOLOGY: FROM OSSEOINTEGRATION BIOLOGY TO FUTURE DIRECTIONS. M. Scarpati Cioffari di Castiglione, S. Lauri, I. Mastrorilli, S. Di Giovanni, R. Trabucco, P. Nunu, M.C. Palumbo and A. Danieli …… 128-135

HYALURONIC ACID RELIEVES PAIN IN A SORE KNEE BUT NOT IN ANTERIOR TALOFIBULAR LIGAMENT INJURY: CASE REPORT. F. Pandolfi, M.J. Conti, M. Di Emidio, A. Coppola, F. Mastrangelo, A. Younes, G. Marinelli, A.M. Inchingolo, A.D. Inchingolo and G. Dipalma ……... 136-140

WATER-BASED BIODANZA AS A MULTISENSORY STIMULATION IN THE MANAGEMENT OF CHRONIC PAIN: A PILOT OBSERVATIONAL STUDY. G. Barassi, V. De Carolis, A. Younes, L. Prosperi, C. Di Matteo, C. Mariani, G. Pasetti, L. Buzzelli, C. Candita and P.E. Gallenga ..…... 141-147

MATERIALS SELECTION AND EVALUATION OF OUTCOMES IN ENDODONTIC SURGERY: AN UPDATE. S. Ceraulo, H.Z. Hao and A. Barbarisi …….. 148-155

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Review

EFFECTS AND CLINICAL IMPLICATIONS OF SERIAL EXTRACTIONS IN ORTHODONTICS: A LITERATURE REVIEW

A. Manti[1], A. Torraco[1], C. Maspero[1,2*] and L. Giannini[1,2]

[1] Department of Biomedical, Surgical and Dental Sciences, School of Dentistry, University of Milan, Milan, Italy;
[2] Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy.

**Correspondence to*:
Cinzia Maspero,
Department of Biomedical, Surgical and Dental Sciences,
School of Dentistry,
University of Milan,
20122 Milan, Italy.
e-mail: cinzia.maspero@unimi.it

ABSTRACT

Background/Objectives: Serial extraction is an interceptive orthodontic procedure used to manage crowding during the mixed dentition phase. This narrative review evaluates the occlusal, skeletal, and functional effects of serial extractions. *Methods:* A narrative review was conducted by analyzing 11 studies published between 2000 and 2025 that investigated the orthodontic outcomes of serial premolar extractions in growing individuals. Data were extracted on protocols, dental/skeletal outcomes, and long-term results. *Results:* Serial extractions improved anterior alignment, reduced incisor protrusion, and promoted third molar eruption. The effects were more favorable in Class I cases than in Class II. Vertical control was observed in hypodivergent subjects, with no adverse impact on airway or sleep. Skeletal sagittal changes were minimal. A 50-year follow-up supported the long-term stability of results. *Conclusions*: When properly indicated, serial extractions provide a safe and effective method for managing dental crowding, facilitating third molar eruption, and achieving functional occlusion, especially in Class I malocclusion. Further standardized studies are needed.

KEYWORDS: *Serial extraction, orthodontics, crowding, premolar extraction, third molar eruption, incisor stability, dentoalveolar changes, occlusal plane, airway dimension, pediatric orthodontics*

INTRODUCTION

Tooth size-arch length discrepancy is a common clinical issue in orthodontics, often manifesting as crowding during the mixed dentition phase. When left untreated, severe crowding may compromise aesthetics, function, and long-term oral health. Among various interceptive approaches, serial extraction has long been considered a valid option to address such discrepancies by guiding the eruption of permanent teeth into a more favorable alignment through the planned and sequential extraction of selected teeth. First described by Kjellgren in the early 20th century and later developed by Hotz and Dewel, this technique has since been the subject of continuous investigation and debate (1-3).

Serial extraction protocols typically involve the early removal of primary canines, followed by primary first molars and finally the first premolars, aiming to resolve crowding by creating space for physiological tooth alignment. Advocates of this method report benefits including improved anterior alignment, reduced incisor protrusion, and shorter active orthodontic treatment.

Furthermore, serial extraction may positively influence the vertical development of the occlusal plane and facilitate the eruption of third molars by increasing retromolar space (4,5).

Received: 16 September, 2025
Accepted: 06 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

However, the approach is not without controversy. Concerns remain regarding its limited skeletal effects, potential for deepening of the bite, and its applicability only in specific malocclusion types, primarily Class I with favorable growth patterns (6).

In recent decades, the orthodontic literature has increasingly examined the long-term outcomes and broader clinical implications of serial extractions. Areas of interest include changes in dentoalveolar relationships, incisor stability, third molar positioning, and even systemic or functional consequences such as upper airway dimensions and sleep quality (7,8).

Although many studies suggest neutral or even favorable effects, others point out methodological limitations and highlight the need for prospective data and standardized protocols.

This narrative literature review aims to synthesize the available scientific evidence on serial extractions in orthodontics, with a particular focus on their effects on occlusal development, skeletal and dentoalveolar changes, third molar eruption, and functional outcomes. By analyzing studies conducted between 2000 and 2025, the review seeks to clarify the clinical indications of serial extractions, assess their long-term effectiveness, and provide guidance for their implementation in contemporary orthodontic practice.

MATERIALS AND METHODS

The narrative review's search process was conducted across multiple databases, including PubMed, Scopus, Cochrane Library, and Web of Science, to comprehensively gather studies on serial extractions in orthodontics published between 2000 and 2025. The search strategy employed the following keywords: "(serial extractions) AND (orthodontics)". This search strategy yielded a total of 2,713 articles within the specified timeframe. Subsequently, the articles underwent a systematic selection process adhering to PRISMA guidelines, leading to the identification of 11 articles that met the inclusion criteria and were deemed appropriate for inclusion in the narrative review (Fig.1). The search and selection of articles for this narrative review were conducted following inclusion and exclusion criteria.

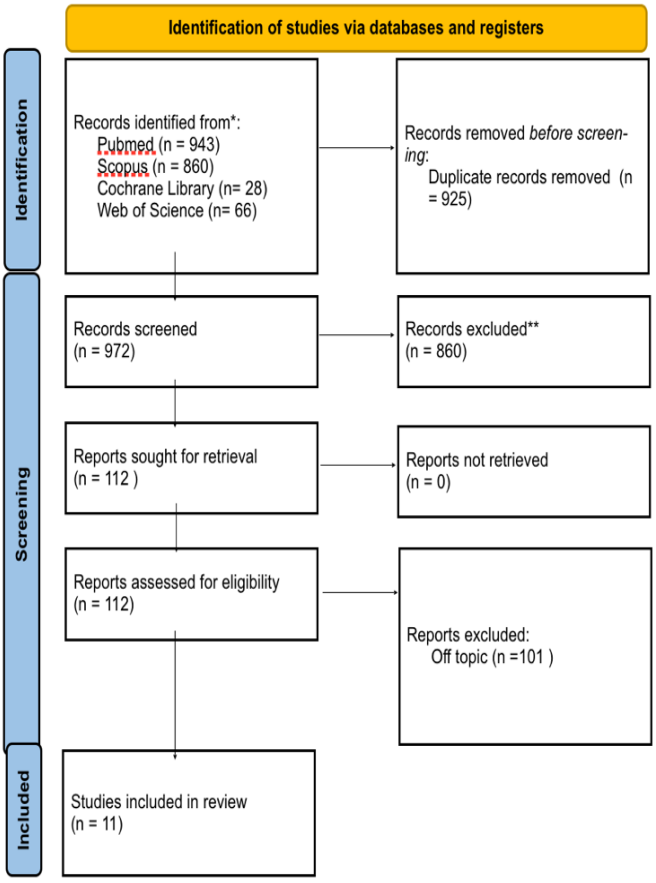

Fig. 1. *PRISMA 2020 flow diagram showing the literature search and study selection process leading to the inclusion of 11 studies.*

Inclusion criteria comprised articles that met the following conditions: (i) Randomized Control Trial (RCT) or randomized controlled clinical trial (RCCT), (ii) case series with more than 5 clinical cases (CS), (iii) studies involving

human participants, (iv) availability as free full-text or accessible with university credentials, and (v) articles published in the English language.

Conversely, exclusion criteria were defined as follows: (i) systematic or literature reviews, (ii) editorials, (iii) case reports (those with only 1 case), (iv) case series with fewer than 5 cases, (v) articles conducted *in vitro*, (vi) studies involving animals, and (vii) articles not published in the English language.

These criteria were applied during the article selection process to ensure the quality and relevance of the chosen studies for the narrative review. These 11 selected articles will form the foundation for a comprehensive analysis of the available literature on serial extractions (Table I).

Table I. *Characteristics of the studies included in the review (n = 11): authors, year, study design, number of patients, mean age, gender, treatment, outcomes.*

Author (Year)	Study Design	Number of Patients	Average Age	Gender	Treatment	Outcomes
Miclotte et al. (2017)	Retrospective longitudinal study	296: -218 non extraction -78 extraction	Not stated	Not stated	Extraction of 1st or 2nd premolars vs non-extraction	Improved eruption space and vertical position of third molars with extractions
Shearn & Woods (2000)	Retrospective cephalometric study	73	13.7 y	36 M, 37 F	Extraction of lower first or second premolars (with upper extractions)	Arch width reduction with 2nd premolar extraction; variable incisor changes
Ekstam et al. (2023)	Retrospective cephalometric study	79: -19 extraction -60 non extraction	Not stated	Not stated	Premolar extraction + fixed appliances	Significant differences in incisor proclination, lip position; no increase in root resorption
Jain & Valiathan (2009)	Retrospective comparative study	50: -25 extraction -25 control	13.5 y (extraction) 13.8 y (non)	17 M, 8 F (extraction)	Extraction of all first premolars	Uprighting of mandibular third molars greater in extraction group
Janson et al. (2014)	Comparative study	107 (75 Class I, 32 Class II)	13.98 y (Class I) 13.19 y (Class II)	47 F, 28 M (Class I); 14 F, 18 M (Class II)	Four premolar extractions	Class II group showed worse occlusal outcome vs Class I
Mintenko et al. (2020)	Retrospective study	85 (serial, late extraction, controls)	Not stated	Not stated	Serial vs late extraction of mandibular 2nd premolars	Initial tipping corrected post-treatment; no incisor tipping differences
Quinzi et al. (2023)	Retrospective controlled study	78 (52 treated, 26 control)	8.5 y ± 1.4	Not stated	Serial extraction ± maxillary expansion	Skeletal vertical parameters improved; similar effects across extraction groups
Chen et al. (2010)	Retrospective cephalometric study	26	16.1 y	Not stated	Extraction of four second premolars	Balanced space closure; controlled incisor inclination; mesial molar movement
Persson et al. (2022)	Longitudinal (50-year follow-up)	45: -24 extraction -21 control	11.5 y (extraction) 13 y (control)	Not stated	Extraction of four first premolars (no ortho)	Extraction group showed stable incisor alignment into late adulthood
Vejwarakul et al. (2023)	Retrospective cohort	79	~23 y	14 M, 65 F	Premolar extraction vs non-extraction	No significant airway differences; good sleep quality in all groups
Zhu et al. (2022)	Retrospective cephalometric	140	Not specified	44 F, 96M	Four premolars	Flattening posterior occlusal plane (≈2.14°)

RESULTS

The analysis of eleven selected studies revealed considerable methodological heterogeneity but also several consistent findings. In patients with Class I malocclusion, serial extractions, particularly of the first premolars, were associated with more predictable and satisfactory occlusal outcomes. As shown by Janson et al. (6), extraction treatment led to significantly improved post-treatment PAR scores (6). In contrast, in Class II cases, the efficacy of extraction protocols was more limited, especially in achieving molar correction (6).

At the dentoalveolar level, several studies (e.g. Ekstam (9), Quinzi (10), Chen (11)) confirmed that premolar extraction resulted in reduced incisor proclination and protrusion, more balanced space closure, and in some cases, favorable soft tissue profile changes. Mintenko et al. found that spontaneous occlusal changes occurring after early extractions were fully normalized by fixed appliance therapy (12).

Regarding third molars, studies by Miclotte (4) and Jain & Valiathan (5) suggested that premolar extractions increase retromolar space and improve vertical position and angulation of mandibular third molars. However, the impact on third molar angulation varied among studies (4,5).

Systemically and functionally, no adverse effects were reported. Vejwarakul et al. demonstrated no significant differences in upper airway patency or sleep quality between extraction and non-extraction groups (7).

DISCUSSION

The use of serial extractions is a well-established orthodontic strategy for managing crowding in mixed dentition and guiding favorable occlusal development. This literature review demonstrates that, when properly indicated and planned, serial extractions can offer numerous advantages, not only in simplifying the active phase of orthodontic treatment, but also in promoting long-term stability, controlled facial growth, and the prevention of occlusal complications.

The most favorable occlusal outcomes are observed in patients with Class I malocclusion, where serial extractions allow partial or complete spontaneous alignment and effective space management. Janson et al. (6) reported a significantly better post-treatment PAR index in Class I patients compared to Class II, indicating that four-premolar extraction protocols are less effective in correcting molar relationships in more complex skeletal cases. This suggests that extractions alone are insufficient to address severe skeletal discrepancies, and that anchorage reinforcement or functional appliances may be needed in Class II patients.

At the dentoalveolar level, the available evidence consistently shows that extraction protocols reduce incisor proclination and protrusion and soft-tissue changes appear partially compensated by growth, with no permanent esthetic impact reported (9-11). Ekstam et al. (9) demonstrated significant retraction of the soft tissues in extraction cases, particularly the lower lip. However, such changes appear to be partially compensated by growth, and no permanent negative impact on facial profile was noted. Tooth selection is critical; extraction of first premolars enables greater anterior retraction, while second premolar extractions, as shown by Chen et al. (11), may offer a more balanced distribution of extraction space, with reduced aesthetic impact (13). In patients with moderate crowding and favorable facial esthetics, this may be a more conservative and appropriate choice (14).

Mintenko et al. (12) observed that although occlusal curves and tipping changes occur during the spontaneous “drift” phase following early extractions, these are fully corrected by fixed orthodontic therapy. This supports the idea that even if spontaneous dental compensations occur temporarily, the overall outcome is not compromised when integrated into a structured treatment plan.

Skeletal changes appear minimal. No significant or clinically relevant variations were reported in sagittal parameters such as ANB, SNA, or SNB, consistent across several studies (Ekstam (9), Quinzi (10), Zhu (15)). However, vertical and occlusal plane parameters show more noteworthy modifications. Zhu et al. (15) reported a compensatory rotation of the occlusal planes, particularly flattening of the posterior occlusal plane, which may influence mandibular rotation and vertical dimension. In hypodivergent patients, this reflects as vertical control; in hyperdivergent subjects, the effect appears less pronounced. This underscores the importance of evaluating vertical facial growth patterns when planning extraction protocols (16).

An important clinical aspect involves third molar eruption. Studies by Miclotte et al. (4) and Jain & Valiathan (5) demonstrate that premolar extractions, either first or second, improve vertical positioning and available space for third molar eruption, potentially reducing impaction risk and the need for surgical removal. However, the angular improvement of third molars is not always significant, suggesting that biomechanics and growth pattern may play a more relevant role than the choice of the extracted tooth.

Functionally and systemically, Vejwarakul et al. (7) provided reassuring data: no significant differences in airway patency or sleep quality were found between extraction and non-extraction patients, even among hyperdivergent

individuals. This finding is particularly relevant, as it dispels the common concern that orthodontic extractions may impair respiratory function.

Finally, the 50-year longitudinal follow-up by Persson et al. (8) provides strong evidence supporting the long-term stability of early extraction protocols. Even in the absence of active orthodontic therapy, patients who underwent serial extractions showed stable incisor alignment and a physiological reduction of tooth-size–arch-length discrepancy, reinforcing the "self-adaptive" capacity of the dentition when extractions are correctly timed and indicated.

CONCLUSIONS

This narrative review confirms that, when properly planned, serial extractions represent a safe and effective therapeutic option for patients with crowding and favorable skeletal growth patterns.

The main benefits include improved incisor position and angulation (9-12), stabilization of the occlusal plane and vertical mandibular growth (8,10,15), increased space for third molar eruption (4,5), and neutral or favorable effects on soft tissue profile (7,9,11).

Careful patient selection, appropriate timing of extractions, and individualized cephalometric evaluation are key elements for treatment success. Further prospective, controlled studies are needed to establish standardized protocols and to better understand long-term outcomes in diverse clinical contexts.

Author Contributions:

Conceptualization, AM and AT; Methodology, AM and AT; software, AM; validation, AM and AT; formal analysis, AM and AT; investigation, AM and AT; resources, AM and AT; data curation, AM and AT; writing—original draft preparation, AM and AT; writing—review and editing, LG and CM; visualization, LG and CM; supervision, LG and CM; project administration, CM; funding acquisition, CM. All authors have read and agreed to the published version of the manuscript.

Funding:

This study was partially funded by the Italian Ministry of Health—Current research IRCCS.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Hotz RP. Guidance of eruption versus serial extraction. *Am J Orthod*. 1970;58(1):1-20. doi:10.1016/0002-9416(70)90125-9.
2. Dewel BF. Serial extraction in orthodontics: Indications, objectives, and treatment procedures. *Am J Orthod*. 1954;40(12):906–926. doi:10.1016/S0002-9416(54)90043-3.
3. Farronato G, Maspero C, Farronato D. Orthodontic movement of a dilacerated maxillary incisor in mixed dentition treatment. *Dent Traumatol.* 2009;25(4):451-6. doi:10.1111/j.1600-9657.2008.00722.x.
4. Miclotte A, Grommen B, Cadenas de Llano-Pérula M, Verdonck A, Jacobs R, Willems, G. The effect of first and second premolar extractions on third molars: A retrospective longitudinal study. *J Dent.* 2017;61:55-66. doi:10.1016/j.jdent.2017.03.007.
5. Jain S, Valiathan A. Influence of First Premolar Extraction on Mandibular Third Molar Angulation. *Angle Orthod*. 2009;79(6):1143-8. doi:10.2319/100708-525R.1.
6. Janson G, Nakamura, A, Barros SE, Bombonatti R, Chiqueto K. Efficiency of class I and class II malocclusion treatment with four premolar extractions. *J Appl Oral Sci*. 2014;22(6):522–527. doi:10.1590/1678-775720130544.
7. Vejwarakul W, Ko EWC, Lin CH. Evaluation of pharyngeal airway space after orthodontic extraction treatment in class II malocclusion integrating with the subjective sleep quality assessment. *Sci Rep*. 2023;13(1):9210. doi:10.1038/s41598-023-36467-9.
8. Persson M, Al-Taai N, Pihlgren K, Westerlund A. Early extractions of premolars reduce age-related crowding of lower incisors: 50 years of follow-up. *Clin Oral Investig*. 2022;26(6):4525-4535. doi:10.1007/s00784-022-04416-x.

9. Ekstam M, Sonesson M, Hellén-Halme K. Effects of premolar extraction and orthodontic treatment in adolescents-retrospective cephalometric study. *Acta Odontol Scand*. 2024:83:92-100. doi:10.1080/00016357.2023.2267145.
10. Quinzi V, Salvati SE, Lerda F, Compri M, Rosa M, Primozic J. Skeletal and dental effects of serial extractions performed with or without maxillary expansion-A retrospective controlled study. *Orthod Craniofac Res.* 2023;26(4):642-649. doi:10.1111/ocr.12647.
11. Chen K, Han X, Huang L, Bai D. Tooth movement after orthodontic treatment with 4 second premolar extractions. *Am J Orthod Dentofacial Orthop*. 2010;138(6):770-7. doi: 10.1016/j.ajodo.2009.01.030.
12. Mintenko R, Kennedy DB, Aleksejuniene J, Hannam AG, Yen EH. Mandibular dental changes following serial and late extraction of mandibular second premolars. *Angle Orthod.* 2020;90(2):187-193. doi:10.2319/041819-272.1.
13. Maspero C, Gaffuri F, Castro IO, Lanteri V, Ugolini A, Farronato M. Correlation between Dental Vestibular-Palatal Inclination and Alveolar Bone Remodeling after Orthodontic Treatment: A CBCT Analysis. *Materials (Basel)*. 2019;12(24):4225. doi:10.3390/ma12244225.
14. Galbiati G, Maspero C, Giannini L, Guenza GC, Zanoni F, Farronato G. Orthodontic–surgical treatment and respiratory function: rhinomanometric assessment. *Minerva Stomatol*. 2017;66(3):91–97. doi:10.23736/S0026-4970.17.04045-6.
15. Zhu Y, Xiong X, Zhang Y, et al. Effect of orthodontic treatment with premolar extractions on occlusal planes: A retrospective study. *Orthod Craniofac Res*. 2023;26(3):356-363. doi:10.1111/ocr.12616.
16. Farronato G, Giannini L, Galbiati G, Sesso G, Maspero C. Orthodontic-surgical treatment: neuromuscular evaluation in skeletal Class II and Class III patients. *Prog Orthod*. 2012;13(3):226-36. doi:10.1016/j.pio.2012.04.003.

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Article

OSTEONECROSIS OF THE JAWS. ANALYSIS OF RISK FACTORS AND DENTAL MANAGEMENT STRATEGIES- PART I

M. Scarpati Cioffari di Castiglione[1], S. Lauri[2*], I. Mastrorilli[3], A. Bonomo[4], F. Ferrantini[4], L.M. Laudiero[4], G.M. Granata[4] and A. Della Corte[5]

[1] Independent researcher, 81021, Caserta, Italy;
[2] Independent researcher, 00073, Rome, Italy;
[3] Independent Researcher, 00135, Rome, Italy;
[4] Department of System Medicine, University of Rome "Tor Vergata", Rome, Italy;
[5] Independent Researcher,72021, Brindisi, Italy.

**Correspondence to*:
Simone Lauri,
Independent Researcher,
00073, Rome, Italy.
e-mail: laurisimone1@gmail.com

ABSTRACT

This comprehensive review examines medication-related osteonecrosis of the jaw (MRONJ), a complex and debilitating pathological condition primarily associated with the use of anti-resorptive agents such as bisphosphonates and denosumab, as well as anti-angiogenic drugs. The article discusses the recent shift from the term BRONJ to MRONJ to reflect the broader range of causative medications. It details the pathophysiological mechanisms—including alterations in bone remodeling, impaired osteoclastic activity, compromised vascularization, and immune dysfunction—that contribute to its development. The review analyzes various risk factors, encompassing pharmacological variables (drug type, dosage, route, and duration), systemic health conditions (such as diabetes, osteoporosis, and cancer metastases), and local factors like invasive dental procedures and chronic inflammatory diseases. Prevention strategies focus on meticulous risk assessment, oral health optimization, timing of treatments, and minimally invasive surgical protocols. The potential utility of biomarkers, particularly serum CTX levels, for early risk prediction is explored, although further validation is needed. The review underscores the importance of further prospective studies to improve understanding of the pathogenetic mechanisms, validate prognostic biomarkers, and evaluate innovative treatment options, ultimately aiming to enhance patient management, reduce incidence, and preserve quality of life in at-risk populations.

KEYWORDS: *MRONJ, anti-resorptive, risk factor, prevention, biomarker*

INTRODUCTION

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recently proposed replacing the term "bisphosphonate-related osteonecrosis of the jaw (BRONJ)" with "medication-related osteonecrosis of the jaw (MRONJ)." This modification takes into account the increase in cases of osteonecrosis due to drug intake. When we talk about osteonecrosis of the jawbones, we refer to a pathological condition in which the bone cells die for various reasons. Anti-angiogenic and anti-resorptive agents can cause drug-induced osteonecrosis, the latter being the result of the combination of drugs, microbiota, and trauma. When we talk about MRONJ, we are referring to a highly debilitating condition that presents a high mortality rate. This pathological condition is associated with problems in swallowing, feeding, and the appearance of oedematous and painful mucous membranes (1). To make a diagnosis, certain criteria are

Received: 04 September, 2025
Accepted: 29 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

taken into consideration: Ongoing or previous therapy with anti-resorptives, exposed bone persisting for more than eight weeks, absence of radiotherapy in the jaw area (2). The risk of developing osteonecrosis is correlated with the type of drug taken, its dosage, the method of administration (parenteral/oral), and also the duration of the treatment. All those that fall under invasive therapies predispose the onset of such a condition, including: dental extractions, periodontal surgery, and implant surgery; as additional risk factors, poor oral hygiene, periodontitis, and other inflammatory conditions are included. This pathology predominantly affects the mandible, particularly the lingual portion, due to its thin mucosa and poor blood supply (1). The American Association of Oral and Maxillofacial Surgeons introduced a classification in 2007 that includes three stages for cases of medication-related osteonecrosis of the jaw. In the First stage, we have exposure of necrotic bone, without painful symptoms and without any signs of infection. In the Second stage, it manifests with exposed necrotic bone accompanied by clinical signs of infection. In the Third stage, we have the presence of exposed necrotic bone, painful symptoms, infection, extraoral fistulas, oroantral and orosinus communications, pathological fractures of the mandible, and extension of necrosis involving: zygoma, maxillary sinus, mandibular ramus, or the lower border of the alveolar bone (3). This article focusses on the phenomenon of medication-induced osteonecrosis of the jaws, analyzing the possible causes, risk factors (pharmacological, systemic, local, genetic, and demographic), the anatomical and pathophysiological characteristics involved, and the prevention strategies and diagnosis. The role of anti-resorptive drugs (such as bisphosphonates and denosumab) and anti-angiogenic agents in the genesis of MRONJ is examined, highlighting the importance of alterations in bone remodeling, osteoclastic activity, vascularization, and immune response. Specific risk factors related to dental procedures and in relation to the anatomical and biomechanical changes of the maxillary bone are also discussed.

MATERIALS AND METHODS

This review article was conducted through a search and critical analysis of the existing scientific literature on medication-related osteonecrosis of the jaw (MRONJ). Electronic databases such as PubMed, Scopus, and Google Scholar were consulted to identify relevant published articles, using specific keywords such as drug-induced osteonecrosis of the jaws, MRONJ, bisphosphonates, denosumab, etc. Clinical studies, reviews, and case reports relevant to the etiopathogenesis, risk factors, diagnosis, prevention, and treatment of MRONJ were included, excluding irrelevant articles. The extracted information was organized into thematic categories (definition, mechanisms, drugs, risk factors, clinical aspects, prevention, biomarkers), synthesized, and critically analysed for a comprehensive overview, with attention to gaps and controversies and an assessment of methodological quality.

DISCUSSION

Among the possible hypotheses that could induce MRONJ are: bone remodeling with alteration of osteoclastic/osteoblastic activity and inhibition of angiogenesis with compromised vascularization due to the drugs, immune dysfunction with possible infections, inflammation, and reduced salivation with the presence of constant microtraumas (4,5). Anti-resorptive drugs inhibit the differentiation of osteoclastic cells, which causes apoptosis and leads to a reduction in bone resorption and remodeling. In particular, bisphosphonates, in addition to osteoclasts, also influence the activity of osteoblasts, fibroblasts, and keratinocytes. When the death of fibroblasts affects the oral epithelial cells, there is bone exposure and delayed healing, which plays a key role in the onset and development of osteonecrosis (2). Although the differentiation and function of osteoclasts play an important role in the process of healing and bone remodeling in all skeletal regions, MRONJ mainly occurs only in the alveolar bone of the maxilla and mandible. The high rate of bone resorption in the maxilla explains the different predisposition to the development of MRONJ compared to other portions of the axial and vertical skeleton (6). It has been demonstrated that human jaws have a higher collagen content compared to long bones, and these anatomical characteristics make the mandible more prone to osteonecrosis. 55 Bisphosphonates act on both cytokines responsible for osteoclastogenesis, such as IL-6, IL-17, IL-23, and IFN-γ, suppressing their action, while increasing the activity of anti-osteoclastogenic cytokines such as IL-4, IL-10, and TGF-β. The first to demonstrate that TGF-β signalling is involved in the pathogenesis of MRONJ were Wehrhan et al.; this signalling pathway is crucial for bone remodeling through increased matrix production and osteoblast differentiation (7). Maxillary osteonecrosis occurs more frequently in the mandible (70%) compared to the maxilla (30%). The occurrence of MRONJ is increasing due to the introduction of more and more new drugs, unlike osteoradionecrosis which is in regression as radiotherapy techniques are continuously improving (1,8).

Risk factors

For conditions like MRONJ, it is essential to classify patients according to the risk level of developing the condition, identifying the risk factors; based on this, the patient may have a high, low, or unidentifiable risk.

One class of risk factors are those related to drugs, where the two main classes of drugs are distinguished preventively: anti-resorptive drugs (e.g., denosumab and bisphosphonates) and drugs with anti-angiogenic activity, among these anti-angiogenic drugs, bevacizumab has been associated with the development of osteonecrosis of the jaw in several cases (9). The type of molecule is a variable, as it varies whether they are bisphosphonates, denosumab, or drugs with predominantly anti-angiogenic activity. Bisphosphonates (BP), especially amino-bisphosphonates like zoledronic acid and risedronic acid, possess a high affinity for bone due to the presence of an amino group and a nitrogen-containing heterocyclic ring in the R2 radical. Ibandronate, with nitrogen fractions in the R2 radical, is more potent than alendronate and pamidronate. Denosumab, on the other hand, inhibits the RANK-L complex, reducing osteoclastic activity, but its effects diminish within six months of discontinuation. This drug also alters the cellular inflammatory response, influencing monocytes. Several studies have highlighted the fundamental role of cells (10) and cytokines (11) in the pathogenesis of oral and intestinal inflammation (12) and in cancer development in diagnosis (13,14). It is also important to consider the route of administration, as orally administered drugs undergo initial metabolism at the intestinal and hepatic levels, which reduces their availability in active form in the bloodstream. The drug administered intravenously is introduced into circulation, bypassing any stations that partially inactivate it, so that it is found in greater quantities in its active form in the blood. For this reason, this second category would be more prone to the onset of ONJ. Another factor is the amount of cumulative dose, this parameter is closely related to the drug's retention in the body and the duration of the treatment; bisphosphonates remain in the skeletal system for a long period of time, with a duration of about 10 years, whereas denosumab has a shorter half-life of about 32 days, and its effects on bone resorption gradually diminish within six months after the end of administration (15,16). As a final factor, we have the duration of treatment, which is a significant factor in the onset of bisphosphonate-associated osteonecrosis of the jaw (ONJ), with manifestation times generally within 2 years for intravenous use and tendentially longer for oral use (usually after 3 years). Regarding denosumab, there are conflicting opinions; some studies suggest that the total dose and duration of treatment do not influence the risk of ONJ, with cases reported even after a single administration, while others indicate that prolonged use may increase the risk (17,18). For anti-angiogenic drugs, simultaneous or subsequent administration with bisphosphonates seems to reduce the onset time of ONJ compared to those who take only bisphosphonates. This period becomes even shorter when only anti-angiogenic drugs are used, both via injection (about 6-7 months) and orally (about 16-17 months).

Another class of risk factors are the systemic ones, which we can distinguish into two groups: In the first group, there are those diseases strongly associated with MRONJ for which the patient is forced to take the drugs considered risk factors, including diseases such as multiple myeloma, prostate cancer, and breast cancer from which bone metastases can arise. In the second group, all those conditions that can generate situations of osteopenia/osteoporosis, altering bone metabolism, are included; among such comorbidities are diabetes, chronic renal failure, and rheumatoid arthritis (15). It has been proven that high blood sugar levels can promote an increase in osteoclast differentiation and cause programmed cell death of osteoblasts. Additionally, the increase in osmolarity caused by hyperglycemia suppresses the expression of osteocalcin, MMP-13, and vascular endothelial growth factor (VEGF), which are essential for osteoblast maturation. Additionally, it has been found that AGEs inhibit the adhesion of osteoblasts to the bone matrix, worsening osteopenia (19). Patients with rheumatoid arthritis receive therapies that include anti-inflammatory drugs, immunosuppressants, and anti-resorptive drugs; it is hypothesized that the increased risk of drug-related ONJ is due not only to the disease itself, which involves a predisposing chronic inflammation, but also especially to the combined effects of anti-resorptive/anti-angiogenic agents on bone metabolism and the immunosuppressive effects of polypharmacological therapy (20). Regarding chronic renal insufficiency, it is associated with reduced calcium reabsorption at the renal level, which can cause secondary osteoporosis (15).

Another class, besides those considered the most important risk factors in the onset of ONJ, are the local factors. Regarding dento-alveolar surgery interventions, there is considerable interest in researching a link between practices such as tooth extraction and the onset of maxillary osteonecrosis. In the 2014 summary document by the American Association of Oral and Maxillofacial Surgeons (AAOMS) on medication-related osteonecrosis of the jaw, oral surgical procedures such as tooth extraction are mentioned as a potential risk factor for the onset of MRONJ (1). Many studies consider tooth extraction to be a risk factor, including a longitudinal cohort study conducted by Vahtsevanos et al., which found that out of a total of 1621 patients with breast cancer, prostate cancer, or multiple myeloma treated with bisphosphonates, 4.9% (60 patients) developed osteonecrosis of the jaws. Moreover, tooth extraction has been associated with a 33-fold increase in the risk of developing MRONJ (21). Numerous studies have shown that among patients with osteonecrosis, tooth extraction is a frequent predisposing factor, occurring in 52%-61% of cases (22). Inflammatory periodontal and peri-

implant diseases also fall under chronic inflammatory conditions, creating local irritation that increases the risk of osteonecrosis in patients taking anti-resorptive medications. Therefore, the effective decontamination of implant surfaces, through the use of ultrasonic ablation, electrolytic cleaning and air-abrasive powders, can help reduce the risk of peri-implant inflammation (23,24). In particular, in the bone, chronic inflammation can predispose to tissue necrosis, which occurs both due to the release of chemical mediators such as cytokines, prostaglandins, and growth factors, which contribute to damaging bone cells, and due to the ischaemic action caused by oedema. A large number of bacteria that we encounter in these inflammatory situations present membrane lipopolysaccharides that have a demolitive effect on bone by activating numerous prostaglandins; Among the most relevant bacterial elements is Porphyromonas gingivalis, which has a direct action on RANK-L and osteoprotegerin (15). In confirmation of this, clinical evidence has shown that periodontitis is frequently found in patients with drug-induced osteonecrosis of the jaws and that the extent and severity of periodontitis may be indicative of the risk of developing osteonecrosis (25). Implant therapy is also considered a risk for the onset of osteonecrosis. Not only the surgical procedure of placing dental implants in patients who have received or are receiving antiresorptive therapy, but also the permanence of the bone implants can be linked to the development of osteonecrosis of the jaws. For this reason, two different categories are discussed: the first concerns osteonecrosis following the surgical act of implant insertion (ISTO), and the second is osteonecrosis due to the presence of an already previously osteointegrated implant (IPTO) (26). Certainly, at the present state, it is noteworthy that the majority of per-implant osteonecrosis is not related to the surgical procedure but rather develops on implants that were previously osteointegrated. Moreover, analyses of some reviews highlight that osteonecrosis is more prevalent in those implants that are under functional load (22). IPTO should be considered closely associated with the appearance of inflammatory phenomena such as peri-implantitis, or the presence of microfractures caused by masticatory occlusal load. In fact, unlike natural teeth, there are no ligaments to absorb the impact of occlusal function, and the forces are transmitted to the peri-implant bone, resulting in the formation of microfractures (15). It is important to emphasise that osseointegration can be influenced by various characteristics of the implants. Studies have highlighted how the macro and nanostructure of the surface (27) and the use or non-use of bone grafts (28) play a crucial role in the biological response and bone integration. A new laser microtopography of dental implants has been shown to positively influence human osteoblast proliferation and bone deposition, potentially improving the outcomes of osseointegration (29). Given that MRONJ can have significant consequences and that implant surgery is a highly selective procedure, it is essential to provide adequate counselling and obtain comprehensive informed consent from the patient (30). Furthermore, the use of innovative grafting biomaterials in regenerated sites has shown promising implant survival rates, improving the predictability of these procedures (31). Despite this, new technologies such as fully digital workflows in implant therapy are improving the precision and predictability of procedures, with potential benefits for osseointegration and trauma reduction (32-34). Therefore, we can say that implant osseointegration is a process that requires proper bone metabolism, namely the resorption of old bone and the formation of new bone by osteoclasts and osteoblasts, respectively. Additionally, for these processes, blood supply and consequently proper angiogenesis will be essential. Both of these elements can be blocked by anti-resorptive drugs, which would therefore inhibit them, leading to the early loss of implants (35).

Finally, it is essential to consider the age of the patient. It has been observed that patients under the age of 24 treated with anti-resorptives for non-malignant bone conditions do not present a risk of developing MRONJ, even with prolonged therapies (1). A systematic review from 2017, considering a group of 4,106 cases of MRONJ, highlighted that 61.5% involved female patients, 31.5% male patients, while in the remaining 7%, the patient's sex had not been clarified. The average age of patients at the time of MRONJ diagnosis was recorded as 65 years. The specific location of MRONJ was reported in only 2,973 cases, with involvement of the mandible in 65% of patients, the maxilla in 28%, while in a minority of cases (7%) both jaws were involved (36). The genetic background can also be a risk factor in the case of MRONJ; a mutation of the CBFA1/RUNX2 gene can be a risk factor (37).

Preventive approaches towards MRONJ

Currently, preventive strategies constitute the most effective method to protect the dental health of patients who need to take, are taking, or have taken medications related to maxillary osteonecrosis. Preventive measures for mandibular osteonecrosis are conducted on patients who are about to start or are already taking drugs related to ONJ, but have not yet shown any oral cavity problems. This type of prevention focusses on controlling the risk factors known to date. Furthermore, treatments for the common side effects of anticancer therapies, such as oral mucositis, can be important. A promising approach for the treatment of oral mucositis is the use of platelet-rich fibrin (PRF), which has shown potential benefits in oncological patients" (38). The main objective is to maintain or restore the health of the patient's periodontium and teeth, both in oncological and osteometabolic contexts. Such an approach aims to reduce the likelihood of developing inflammatory or infectious events that could require invasive procedures. The data in the literature show that there is a

higher risk of osteonecrosis in oncological patients compared to patients undergoing treatment for osteometabolic disorders. For this reason, some authors believe that patients not undergoing oncological therapy need a less rigid preventive protocol, and that these types of patients should start dental treatments 6 months before the start of therapy and undergo regular check-ups every 6 months, similar to a subject without pathology. In oncological patients, however, the state of oral health should be arbitrarily checked 6 months before the start of therapy, and check-ups should be strictly performed every 4 months; if there is a need to perform extractions, they should be carried out 6 months before the start of the therapy, and the latter could be postponed until the complete healing of the site (39). Patients are divided into two categories: those who are scheduled to take drugs related to osteonecrosis but have not yet started the therapy, and those who have already started the therapy or have already completed the therapy. It is necessary to consider the dose of the drug that the patient is taking, and especially for how long. Based on this information, we can distinguish between two categories of patients: high risk and low risk. The patient who receives low doses of medication (bisphosphonates taken orally/denosumab 60 mg every 6 months) for a period of less than 4 years is considered, provided there are no additional risk factors, to be at low risk. Regarding patients who take high doses (intravenous bisphosphonates / denosumab 120 mg every 4 weeks), they are considered at high risk of developing osteonecrosis. Low-risk patients in pre-therapy are those who have yet to start treatment with drugs associated with osteonecrosis of the mandible and should undergo a preventive dental visit before starting the treatments, eliminating inflammations or infections, adjusting any prostheses, and maintaining oral hygiene, waiting for the surgical sites to heal completely before starting the therapy. For those already undergoing therapy, it is important to maintain an optimal state of oral health with regular check-ups and conservative interventions such as root canals and periodontal treatments, avoiding unnecessary invasive procedures, although simple extractions can be performed if the treatment has been initiated for less than three years, considering the low risk. Implant therapy can also be considered for these patients but always informing them about the risks and carefully evaluating each case. Essentially, the goal is to adopt preventive measures and constant monitoring to reduce the risk of complications and osteonecrosis. Instead, in patients identified as high risk, the approaches change. For patients in pre-therapy, that is, those who have yet to start treatment with drugs at risk of ONJ, it is essential to conduct a preventive dental evaluation before starting the therapy. This includes a complete mouth examination, X-rays, and conservative interventions such as root canals and prosthetic systems, prioritizing healthy teeth and removing those that are compromised and could become risk factors. All necessary surgical interventions must be completed before the start of therapy, and the tissues must be completely healed, generally after 2 weeks to a month, accompanied by excellent oral hygiene and good adaptability of the prostheses. For patients already undergoing therapy, the risk of osteonecrosis is higher. In these cases, it is important to promptly identify and treat any infections or periapical issues, generally with conservative care and non-surgical endodontic treatments, avoiding invasive procedures if possible. The preservation of teeth through conservative treatments and stabilization is preferable; in some cases, extractions may be necessary, but they should be done with caution and following precise protocols to reduce the risk of developing ONJ. Many researchers have observed the development of several inflammatory processes around teeth, novel dental implant, regenerated maxillary sites with biomaterials. (41,42) Recent sentences have determined the crucial role of the biofilm adhesion and bacterial colonization to promote hard and soft tissues pathogenesis (43,44) with bone loss, gingivitis, periodontitis, carcinogenesis, mucositis and peri-implantitis consequences related to the immune-cells genetic (45, 46) and cytokines cascade activation. (47)

In this context, innovative alveolar preservation techniques have been developed that demonstrate promising results in improving clinical outcomes and potentially facilitating subsequent implant placement (40). Furthermore, preventive measures can be adopted such as the use of biomarkers (e.g., sCTX) to assess bone risk, adhering to strict surgical protocols, and, if indicated, temporarily suspending high-risk medications before surgical interventions, under medical supervision, to improve prognosis and reduce incidents of osteonecrosis (48).

Biomarkers

It is widely recognized that the development of MRONJ is closely linked to the decrease in bone turnover. This condition can be monitored through various biomarkers that reflect the levels of bone resorption and formation. Numerous studies have identified various potentially useful biomarkers for predicting the onset of MRONJ, such as bone-specific alkaline phosphatase (BAP), parathyroid hormone (PTH), osteocalcin (OC), type 1 collagen amino-terminal propeptide (P1NP), and others; among these, the C-terminal telopeptide of type I collagen (CTX) has been the most studied. The evaluation of serum levels of the C-terminal telopeptide, which is the degradation product of the carboxy-terminal portion of the non-helical regions of type I collagen, by the action of osteoclastic cathepsin K, is a predictor of the risk of developing osteonecrosis of the jaws; in fact, its study provides a value that indicates osteoblastic and osteoclastic activity. The value that many researchers consider as the threshold is 150 pg/ml; in fact, above this value the doctor can perform surgical therapy, as the risk is minimal; instead, in situations where the values are equal to or below 100 pg/ml, the higher

risk of developing osteonecrosis must be taken into consideration; for values between 100 and 150 pg/ml, the risk is moderate. Some authors recommend discontinuing the drug for values below 150 pg/ml. Bone turnover and angiogenesis biomarkers are considered ideal for this assessment, as they could contribute to more effective preventive strategies. Several cross-sectional studies have attempted to explore the predictive value of these markers, but so far there is insufficient scientific evidence to support the use of such biomarkers to assess the risk of MRONJ (49). The use of predictive biomarkers would represent a significant advancement for patients taking drugs associated with osteonecrosis; however, in the literature, there are no data that significantly support a certain correlation between these markers and the risk of developing osteonecrosis of the jaws (50).

CONCLUSIONS

In conclusion, MRONJ represents a complex and debilitating multifactorial pathology associated with the use of anti-resorptive and anti-angiogenic drugs. The etiopathogenesis involves alterations in bone remodeling, osteoclastic activity, vascularization, and immune response. Pharmacological risk factors (type of drug, route of administration, dose, duration), systemic factors (comorbidities, immune status), and local factors (invasive dental procedures, chronic inflammations) play a crucial role. Prevention, through a meticulous risk assessment, optimization of oral health, and the adoption of minimally invasive surgical protocols, represents the most effective strategy. The use of biomarkers for risk stratification is promising but requires further validation. Further prospective and controlled studies are necessary to clarify the pathogenetic mechanisms, identify reliable predictive biomarkers, and evaluate the effectiveness of innovative therapeutic strategies, in order to improve the management of this complex pathology and preserve the quality of life of at-risk patients.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72(10):1938-1956. doi:10.1016/j.joms.2014.04.031.
2. Lončar Brzak B, Brkić H, Barišić I, et al. Osteonecrosis of the jaw. Dent J (Basel). 2023;11(1):23. doi:10.3390/dj11010023.
3. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. *J Int Soc Prev Community Dent*. 2016;6(2):97-104. doi:10.4103/2231-0762.178742.
4. Landì L, Tranquilli Leali P, Barbato L, et al. Anti-resorptive therapy in osteometabolic patients affected by periodontitis: Joint position paper of the Italian Society of Orthopaedics and Traumatology (SIOT) and the Italian Society of Periodontology and Implantology (SIdP). Punto Su. 2023;6(2):1-10. doi:10.32050/0390-0134-N303.
5. Kün-Darbois JD, Fauvel F. Medication-related osteonecrosis and osteoradionecrosis of the jaws: update and current management. Morphologie. 2021;105(349):170-187. doi:10.1016/j.morpho.2020.11.008.
6. He L, Sun X, Liu Z, et al. Pathogenesis and multidisciplinary management of medication-related osteonecrosis of the jaw. Int J Oral Sci. 2020;12(1):30. Published 2020 Oct 21. doi:10.1038/s41368-020-00093-2.
7. Wehrhan F, Hyckel P, Guentsch A, et al. Bisphosphonate-associated osteonecrosis of the jaw is linked to suppressed TGFβ1-signaling and increased Galectin-3 expression: a histological study on biopsies. *J Transl Med*. 2011;9:102. doi:10.1186/1479-5876-9-102.
8. Woo SB, Hellstein JW, Kalmar JR. Narrative (corrected) review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144(10):753-761. doi:10.7326/0003-4819-144-10-200605160-00009.
9. Serra E, Paolantonio M, Spoto G, Mastrangelo F, Tetè S, Dolci M. Bevacizumab-related osteonecrosis of the jaw. Int J Immunopathol Pharmacol. 2009;22(4):1121-1123. doi:10.1177/039463200902200429.
10. Lauritano D, Mastrangelo F, D'Ovidio C, et al. Activation of Mast Cells by Neuropeptides: The Role of Pro-Inflammatory and Anti-Inflammatory Cytokines. Int J Mol Sci. 2023;24(5):4811. Published 2023 Mar 2. doi:10.3390/ijms24054811.
11. Tettamanti L, Kritas SK, Gallenga CE, et al. IL-33 mediates allergy through mast cell activation: Potential inhibitory effect of

certain cytokines. J Biol Regul Homeost Agents. 2018;32(5):1061-1065.

12. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in mucosal immunity of intestinal inflammation: Inhibitory effect of IL-37. Eur J Pharmacol. 2018;818:294-299. doi:10.1016/j.ejphar.2017.09.044.
13. Minetti E, Palermo A, Ferrante F, et al. Autologous tooth graft after endodontically treated used for socket preservation: a multicenter clinical study. Appl Sci. 2019;9(24):5396. doi:10.3390/app9245396.
14. Pomella S, Melaiu O, Dri M, et al. Effects of Angiogenic Factors on the Epithelial-to-Mesenchymal Transition and Their Impact on the Onset and Progression of Oral Squamous Cell Carcinoma: An Overview. Cells. 2024;13(15):1294. doi:10.3390/cells13151294.
15. Campisi G, Bedogni A, Fusco V; Società Italiana di Chirurgia Maxillo-Facciale; Società di Patologia e Medicina Orale. Clinical and therapeutic recommendations on medication-related osteonecrosis of the jaw (ONJ) and its prevention. New Digital Press; 2020. ISBN: 9788855091473.
16. Fusco V, Santini D, Armento G, Tonini G, Campisi G. Osteonecrosis of jaw beyond antiresorptive (bone-targeted) agents: new horizons in oncology. Expert Opin Drug Saf. 2016;15(7):925-935. doi:10.1080/14740338.2016.1177021.
17. de Oliveira CC, Brizeno LA, de Sousa FB, Mota MR, Alves AP. Osteonecrosis of the jaw induced by receptor activator of nuclear factor-kappa B ligand (Denosumab) - Review. Med Oral Patol Oral Cir Bucal. 2016;21(4):e431-e439. Published 2016 Jul 1. doi:10.4317/medoral.21044.
18. Watts NB, Grbic JT, Binkley N, et al. Invasive Oral Procedures and Events in Postmenopausal Women With Osteoporosis Treated With Denosumab for Up to 10 Years. J Clin Endocrinol Metab. 2019;104(6):2443-2452. doi:10.1210/jc.2018-01965.
19. Peer A, Khamaisi M. Diabetes as a risk factor for medication-related osteonecrosis of the jaw. J Dent Res. 2015;94(2):252-260. doi:10.1177/0022034514560768.
20. Di Fede O, Bedogni A, Giancola F, et al. BRONJ in patients with rheumatoid arthritis: a multicenter case series. Oral Dis. 2016;22(6):543-548. doi:10.1111/odi.12490.
21. Vahtsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol. 2009;27(32):5356-5362. doi:10.1200/JCO.2009.21.9584.
22. Escobedo MF, Cobo JL, Junquera S, Milla J, Olay S, Junquera LM. Medication-related osteonecrosis of the jaw. Implant presence-triggered osteonecrosis: Case series and literature review. J Stomatol Oral Maxillofac Surg. 2020;121(1):40-48. doi:10.1016/j.jormas.2019.04.012.
23. Gianfreda F, Bollero P, Muzzi M, di Giulio A, Nicolai E, Canullo L. The effects of ultrasonic scaling and air-abrasive powders on the decontamination of 9 implant-abutment surfaces: scanning electron analysis and in vitro study. Dent J. 2022;10(3):36. doi:10.3390/dj10030036.
24. Gianfreda F, Punzo A, Pistilli V, et al. Electrolytic Cleaning and Regenerative Therapy of Peri-implantitis in the Esthetic Area: A Case Report. Eur J Dent. 2022;16(4):950-956. doi:10.1055/s-0042-1750773.
25. Troeltzsch M, Zeiter S, Arens D, et al. Chronic Periodontal Infection and Not Iatrogenic Interference Is the Trigger of Medication-Related Osteonecrosis of the Jaw: Insights from a Large Animal Study (PerioBRONJ Pig Model). Medicina (Kaunas). 2023;59(5):1000. Published 2023 May 22. doi:10.3390/medicina59051000.
26. Giovannacci I, Meleti M, Manfredi M, et al. Medication-Related Osteonecrosis of the Jaw Around Dental Implants: Implant Surgery-Triggered or Implant Presence-Triggered Osteonecrosis?. J Craniofac Surg. 2016;27(3):697-701. doi:10.1097/SCS.0000000000002564.
27. Tetè S, Mastrangelo F, Traini T, et al. A macro- and nanostructure evaluation of a novel dental implant. Implant Dent. 2008;17(3):309-320. doi:10.1097/ID.0b013e318182d494.
28. Mastrangelo F, Gastaldi G, Vinci R, Troiano G, Tettamanti L, Gherlone E, Lo Muzio L. Immediate Postextractive Implants With and Without Bone Graft: 3-year Follow-up Results From a Multicenter Controlled Randomized Trial. Implant Dent. 2018 Dec;27(6):638-645. doi: 10.1097/ID.0000000000000816.
29. Mastrangelo F, Quaresima R, Canullo L, Scarano A, Muzio LL, Piattelli A. Effects of Novel Laser Dental Implant Microtopography on Human Osteoblast Proliferation and Bone Deposition. Int J Oral Maxillofac Implants. 2020;35(2):320-329. doi:10.11607/jomi.7606.

30. Otto S. Medication-Related Osteonecrosis of the Jaws. Springer Berlin Heidelberg; 2015. doi:10.1007/978-3-662-43733-9.
31. Minetti E, Celko M, Contessi M, et al. Implants Survival Rate in Regenerated Sites with Innovative Graft Biomaterials: 1 Year Follow-Up. Materials (Basel). 2021;14(18):5292. Published 2021 Sep 14. doi:10.3390/ma14185292.
32. Gianfreda F, Pesce P, Marcano E, Pistilli V, Bollero P, Canullo L. Clinical Outcome of Fully Digital Workflow for Single-Implant-Supported Crowns: A Retrospective Clinical Study. Dent J (Basel). 2022;10(8):139. Published 2022 Jul 27. doi:10.3390/dj10080139.
33. Grassi A, Monica D, Minetti E, et al. Innovative Alveolar Ridge Preservation Surgical Technique with Immediate Dental Implant Placement: A Retrospective Case Report of 1-Year Follow-Up. Eur J Dent. 2024;18(1):408-414. doi:10.1055/s-0043-1772676.
34. Canullo L, Iacono R, Godoy E, et al. Hybrid funnel technique: a novel approach for implant site preparation: a pilot study. Dent J. 2022;10(9):157. doi:10.3390/dj10090157.
35. Sher J, Kirkham-Ali K, Luo JD, Miller C, Sharma D. Dental Implant Placement in Patients With a History of Medications Related to Osteonecrosis of the Jaws: A Systematic Review. J Oral Implantol. 2021;47(3):249-268. doi:10.1563/aaid-joi-D-19-00351.
36. McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: A systematic review. Oral Dis. 2018;24(4):527-536. doi:10.1111/odi.12708.
37. Lo Muzio L, Tetè S, Mastrangelo F, et al. A novel mutation of gene CBFA1/RUNX2 in cleidocranial dysplasia. Ann Clin Lab Sci. 2007;37(2):115-120.
38. Miranda M, Gianfreda F, Rosa A, et al. Treatment of Oral Mucositis Using Platelet-Rich-Fibrin: A Retrospective Study on Oncological Patients. J Craniofac Surg. 2023;34(5):1527-1529. doi:10.1097/SCS.0000000000009450.
39. Weitzman R, Sauter N, Eriksen EF, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients--May 2006. Crit Rev Oncol Hematol. 2007;62(2):148-152. doi:10.1016/j.critrevonc.2006.12.005.
40. Raffone C, Gianfreda F, Antonacci D, Pompeo MG, Bollero P, Canullo L. Chairside virtual patient protocol. Part 3: In vitro accuracy of a digital facebow. J Dent. 2023;137:104622. doi:10.1016/j.jdent.2023.104622.
41. Conti P, Caraffa A, Ronconi G, et al. Mast cells participate in allograft rejection: can IL-37 play an inhibitory role? Inflamm Res. 2018;67(9):747-755. doi:10.1007/s00011-018-1166-3
42. Mastrangelo F, Dedola A, Cattoni F, et al. Etiological periodontal treatment with and without low-level laser therapy on IL-1β level in gingival crevicular fluid: an in vivo multicentric pilot study. J Biol Regul Homeost Agents. 2018;32(2):425-431.
43. Tettamanti L, Kritas SK, Gallenga CE, et al. IL-33 mediates allergy through mast cell activation: Potential inhibitory effect of certain cytokines. J Biol Regul Homeost Agents. 2018;32(5):1061-1065.
44. Sammartino G, Marenzi G, Tammaro L, et al. Anti-inflammatory drug incorporation into polymeric nano-hybrids for local controlled release. Int J Immunopathol Pharmacol. 2005;18(3 Suppl):55-62.
45. Tranasi M, Sberna MT, Zizzari V, et al. Microarray evaluation of age-related changes in human dental pulp. J Endod. 2009;35(9):1211-7. doi: 10.1016/j.joen.2009.05.026.
46. Carinci F, Arcelli D, Lo Muzio L, et al. Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. Transl Res. 2007;150(4):233-245. doi:10.1016/j.trsl.2007.03.011
47. Grassi A, Monica D, Minetti E, et al. Innovative Alveolar Ridge Preservation Surgical Technique with Immediate Dental Implant Placement: A Retrospective Case Report of 1-Year Follow-Up. Eur J Dent. 2024;18(1):408-414. doi: 10.1055/s-0043-1772676.
48. Schwartz HC. Serum CTX testing. J Oral Maxillofac Surg. 2008;66(6):1319-1320. doi:10.1016/j.joms.2007.12.048.
49. Matus-Miranda G, Mancilla A, Martinez R, et al. Utility of biomarkers in predicting the development of medication-related osteonecrosis of the jaws: a scoping review. J Oral Maxillofac Surg Med Pathol. 2023;36:e10.1016/j.ajoms.2023.09.001.
50. Lee CY, Suzuki JB. CTX biochemical marker of bone metabolism. Is it a reliable predictor of bisphosphonate-associated osteonecrosis of the jaws after surgery? Part II: a prospective clinical study. Implant Dent. 2010;19(1):29-38. doi:10.1097/ID.0b013e3181cec8bc.

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Article

OSTEONECROSIS OF THE JAWS. ANALYSIS OF RISK FACTORS AND DENTAL MANAGEMENT STRATEGIES- PART II

M. Scarpati Cioffari di Castiglione[1], S. Lauri[2*], C. Moscetta[3], F. Ferrantini[4], L.M. Laudiero[4], G.M. Granata[4], V.M. Spadoni[4] and I. Mastrorilli[5]

[1] Independent researcher, 81021, Caserta, Italy;
[2] Independent researcher, 00073, Rome, Italy;
[3] Independent researcher, 03018, Frosinone, Italy;
[4] Department of System Medicine, University of Rome "Tor Vergata", Rome, Italy;
[5] Independent Researcher, 00135, Rome, Italy.

**Correspondence to*:
Simone Lauri,
Independent Researcher,
00073, Rome, Italy.
e-mail: laurisimone1@gmail.com

ABSTRACT

Introduction: Medication-related osteonecrosis of the jaw (MRONJ) presents a significant clinical challenge due to the increasing use of anti-resorptive drugs. Characterized by exposed necrotic bone, pain, and infection, MRONJ requires a multidisciplinary approach. This review aims to synthesize current evidence and emerging innovations in the surgical and medical management of MRONJ. *Materials and Methods:* A critical review of the existing scientific literature on MRONJ was conducted, using electronic databases such as PubMed, Scopus, and Google Scholar. Extracted information was organized by thematic categories, synthesized, and critically analyzed for a comprehensive overview. *Discussion:* The surgical protocol involves careful preoperative evaluation, professional oral hygiene, and the use of antiseptic mouthwashes. Surgical techniques range from debridement and curettage to aggressive resection, with the aim of completely removing necrotic tissue. New protocols integrate laser photobiomodulation, platelet-rich plasma, and deferoxamine to promote tissue regeneration. Suspension of anti-resorptive therapy, in agreement with the attending physician, is crucial. Treatment can be surgical and non-surgical. *Conclusions:* Optimal management of MRONJ requires a personalized, multidisciplinary approach. Implementing preventive protocols, early diagnosis, and adopting updated treatments, combining conservative and surgical strategies, are key to reducing the incidence of MRONJ and improving the quality of life for affected patients.

KEYWORDS: *MRONJ, bisphosphonate, regenerative therapy, oral surgery, therapeutic innovation*

INTRODUCTION

The management of medication-related osteonecrosis of the jaw (MRONJ) has become an increasingly important focus within oral and maxillofacial surgery and related medical fields, due to the widespread use of antiresorptive agents such as bisphosphonates and denosumab, as well as other targeted therapies (1). Characterized by exposed necrotic bone in the maxillofacial region that persists for more than eight weeks and is often associated with pain, infection, and impaired healing, MRONJ represents a significant clinical challenge that affects patients' quality of life and complicates various dental and surgical procedures (2). Over the years, our understanding of MRONJ has evolved from viewing it primarily as a surgical problem to recognizing its multifactorial pathogenesis involving impaired bone remodeling, vascular

Received: 04 September, 2025
Accepted: 27 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

damage, and inflammatory processes, which necessitates a multidisciplinary approach to treatment (3). Several studies have highlighted the fundamental role of cells (4) and cytokines (5) in the pathogenesis of oral and intestinal inflammation (6) and in cancer development for diagnosis (7-9). Traditional conservative therapies, focused on antimicrobial management and symptom control, have been integrated and, in many cases, replaced by increasingly sophisticated surgical interventions aimed at removing necrotic tissue and promoting regeneration. Advances in imaging, digital workflow planning, and minimally invasive surgical techniques have paved the way for more precise and effective treatments (10). In addition to conventional surgical and pharmacological methods, recent developments have introduced innovative additional therapies that utilize regenerative medicine, laser biostimulation, and bioengineering strategies. Techniques such as laser photobiomodulation, platelet-rich plasma, deferoxamine, hyperbaric oxygen therapy, and the application of growth factors like BMP-2 are increasingly integrated into treatment protocols to stimulate tissue regeneration, reduce inflammation, and improve healing outcomes (11). Additionally, emerging approaches involving biomaterials such as human amniotic membranes and nanoscale drug delivery systems offer promising future directions in the fight against MRONJ (12). This review aims to synthesize current evidence and emerging innovations in the surgical and medical management of MRONJ, highlighting protocols for preoperative planning, surgical techniques, and adjuvant therapies. By understanding these evolving strategies, clinicians can better adapt treatment plans, reduce morbidity, and improve the prognosis for patients affected by this debilitating condition.

MATERIALS AND METHODS

This review article was created through a critical search and analysis of the existing scientific literature on drug-induced osteonecrosis of the jaw (MRONJ). Electronic databases such as PubMed, Scopus, and Google Scholar were consulted to identify relevant published articles, using specific keywords such as mandibular osteonecrosis, drug-induced mandibular osteonecrosis, pharmacological treatment of mandibular osteonecrosis, and surgical treatment of mandibular osteonecrosis. Clinical studies, reviews, and case reports relevant to the aetiology, risk factors, diagnosis, prevention, and treatment of MRONJ were included, excluding irrelevant articles. The extracted information was organized into thematic categories (definition, mechanisms, drugs, risk factors, clinical aspects, prevention, biomarkers), synthesized, and critically analysed for a comprehensive overview, with attention to gaps and controversies and an assessment of methodological quality.

DISCUSSION

Surgical protocol

After conducting a thorough clinical evaluation and analyzing the patient's medical history, if it is decided to proceed with surgery to remove an infectious focus, it is essential to follow a strict protocol. In cases of MRONJ requiring extensive resections, preoperative planning is essential to guide reconstruction and prosthetic rehabilitation. To this end, advanced digital workflows can be employed. The use of digital facebows has demonstrated high precision in vitro, facilitating the creation of accurate diagnostic models and surgical guides (13,14). Before the intervention, it is necessary to undergo a thorough professional oral hygiene session, preferably two or three weeks before the operation, to eliminate any infectious foci that could complicate the postoperative period. It is also important to use a 0.2% alcohol-free chlorhexidine mouthwash, which should be used a few weeks before the procedure and also one minute before the procedure, to reduce the bacterial load. Surgically, it is necessary to close with first intention sutures, and during the procedure, one should try to keep the intervention as minimally invasive as possible, avoiding trauma and attempting to remove granulation tissue with minimal invasiveness. Immediately afterwards, the area is washed with antibacterial solutions for about two minutes to further reduce the presence of bacteria (15). Regarding antibiotic prophylaxis, specific regimens are generally recommended, although there is no single uniform protocol; Commonly, penicillins such as amoxicillin (1 gramme three times a day), with or without clavulanic acid, are used in combination with metronidazole (500 mg three times a day) to cover a wide range of bacteria. In case of penicillin allergy, alternatives such as erythromycin, clindamycin, or ciprofloxacin can be used, with dosages and administration times adjusted based on the presence or absence of suppuration at the treatment site. If there are no infections or pus formation, the antibiotic can be started the day before the procedure and continued for about 7-10 days; If there are signs of suppuration, it should be started about a week before extraction and continued for 7-10 days.

New Protocols to Reduce Risk

Recently, thanks to significant advancements in medical technology, new surgical protocols have emerged that utilize laser photobiomodulation (Nd:YAG, diode laser), the use of non-transfusional blood components (such as PRP), and the use of deferoxamine.

Platelet-rich plasma (PRP) is an autologous concentration of platelets obtained by centrifuging the patient's blood, also containing inflammatory cells such as monocytes and neutrophils, and rich in proteins with growth factors like PDGF, TGF-β, VEGF, and EGF. These elements promote recruitment, cell proliferation, and the formation of new blood vessels, contributing to tissue regeneration and healing processes (16,17).

Laser Photobiomodulation in oral surgery helps reduce pain and inflammation and promotes wound healing by improving cellular activity and altering the permeability of cell membranes. It works by increasing the hyperpolarization state of nerve endings, thus inhibiting pain transmission to the central nervous system and reducing the activity of mediators such as prostaglandins, interleukins, tumour necrosis factor, and cyclooxygenase (18).

Deferoxamine (DFO) is a medication used in iron poisoning and to accelerate the healing of pathological fractures after radiotherapy, as it inhibits the enzyme prolyl hydroxylase, promoting the formation of new blood vessels through the stimulation of VEGF. Experimental studies, including those on rodents, suggest that local application of DFO via gelatin sponges can improve bone regeneration, promote neovascularization, and offer protection against MRONJ, accelerating healing after tooth extraction (19).

Suspension of therapy

The therapy suspension strategy aims to reduce the accumulation of anti-resorptive drugs at the surgical site, promoting an improvement in healing conditions. In the case of bisphosphonates, their long half-life can prolong their effects on bone even after a single administration, particularly in cancer patients with bone metastases or multiple myeloma. For this reason, it is recommended to discontinue them at least one week before surgery and to stop therapy for at least three months, depending on clinical conditions, in close consultation with the treating physician (15). For denosumab, which has a short and dose-dependent half-life, discontinuation should occur at least 21 days before invasive procedures, with therapy able to be resumed after 4-6 weeks (20). If the treatment is aimed at osteometabolic disorders, such as Prolia, it is recommended to perform the procedures at least 3 weeks after the last administration and to resume the medication at least one month after the surgery, preferably after the fifth month from the last dose if not urgent. Anti-angiogenic drugs, such as Bevacizumab, also benefit from preoperative suspensions (21). It is advisable to discontinue them at least 5-8 weeks before surgery to allow for complete elimination from the body and reduce the antiangiogenic effect, minimizing the risk of complications and improving the chances of optimal healing. The drug should be resumed at least 28 days after the surgery. For tyrosine kinase or m-TOR inhibitors, which have a known half-life, it is suggested that invasive procedures be performed at least one week after the last administration (22).

Treatment

When we talk about the treatment of medication-related osteonecrosis of the jaw, we are faced with two possible therapeutic options: surgical therapy and non-surgical therapy.

Non-surgical therapy

Non-surgical therapy primarily focusses on the use of medications to control the infectious process and alleviate pain, with the aim of slowing the progression of the disease and stabilizing its symptoms. This approach proves particularly effective in the early stages of the disease, while it is less useful in the advanced stages. This class of therapy includes a subset of treatments. Pharmacological pain management is a fundamental component, as the pain can be intense and persistent, significantly limiting the patient's quality of life. In such cases, the use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, or ketamine is recommended, to be administered under the supervision of specialists to avoid the risk of toxicity (23). At the same time, antiseptic therapy is used with mouthwashes containing chlorhexidine digluconate, available in 0.12% alcohol-free concentrations or 0.20% containing alcohol. It is recommended to use these mouthwashes for a maximum of two weeks, preferably one week before and one week after any surgical procedure, to reduce bacterial load and prevent complications. In patients for whom surgical treatment is not possible, or in cases of refractory MRONJ, maintenance therapy with chlorhexidine twice daily for one month can be used. Alternatively, to chlorhexidine, other disinfectants such as hydrogen peroxide or baking soda solution can be used (24). Antibiotic therapy plays a key role in managing the infection that characterizes this condition. However, the exclusive use of antibiotics is not sufficient to completely resolve the problem, but it proves useful in controlling infectious exacerbations or in patients with complications that prevent more invasive treatments.

The typical therapeutic strategy involves a combination of penicillins and metronidazole, administered for 7-14 days. In case of allergy to these molecules, alternatives such as erythromycin, clindamycin, or ciprofloxacin are chosen.

Surgical therapy

Therapeutic strategies for drug-induced osteonecrosis of the jaw have changed over time due to the accumulation of new knowledge and clinical experience, leading to an increasing recognition of the importance of surgical therapy. For many years, this method was considered a second-line option, reserved primarily for the most severe forms or those unresponsive to conservative treatments. However, in recent years, numerous experts have suggested considering surgery even in the early stages of the disease, with the aim of stopping its progression as soon as possible. Numerous studies show that the surgical approach can achieve better results compared to conservative therapies, as it allows for the complete removal of necrotic tissue, promoting the formation of healthy tissue and thus accelerating bone healing. It is essential to completely and safely remove the necrotic tissue, precisely defining the margins of the lesion's extent through both intraoperative assessments and preoperative radiological examinations. During the procedure, observing bone bleeding is a common method for identifying viable bone, while a fluorescent lamp can also be used, which exploits the different fluorescence between viable bone and necrotic bone (25,26). Surgical treatment for MRONJ includes various techniques such as debridement, curettage, sequestrectomy, and resection, with or without microvascular reconstruction. According to the literature, bone curettage without extension and sequestrectomy are considered part of conservative surgical treatment, while a more extensive or complete resection of the necrotic lesion, with or without microvascular reconstruction, is classified as aggressive surgical treatment (27).

i. Conservative surgical treatment: The main objective of conservative treatment is the complete removal of necrotic tissue, extending as far as possible towards the surrounding tissue which, macroscopically and radiographically, appears healthy and well-vascularized. It is essential to avoid interrupting the continuity of the mandibular body and extending into the paranasal sinuses. The treatment concludes with the repositioning and suturing of the mucosal flaps, closing by first intention to prevent bacterial entry and promote healing.
ii. Bone curettage: This treatment involves the removal of necrotic bone tissue until a bleeding bone surface is reached, followed by the complete closure of the defect through the mobilization of a mucoperiosteal flap. This procedure is performed under local anesthesia and can be carried out using rotary burs or less invasive instruments like sonic instruments. It is important to emphasize that during curettage, the necrotic tissue should not yet be completely separated from the surrounding viable bone; Otherwise, it would be a sequestrectomy. To promote a good outcome, osteoplasty of the bone surface can also be performed to eliminate residual roughness and facilitate site closure (28).
iii. Sequestrectomy: allows for the removal of the sequestrum, a necrotic portion that separates spontaneously from healthy bone and is expelled naturally or through surgery. The procedure involves the removal of necrotic tissue affecting the alveolar process, followed by osteoplasty and closure with a mucoperiosteal flap (29).
iv. Aggressive surgical treatment: Resective surgery represents the most invasive and radical strategy. The goal is to remove all the diseased bone tissue until healthy and viable tissue is reached. It is essential to perform marginal osteoplasty, utilizing full-thickness flap mobilization to ensure primary intention closure of the defect. The difference between resection techniques lies in the fact that marginal resection preserves the continuity of the bone segment, removing only the block of necrotic tissue, while segmental resection involves the interruption of the bone segment. To preserve alveolar bone volume and support the implant site, various studies have described innovative surgical techniques for alveolar ridge preservation with immediate dental implant placement (30,31), while others have focused on the effectiveness of electrolytic cleaning and regenerative therapy in the treatment of peri-implantitis (32). Moreover, employing innovative graft biomaterials has been shown to positively influence implant survival rates in regenerated sites (33). The standard procedure for treating the mandible is mandibulectomy, which unfortunately always results in a loss of facial symmetry and occlusion. It is widely accepted that when a full-thickness defect is created in the mandible, it is important to immediately reconstruct the bone continuity to restore facial shape and ensure the best functional recovery. Following mandibulectomy, the reconstruction of mandibular integrity can be achieved through the use of a titanium plate to replace the removed bone, anatomical replicas of the mandible, or alternatively, through the use of vascularized bone flaps (34).

Additional therapies

The evolution of therapeutic strategies for managing MRONJ has led to greater emphasis on the use of innovative and multimodal approaches.

Among these, treatment with teriparatide has shown promise, thanks to the short-term benefits observed in clinical trials. This recombinant human protein, consisting of the 1-34 portion of parathyroid hormone (rhPTH 1-34), is the only FDA-approved anabolic therapy for the treatment of severe osteoporosis. Its action promotes osteoblastic activity, stimulating the formation of new bone tissue and improving radiographic signs of healing. Although the hormone can have both anabolic and catabolic effects on bone, intermittent exposure stimulates its formation, contributing to increased bone mass and offering a promising therapeutic context even in cases of MRONJ, with potential reparative effects on maxillary bone defects (35).

In both surgical and conservative settings, the use of low-intensity laser has been successfully recognized as an effective complementary treatment in both the medical and surgical management of MRONJ. Different laser wavelengths have demonstrated a biostimulating effect, improving repair processes and promoting bone growth, osteoblast mitotic activity, and the development of blood and lymphatic vessels. Studies have indicated that LLLT (Low-Level Laser Therapy) promotes bone healing in traumatic areas and increases mineralization during regeneration processes, stimulating the activity and differentiation of osteoblasts. Additionally, it has been observed that laser biostimulation could also be beneficial in the treatment of "early" forms of MRONJ, offering a safe, minimally invasive, and well-tolerated therapeutic option. In conservative surgery, the laser can target necrotic bone, vaporizing it until healthy bone is reached. In these cases, the Er:YAG laser (2,940 nm) is used, a laser that gently penetrates only 0.1 mm, ensuring a highly conservative and precise treatment is performed (36,37). Instead, for adequate implant therapy, an innovative technique called the "Hybrid Funnel Technique" has recently been proposed, which aims to optimize implant site preparation by minimizing trauma and preserving local vascularization. A pilot study explored the effectiveness of this technique, suggesting potential benefits in terms of osseointegration and soft tissue healing (38). It is important to note that implant surface microtopography can play a crucial role in the success of osseointegration. Recent studies have demonstrated that laser microtopographies can promote osteoblast proliferation and bone deposition, potentially improving long-term implant outcomes (39).

Another strategy to use is hyperbaric oxygen therapy and ozone therapy, which are two complementary therapies frequently employed as neoadjuvant or adjuvant interventions in the treatment of advanced mandibular osteonecrosis, particularly in cases where bone healing is compromised and invasive surgical procedures, such as maxillary resections or microvascular reconstructions, are not indicated or are contraindicated. Various scientific evidence suggests that these approaches could offer significant benefits, improving the chances of resolution and recovery in patients affected by this complex condition. Hyperbaric oxygen therapy involves inhaling pure oxygen in pressurized chambers where the air pressure exceeds atmospheric pressure (40,41). This non-invasive treatment causes an increase in reactive nitrogen and oxygen species, which promote the production of substrates necessary for the enzyme nitric oxide synthase. These mediators play a crucial role in bone metabolism by modulating the activity of osteoclasts and osteoblasts. Specifically, nitric oxide is produced constitutively by both the latter and the former, and its role in the bone process is characterized by dual effects depending on the concentrations. At moderate levels, nitric oxide promotes bone turnover, contributing to the replacement of old bone tissue with new and reducing bone resorption, thus facilitating the restoration of physiological balance. However, at higher concentrations, its role becomes more complex and can be detrimental, promoting inflammatory processes in bone tissue and contributing to the progression of conditions like osteoporosis. An excessive increase in this reactive species can also inhibit the formation of new bone tissue, interfering with the regeneration and repair of damaged tissues. Reactive oxygen species (ROS), produced during hyperbaric oxygen therapy, appear to positively influence bone homeostasis by modulating the expression of key factors such as RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) and osteoprotegerin. This regulation promotes the controlled differentiation of osteoclasts, contributing to an optimal balance between bone formation and resorption and reducing the risk of pathological conditions such as osteopetrosis, which is often present in animal models of osteonecrosis. An emerging hypothesis suggests that ROS generated during hyperbaric oxygen (HBO) treatment may exert a beneficial effect by suppressing osteoclast activity and promoting bone healing processes, thanks to the modulation of the local environment and the stimulation of tissue regeneration. Several studies showed how inflammatory processes (42,43) around teeth (44,45), novel dental implant, regenerated maxillary sites with biomaterials (46), derived from biofilm adhesion and bacterial colonization (42), promote hard and soft tissues pathogenesis (43) as bone loss, gingivitis, periodontitis, carcinogenesis, (47,48) mucositis and peri-implantitis related to the immune-cells genetic and cytokines cascade activation. (42,43,49) These effects, although still under investigation, open up interesting therapeutic prospects for the use of this technology in complex cases of osteonecrosis, where the primary goal is to promote bone repair and recovery

through a biochemical action that enhances the natural tissue response (50). Ozone therapy has shown promising results in the treatment of MRONJ, acting as an effective biostimulation method to enhance the repair processes in the affected area. This therapy is known for its ability to hinder the growth of microorganisms (bacteria, fungi, and viruses), stimulate blood circulation, and increase the amount of oxygen in tissues. Additionally, ozone can help reduce pain and improve local immune activity. Ozone application can be done through two main methods: insufflations obtained with special equipment or through the use of ozonated oil. Studies in the literature suggest that this therapy promotes neoangiogenesis and stimulates the immune system, facilitating the formation of granulation tissue that demarcates the area of bone necrosis and contributes to the healing of the tissues involved (15). The use of BMP-2 (bone morphogenetic protein-2) represents a promising therapeutic option in the treatment of MRONJ. Originally approved by the Food and Drug Administration (FDA) for applications such as maxillary sinus augmentation and alveolar preservation, the recombinant form of human BMP-2 (rhBMP-2) has been shown to possess broader osteoinductive properties. Given the excessive suppression of bone remodeling typical of MRONJ, it is hypothesized that BMPs can stimulate the formation of new bone tissue and promote the healing process. Studies on post-sequestrectomy sites treated with rhBMP-2/ACS have demonstrated a significant increase in bone regeneration, suggesting effective potential in treating the condition, although official FDA approval is still lacking at this time. This therapy is expected to play a significant role in the future as well (51).

A final innovative strategy involves the use of human amniotic membrane, rich in epithelial and mesenchymal stromal cells, along with various growth factors such as EGF, FGF, and TGF. This membrane is distinguished by its biocompatibility, permeability, stability, elasticity, and reabsorbability. It has antimicrobial, anti-inflammatory, antifibrotic, and analgesic effects, and has been shown to promote neovascularization, encouraging the formation of new blood vessels and supporting epithelial regrowth and wound healing. The presence of metalloproteinase inhibitors and reduced immunogenicity, due to low expression of human leukocyte antigens (HLAs), make it a material of great interest as a support in the prevention and treatment of bisphosphonate-associated osteonecrosis of the jaw (52). Finally, research is focusing on controlled-release systems for anti-inflammatory drugs, such as those based on nanoscale polymeric hybrids, which could offer advantages in local inflammation control. These systems aim to release the drug in a targeted manner, minimizing systemic side effects (53).

CONCLUSIONS

Drug-induced osteonecrosis of the jaw (MRONJ) requires a thorough understanding of the causes, risk factors, and available treatment options. Conservative therapies, such as pharmacological management of pain and infection, are useful in the initial stages, but are often insufficient to resolve the pathology. Surgical intervention, ranging from curettage to aggressive resection, has proven effective in removing necrotic tissue and promoting bone healing. Innovative protocols that integrate laser photobiomodulation, the use of PRP, and deferoxamine administration show promising results in improving vascularization and tissue regeneration. Targeted suspension of pharmacological therapy, in agreement with the attending physician, is crucial to reduce the accumulation of anti-resorptive drugs at the surgical site. Ultimately, optimal management of MRONJ requires a personalized multidisciplinary approach that takes into account the patient's individual risk assessment, the specific characteristics of the lesion, and the response to therapies. Implementing preventive protocols, early diagnosis, and adopting updated treatments, combining conservative and surgical strategies, are key to reducing the incidence of MRONJ and improving the quality of life for affected patients.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Ruggiero SL, et al. "Management of osteonecrosis of the jaws: a systematic review and international consensus." Oral Oncology. 2014;50(3):239-246.
2. Khan AA, Morrison A, Hanley DA, et al. Bisphosphonate-related osteonecrosis of the jaw: position of the American Association of Oral and Maxillofacial Surgeons. J Oral Maxillofac Surg. 2015;73(11):1977-1991.
3. Shah PS, et al. "Evolving management strategies in bisphosphonate-related osteonecrosis of the jaw." Current Oncology Reports. 2020;22(6):57.

4. Lauritano D, Mastrangelo F, D'Ovidio C, et al. Activation of Mast Cells by Neuropeptides: The Role of Pro-Inflammatory and Anti-Inflammatory Cytokines. Int J Mol Sci. 2023;24(5):4811. doi:10.3390/ijms24054811.
5. Tettamanti L, Kritas SK, Gallenga CE, et al. IL-33 mediates allergy through mast cell activation: Potential inhibitory effect of certain cytokines. J Biol Regul Homeost Agents. 2018;32(5):1061-1065.
6. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in mucosal immunity of intestinal inflammation: Inhibitory effect of IL-37. Eur J Pharmacol. 2018;818:294-299. doi:10.1016/j.ejphar.2017.09.044.
7. Minetti E, Palermo A, Ferrante F, et al. Autologous tooth graft after endodontically treated used for socket preservation: a multicenter clinical study. Appl Sci. 2019;9(24):5396. doi:10.3390/app9245396.
8. Pomella S, Melaiu O, Dri M, Martelli M, Gargari M, Barillari G. Effects of Angiogenic Factors on the Epithelial-to-Mesenchymal Transition and Their Impact on the Onset and Progression of Oral Squamous Cell Carcinoma: An Overview. Cells. 2024;13(15):1294. doi:10.3390/cells13151294.
9. Carinci F, Arcelli D, Lo Muzio L, Francioso F, Valentini D, Evangelisti R, Volinia S, D'Angelo A, Meroni G, Zollo M, Pastore A, Ionna F, Mastrangelo F, Conti P, Tetè S. Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. Transl Res. 2007;150(4):233-245. doi:10.1016/j.trsl.2007.03.011
10. Bagan JV, et al. "Osteonecrosis of the jaw related to bisphosphonate therapy: clinical guidelines and management." Journal of Clinical Medicine. 2022;11(10):2902.
11. Grigolato R, et al. "Laser therapy in the management of osteonecrosis of the jaw: review of the literature." Photomedicine and Laser Surgery. 2017;35(9):468-475.
12. Meloni S, et al. "Regenerative approaches in the management of medication-related osteonecrosis of the jaw." Biomedicines. 2021;9(10):1438.
13. Raffone C, Gianfreda F, Antonacci D, Pompeo MG, Bollero P, Canullo L. Chairside virtual patient protocol. Part 3: In vitro accuracy of a digital facebow. J Dent. 2023;137:104622. doi:10.1016/j.jdent.2023.104622.
14. Gianfreda F, Pesce P, Marcano E, Pistilli V, Bollero P, Canullo L. Clinical Outcome of Fully Digital Workflow for Single-Implant-Supported Crowns: A Retrospective Clinical Study. Dent J (Basel). 2022;10(8):139. doi:10.3390/dj10080139.
15. Campisi G, Bedogni A, Fusco V; Società Italiana di Chirurgia Maxillo-Facciale; Società di Patologia e Medicina Orale. Clinical and therapeutic recommendations on medication-related osteonecrosis of the jaw (ONJ) and its prevention. New Digital Press; 2020. ISBN: 9788855091473.
16. Franchini M, et al. The use of platelet-rich plasma in oral surgery: a systematic review and meta-analysis. Blood Transfus. 2019;17(3):357-367.
17. Miranda M, Gianfreda F, Rosa A, et al. Treatment of Oral Mucositis Using Platelet-Rich-Fibrin: A Retrospective Study on Oncological Patients. J Craniofac Surg. 2023;34(5):1527-1529. doi:10.1097/SCS.0000000000009450.
18. Hosseinpour S, Tunér J, Fekrazad R. Photobiomodulation in Oral Surgery: A Review. Photobiomodul Photomed Laser Surg. 2019;37(12):814-825. doi:10.1089/photob.2019.4712.
19. Yalcin-Ülker GM, Günbatan M, Duygu G, Soluk-Tekkesin M, Özcakir-Tomruk C. Could Local Application of Hypoxia Inducible Factor 1-α Enhancer Deferoxamine Be Promising for Preventing of Medication-Related Osteonecrosis of the Jaw?. Biomedicines. 2023;11(3):758. doi:10.3390/biomedicines11030758.
20. Sølling AS, Tsourdi E, Harsløf T, Langdahl BL. Denosumab discontinuation. Curr Osteoporos Rep. 2023;21(1):95-103. doi:10.1007/s11914-022-00771-6.
21. Serra E, Paolantonio M, Spoto G, Mastrangelo F, Tetè S, Dolci M. Bevacizumab-related osteneocrosis of the jaw. Int J Immunopathol Pharmacol. 2009;22(4):1121-1123. doi:10.1177/039463200902200429
22. Pimolbutr K, Porter S, Fedele S. Osteonecrosis of the Jaw Associated with Antiangiogenics in Antiresorptive-Naïve Patient: A Comprehensive Review of the Literature. Biomed Res Int. 2018;2018:8071579. doi:10.1155/2018/8071579.
23. Jackson K, Ashby M, Martin P, Pisasale M, Brumley D, Hayes B. "Burst" ketamine for refractory cancer pain: an open-label audit of 39 patients. J Pain Symptom Manage. 2001;22(4):834-842. doi:10.1016/s0885-3924(01)00340-2.

24. Shahraki M, Khazaei AH, Hakimi S, Hasheminasab M, Haradasht SA. Effect of chlorhexidine, povidone-iodine, and hydrogen peroxide irrigation on pain and swelling after mandibular third molar surgery: randomized controlled trial. Int J Oral Maxillofac Surg. 2025;54(7):677-683. doi:10.1016/j.ijom.2025.01.021
25. Lesclous P, Grabar S, Abi Najm S, et al. Relevance of surgical management of patients affected by bisphosphonate-associated osteonecrosis of the jaws. A prospective clinical and radiological study. Clin Oral Investig. 2014;18(2):391-399. doi:10.1007/s00784-013-0979-2.
26. Pautke C. Treatment of medication-related osteonecrosis of the jaw. In: Medication-Related Osteonecrosis of the Jaws. Springer Berlin Heidelberg; 2015:79-91. doi:10.1007/978-3-662-43733-9_7.
27. On SW, Cho SW, Byun SH, Yang BE. Various Therapeutic Methods for the Treatment of Medication-Related Osteonecrosis of the Jaw (MRONJ) and Their Limitations: A Narrative Review on New Molecular and Cellular Therapeutic Approaches. Antioxidants (Basel). 2021;10(5):680. doi:10.3390/antiox10050680.
28. El-Rabbany M, Lam DK, Shah PS, Azarpazhooh A. Surgical Management of Medication-Related Osteonecrosis of the Jaw Is Associated With Improved Disease Resolution: A Retrospective Cohort Study. J Oral Maxillofac Surg. 2019;77(9):1816-1822. doi:10.1016/j.joms.2019.03.040.
29. Nisi M, La Ferla F, Karapetsa D, et al. Conservative surgical management of patients with bisphosphonate-related osteonecrosis of the jaws: a series of 120 patients. Br J Oral Maxillofac Surg. 2016;54(8):930-935. doi:10.1016/j.bjoms.2016.06.015.
30. Grassi A, Monica D, Minetti E, et al. Innovative Alveolar Ridge Preservation Surgical Technique with Immediate Dental Implant Placement: A Retrospective Case Report of 1-Year Follow-Up. Eur J Dent. 2024;18(1):408-414. doi:10.1055/s-0043-1772676.
31. Mastrangelo F, Gastaldi G, Vinci R, et al. Immediate Postextractive Implants With and Without Bone Graft: 3-year Follow-up Results From a Multicenter Controlled Randomized Trial. Implant Dent. 2018;27(6):638-645. doi:10.1097/ID.0000000000000816.
32. Gianfreda F, Punzo A, Pistilli V, et al. Electrolytic Cleaning and Regenerative Therapy of Peri-implantitis in the Esthetic Area: A Case Report. Eur J Dent. 2022;16(4):950-956. doi:10.1055/s-0042-1750773.
33. Minetti E, Celko M, Contessi M, et al. Implants Survival Rate in Regenerated Sites with Innovative Graft Biomaterials: 1 Year Follow-Up. Materials (Basel). 2021;14(18):5292. doi:10.3390/ma14185292.
34. Bedogni A., Bettini G., Ferronato G., Fusetti S., Saia G. Replacement of fractured reconstruction plate with customized mandible implant: A novel technique. Laryngoscope 2014;124(2):401–4. Doi: 10.1002/lary.24230
35. Kwon Y-D, Kim D-Y. Role of teriparatide in medication-related osteonecrosis of the jaws (MRONJ). Dent J (Basel). 2016;4(1):41.
36. Inchingolo A, et al. MRONJ treatment strategies: a systematic review and two case reports. Appl Sci. 2023;13(8):4370.
37. Vescovi, P., Manfredi, M. & Merigo, E. Adjuvant Treatment Options in the Management of Medication-Related Osteonecrosis of the Jaw. in Medication- Related Osteonecrosis of the Jaws 103–109 (Springer Berlin Heidelberg, Ber-lin, Heidelberg, 2015). doi:10.1007/978-3-662-43733-9_9.
38. Canullo L, Iacono R, Pires Godoy E, et al. Hybrid Funnel Technique: A Novel Approach for Implant Site Preparation: A Pilot Study. Dent J (Basel). 2022;10(9):157. doi:10.3390/dj10090157.
39. Mastrangelo F, Quaresima R, Canullo L, Scarano A, Muzio LL, Piattelli A. Effects of Novel Laser Dental Implant Microtopography on Human Osteoblast Proliferation and Bone Deposition. Int J Oral Maxillofac Implants. 2020;35(2):320-329. doi:10.11607/jomi.7606.
40. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O, Peter JU. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst Rev. 2022;7(7):CD012432. doi:10.1002/14651858.CD012432.pub3.
41. El-Rabbany M, Sgro A, Lam DK, Shah PS, Azarpazhooh A. Effectiveness of treatments for medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. J Am Dent Assoc. 2017;148(7):584-594.e2. doi:10.1016/j.adaj.2017.04.002.
42. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in mucosal immunity of intestinal inflammation: Inhibitory effect of IL-37. Eur J Pharmacol. 2018;818:294-299. doi:10.1016/j.ejphar.2017.09.044
43. Conti P, Caraffa A, Ronconi G, et al. Mast cells participate in allograft rejection: can IL-37 play an inhibitory role? Inflamm Res. 2018;67(9):747-755. doi:10.1007/s00011-018-1166-3
44. Mastrangelo F, Dedola A, Cattoni F, et al. Etiological periodontal treatment with and without low-level laser therapy on IL-1β level in gingival crevicular fluid: an in vivo multicentric pilot study. J Biol Regul Homeost Agents. 2018;32(2):425-431.

45. Tetè S, Mastrangelo F, Traini T, et al. A macro- and nanostructure evaluation of a novel dental implant. Implant Dent. 2008;17(3):309-20. doi: 10.1097/ID.0b013e318182d494.
46. Minetti E, Palermo A, Ferrante F, et al. Autologous Tooth Graft after Endodontical Treated Used for Socket Preservation: A Multicenter Clinical Study. Applied Sciences. 2019; 9(24):5396. https://doi.org/10.3390/app9245396
47. Carinci F, Arcelli D, Lo Muzio L, et al. Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. Transl Res. 2007;150(4):233-245. doi:10.1016/j.trsl.2007.03.011
48. Lo Muzio L, Tetè S, Mastrangelo F, et al. A novel mutation of gene CBFA1/RUNX2 in cleidocranial dysplasia. Ann Clin Lab Sci. 2007;37(2):115-20.
49. Tranasi M, Sberna MT, Zizzari V, et al. Microarray evaluation of age-related changes in human dental pulp. J Endod. 2009;35(9):1211-7. doi: 10.1016/j.joen.2009.05.026.
50. Sacco R, et al. A systematic review of oxygen therapy for the management of medication-related osteonecrosis of the jaw (MRONJ). Appl Sci. 2019;9(3):1026.
51. Min SH, Kang NE, Song SI, Lee JK. Regenerative effect of recombinant human bone morphogenetic protein-2/absorbable collagen sponge (rhBMP-2/ACS) after sequestrectomy of medication-related osteonecrosis of the jaw (MRONJ). J Korean Assoc Oral Maxillofac Surg. 2020;46(3):191-196. doi:10.5125/jkaoms.2020.46.3.191.
52. Sacco R, Akintola O, Sacco N, et al. The Use of Human Amniotic Membrane (hAM) as a Treatment Strategy of Medication-Related Osteonecrosis of the Jaw (MRONJ): A Systematic Review and Meta-Analysis of the Literature. Medicina (Kaunas). 2023;59(5):968. doi:10.3390/medicina59050968.
53. Sammartino G, Marenzi G, Tammaro L, et al. Anti-inflammatory drug incorporation into polymeric nano-hybrids for local controlled release. Int J Immunopathol Pharmacol. 2005;18(3 Suppl):55-62.

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Article

IMPLANT SURFACES IN ORAL IMPLANTOLOGY: FROM OSSEOINTEGRATION BIOLOGY TO FUTURE DIRECTIONS

M. Scarpati Cioffari di Castiglione[1], S. Lauri[2*], I. Mastrorilli[3], S. Di Giovanni[4], R. Trabucco[4], P. Nunu[4], M.C. Palumbo[4] and A. Danieli[5]

[1] Independent researcher, 81021, Caserta, Italy;
[2] Independent researcher, 00073, Rome, Italy;
[3] Independent Researcher, 00135, Rome, Italy;
[4] Department of System Medicine, University of Rome "Tor Vergata", Rome, Italy;
[5] Independent Researcher, 00010, Rome, Italy.

**Correspondence to*:
Simone Lauri,
Independent Researcher,
00073, Rome, Italy.
e-mail: laurisimone1@gmail.com

ABSTRACT

Introduction: This review examines the pivotal role of implant surface characteristics in oral implantology, moving beyond basic osseointegration towards actively influencing tissue response. Modern implant success relies on the implant's surface properties, affecting bone integration and the quality of the bone-implant interface. This article provides a comprehensive overview of implant surfaces, analyzing treatments, clinical evidence, biological implications, and future directions. *Materials and Methods:* A literature review was conducted using scientific articles from peer-reviewed sources. Studies addressing implant surface characteristics and their impact on osseointegration were included, and the extracted data was analyzed and synthesized into thematic sections. *Discussion:* The surface of an implant is a biological interface profoundly influencing osseointegration. Key findings include the role of surface roughness in promoting cell adhesion and bone formation, with moderately rough surfaces (Sa values between 1 and 2 µm) being most effective. Chemical surface properties, such as titanium oxides, influence surface energy and wettability, impacting protein adhesion and osteoblastic activity. Surface modifications like alumina blasting and acid etching optimize the titanium-bone interface. Furthermore, soft tissue attachment and transmucosal designs play a crucial role in long-term peri-implant health. The review also addresses advanced strategies such as bioactive surfaces, immediate loading protocols, and considerations for medically compromised patients, as well as digital innovations. *Conclusions:* Implant surfaces are dynamic and strategic in modern implantology. Optimizing surfaces and employing proper clinical management are essential for achieving optimal and lasting aesthetic and functional results.

KEYWORDS: *Implant surface, osseointegration, bioactive surface, surface roughness, peri-implant tissue*

INTRODUCTION

In recent decades, oral implantology has made significant progress, evolving from a pioneering discipline to a highly predictable clinical procedure (1). The success of a dental implant no longer depends solely on its macroscopic design or the material used, but also, and above all, on the implant's surface characteristics (2-4). The interface between the implant and the bone is the focal point of the osseointegration process, a complex biological phenomenon involving the interaction between artificial surfaces and living tissues (5). The surfaces of implants are no longer considered simple passive

Received: 04 September, 2025
Accepted: 27 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

components (6). On the contrary, they actively modulate cellular responses, influencing not only the extent and speed of bone integration, but also the quality of the interface that develops. Their structure, chemical composition, degree of roughness, and surface energy determine how serum proteins are adsorbed, how cells are activated, and how regenerative processes are initiated (7). Scientific literature has clearly demonstrated that intentional surface modifications through mechanical, chemical, or physicochemical treatments can accelerate osteoconduction, increase bone-implant contact (BIC), and improve outcomes even in challenging clinical scenarios such as immediate loading or low-density bone conditions (8,9). These modifications not only facilitate colonization by osteoprogenitor cells but also reduce the risk of early failure, particularly in systemically compromised patients or regenerated sites (10). At the same time, increasing attention has been focused on the transmucosal interface: It is now well-known that the surface of prosthetic abutments and implant collars can significantly influence soft tissue responses. Maintaining peri-implant health depends not only on solid bone anchorage but also on the formation of a stable soft tissue seal capable of protecting the underlying bone from bacterial infiltration and chronic inflammation (11). This article aims to provide a comprehensive and up-to-date overview of the role of implant surfaces in osseointegration, critically analyzing the main available treatments, clinical evidence, biological implications, and future prospects.

MATERIALS AND METHODS

This article is a literature review that aims to provide a comprehensive and up-to-date overview of the role of implant surfaces in osseointegration.

Data Sources

Search for scientific articles published in peer-reviewed journals, specialised textbooks, and online databases (e.g., PubMed, Scopus, Web of Science). *In vitro* studies, *in vivo* studies, systematic reviews, and meta-analyses were considered.

Selection Criteria

The articles were selected based on specific inclusion and exclusion criteria. Inclusion criteria included studies addressing implant surface characteristics (e.g., topography, chemical composition, surface treatments), their influence on osseointegration, soft and hard tissue response, clinical implications, and applied new technologies. Studies that were not relevant to the topic, had inadequate methodology, or insufficient data were excluded.

Data Analysis and Synthesis

The extracted data was critically analysed and synthesised to provide an overview of the topic. The information has been organised into thematic sections to facilitate understanding and discussion of the results. Controversies and areas of uncertainty were highlighted and discussed in light of the available evidence.

DISCUSSION

In modern implantology, the implant surface represents much more than just an area of mechanical contact with the bone: It acts as a true biological interface capable of profoundly influencing the entire process of osseointegration. When an implant is inserted into bone, its surface characteristics determine cellular and molecular responses. The interaction between the implant and the tissue begins with the adsorption of plasma proteins onto the titanium surface, an event that occurs within seconds and shapes everything that follows. The composition, topography, and surface energy determine which proteins bind, in what conformation, and consequently influence the behavior of immune cells, fibroblasts, and, most importantly, osteoblasts. Osteointegration is therefore not a static event, but a dynamic and orchestrated sequence of processes initiated by this first micro-interaction. Pioneering studies by Albrektsson and Brånemark have shown that the stable attachment of bone to the implant surface – what we call osseointegration – is not simply a mechanical result, but is mediated by a specific biological response, favored by certain topographical and chemical characteristics of the surface (1,2). Over the years, research has focused on optimizing this interface, leading to the development of roughened, treated, nanostructured, and even bioactive surfaces. One of the key findings was the role of surface roughness. Moderately rough surfaces, with Sa (Surface Area) values between 1 and 2 μm, have proven to be the most effective in promoting cell adhesion and early bone formation in direct contact with the implant (5). This level of roughness elicits a more favorable cellular response compared to smooth surfaces, which tend to induce distant osteogenesis with longer healing times. Simultaneously, it has been demonstrated that the chemical nature of the surface, particularly its elemental composition and the presence of titanium oxides, influences the surface energy and thus the wettability, a key factor for protein adhesion. Hydrophilic and negatively charged surfaces appear to enhance osteoblastic activity and promote faster mineralization (9). These discoveries have prompted manufacturers to develop sophisticated treatments aimed at

improving the biological properties of implant surfaces. Techniques such as alumina blasting, acid etching, anodic oxidation, and the application of bioactive coatings are now widely used to optimize the titanium-bone interface (6,10). Surfaces treated with aluminium oxide blasting, strong acid etching, or combined techniques such as blasting followed by acid etching (SLA) have demonstrated an increased ability to induce direct bone formation and increase bone-implant contact (BIC) (5,6). These effects also occur in the first few days after implant insertion, positively influencing secondary stability. Furthermore, surfaces with micro- and nanoscale structures have proven particularly effective in influencing osteoblastic behavior, improving cell adhesion, proliferation, and differentiation (12). In these scenarios, surface roughness becomes a strategic factor for the success of the implant.

Chemical and physical characteristics of the implant surface

In addition to morphology, the chemical and physical characteristics of the implant surface play a crucial role in determining the host's biological response. Surface treatments that improve wettability have been shown to significantly improve biological responses both *in vitro* and *in vivo* (13). For example, etching sandblasted surfaces with sulphuric acid and hydrochloric acid produces a multiscale topography that combines micro- and nano-roughness, while simultaneously increasing surface energy. Anodizing not only modifies the topography but also leads to the controlled thickening of the titanium oxide (TiO_2) layer, giving the surface new chemical properties and increased stability. This oxide coating, often enriched with calcium and phosphate, can act as an osteoinductive substrate that stimulates early mineralization (14). The use of bioactive surfaces coated with hydroxyapatite (HA) has also aimed to mimic the composition of natural bone. However, despite their high osteoconductive potential, such surfaces have shown limitations related to poor coating stability and delamination phenomena (15). More recently, the introduction of nanotechnology has enabled the creation of hierarchical surfaces that interact directly with subcellular components, such as integrins and filopodia, thus modulating cell behavior in a targeted manner (16).

Tissue response to the implant surface

The success of a dental implant depends not only on its initial mechanical stability, but, more importantly, on the quality of the biological interaction established between the implant surface and the surrounding tissues. This interaction involves both hard tissues (bone) and soft tissues (mucosa), each of which responds differently depending on the surface characteristics. Osteoprogenitor cells and osteoblasts migrate towards the implant surface in response to mechanical-chemical signals, attach via integrins, and initiate the deposition of the extracellular matrix. This process is strongly influenced by topographies that mimic the native extracellular matrix (12,13). On the contrary, the response of soft tissues is more complex. The formation of a stable epithelial and connective tissue attachment around the implant collar is essential for creating a barrier against bacterial infiltration and ensuring long-term peri-implant health. Animal studies have shown that the morphology of the transmucosal surface influences the height of the junctional epithelium and the arrangement of collagen fibers (17,18). Specifically, surfaces with controlled micro-roughness, micro-channels, or laser-generated patterns (e.g., Laser-Lok®, laser micro-channels) appear to promote parallel or perpendicular alignment of connective tissue fibers relative to the implant axis, partially mimicking the attachment found around natural teeth (19). This translates into greater stability of the mucosal seal and a reduced incidence of mucositis (20) and peri-implantitis over time. However, when peri-implantitis does occur, effective treatment strategies are needed to restore tissue health and prevent further bone loss. Electrolytic cleaning combined with regenerative therapy has shown promise in achieving these goals (21). Additionally, soft tissue management is influenced by the number and timing of stump disconnections and reconnections. The "one pillar, one time" protocol - which involves leaving the pillar in place from the initial placement - has shown positive effects on maintaining biological width and mucosal stability (22).

Connecting and managing the biological seal system

The implant-abutment connection is a critical factor in preserving long-term tissue integrity. It's not simply a mechanical issue – concerning the stability between the implant and the prosthetic component – but also a biological one, as the transmucosal interface acts as the first line of defense against bacterial infiltration. Numerous studies have shown that the connection design directly influences the quality of soft tissue attachment and the prevention of crestal bone resorption (18,22). Flat-top or platform-switching connections have been shown to be more effective in minimizing initial bone loss compared to traditional conical-cylindrical designs, primarily due to their ability to move the implant microgap away from the bone. Additionally, laser-treated surfaces with microstructures, such as circumferential grooves (e.g., Laser-Lok), appear to guide the orientation of collagen fibers, promoting a parallel arrangement that mimics the connective attachment of a natural tooth and improves soft tissue adhesion to the abutment surface (19,22). Recent research has also highlighted how laser-created microtopography can positively influence osteoblast proliferation and bone deposition (23). This results in a more stable mucosal seal and a more effective barrier against microbial invasion.

Prosthetic management also plays a fundamental role: Each disconnection and reconnection of the stump disrupts the seal of the epithelial and connective tissue, increasing the risk of inflammation and bone remodeling (17,24). For this reason, the clinical strategy of "one abutment, once" has become widespread, involving the definitive positioning of the abutment during surgery and maintaining it throughout all prosthetic phases. Geometry has led to the development of convergent or concave collars, which appear to improve soft tissue maturation and aesthetic outcomes, particularly in the anterior region (25).

Advanced Strategies for Implant Surface Optimization

In recent years, scientific interest has increasingly focused on implant surfaces that actively influence cellular and microbial behavior through multifactorial approaches. The goal is no longer just to achieve successful osseointegration, but also to elicit a controlled and lasting tissue response in complex clinical environments. Bioactive surfaces represent an evolution beyond osteoconductive ones: Instead of simply supporting bone growth, they actively stimulate it. Coatings containing calcium phosphate, biofunctional peptides, or growth factors have shown promising results both in vitro and in vivo, although issues regarding the long-term stability of the coating remain (15,26). While traditional surfaces are effective in promoting osseointegration, they often fail to prevent bacterial adhesion, a key factor in the development of mucositis and peri-implantitis. To address this issue, bacteriostatic or bactericidal surfaces have been developed by incorporating silver, zinc, or copper ions, or through laser treatment, nanostructuring, or antibacterial coatings (27). However, the antibacterial effectiveness must be carefully balanced with biocompatibility: Many surfaces that inhibit microbial growth also show cytotoxic effects on human cells. Current research is therefore focused on the development of "smart" surfaces that release antimicrobial agents in a controlled manner or become active only in the presence of bacterial biofilm (28). Finally, multifunctional surfaces, which combine osteoconductive, antibacterial, and immunomodulatory properties, represent the future of implantology. The use of composite biomaterials, engineered microenvironments, and patient-specific genetic customization are among the evolving approaches currently being explored in preclinical and clinical research.

Implant Surfaces and Immediate Loading

The concept of immediate loading represents one of the most advanced and ambitious frontiers in implantology. This protocol offers significant advantages in terms of reducing treatment time and improving the patient experience, but it also requires favorable clinical conditions to ensure long-term success. Therefore, innovative alveolar ridge preservation techniques combined with immediate implant placement can improve outcomes and predictability in these cases. (29) One of the key factors influencing the predictability of immediate loading is the implant surface area. To achieve sufficient short-term secondary stability, it is necessary to promote a rapid biological response and early contact between the implant and the surrounding bone tissue. Moderately rough surfaces have demonstrated greater osteoconductive potential compared to smooth or turned surfaces, contributing to faster bone formation that adheres directly to the implant surface (5,6). An "active" surface accelerates the adsorption of plasma proteins, cell recruitment, and neovascularization, key factors for early integration under functional load. It has also been observed that the surgical protocol, optimization of the implant site, and the adoption of minimally invasive techniques contribute to maintaining high primary stability, an essential prerequisite for initiating early loading (30). These approaches have also proven effective in post-extraction treatments, with or without bone grafting, as demonstrated by Mastrangelo et al. in a multicenter study with a 3-year follow-up, which reported comparable implant survival rates (31). In patients with low bone density, such as the posterior maxilla or systemically compromised individuals, the effectiveness of treated surfaces becomes even more evident. Under such difficult conditions, the surface's ability to stimulate an early osteogenic response can be the determining factor between success and failure (7). Ultimately, the success of immediate loading is closely linked to the quality of the interface established between the implant and the host tissue: An optimized surface, designed to maximize biochemical and cellular interactions during the early stages of healing, is now considered essential for the safe application of early or immediate loading protocols.

Implant surfaces in medically compromised patients

Implant treatment in medically compromised patients or in unfavorable clinical conditions represents a growing challenge in modern dentistry. Conditions such as diabetes, osteoporosis, immunosuppression, smoking, drug-induced osteonecrosis (32), cancer therapies, or bisphosphonate use negatively impact bone healing and increase the risk of early and late implant failure. In scenarios like this, the choice of implant surface becomes even more critical. Studies have shown that moderately rough or bioactive surfaces can partially compensate for the biological limitations of these patients, promoting faster cell colonization and increased extracellular matrix deposition even when regenerative capacity is reduced (6,33). A particularly critical situation concerns regenerated sites or those that have undergone pre-implant

surgery. In these cases, the remaining bone quality and quantity can be compromised, necessitating the use of highly osteoconductive surfaces capable of stimulating new bone formation even under mechanically unfavorable conditions (7). Recent studies have shown promising survival rates for implants placed in regenerated sites using innovative biomaterials (34). In an in vitro study, Gianfreda et al. demonstrated the effectiveness of various decontamination protocols on the surfaces of contaminated implants, highlighting that surface characteristics influence both the response to treatment and the potential for functional osseointegration (35). Finally, in cancer patients undergoing chemotherapy or radiotherapy, the use of biofunctional surfaces and treatments that minimize healing times can improve long-term outcomes. Understanding the molecular state of the disease could contribute to further personalizing the implant approach in the future (36). However, treatment planning in these cases must be multidisciplinary and highly individualized.

Implant Surfaces and Digital Innovation

The advent of digital technology has revolutionized the entire workflow in implantology, including the design and management of implant surfaces (37). Digitalization, from virtual planning to guided surgery (38) and CAD/CAM prosthetics, has made possible a level of precision that was unimaginable just a few years ago. The use of digital facebows is also becoming increasingly widespread, with studies demonstrating their accuracy in vitro (39). Its impact goes beyond technical aspects, influencing biology and the interaction between implants and surrounding tissues. Pre-surgical digital planning, combined with high-resolution three-dimensional imaging and design software, allows for highly precise implant placement, optimizing bone-implant contact in areas of higher bone density. This directly affects initial integration, making the implant surface characteristics even more critical. The adoption of guided surgery and custom implants also minimizes surgical trauma and preserves vascularization at the recipient site. Consequently, the surface quality can express its full osteoconductive potential, especially when combined with immediate loading protocols. Simultaneously, 3D printing and additive manufacturing technologies are opening up new frontiers in the development of customized surfaces, characterized by textures and microtopographies tailored to the recipient site or the patient's clinical condition. Research is currently underway to create customized surfaces with roughness gradients and localized surface functionalization, which could further improve predictability in complex cases. The management of prosthetic restorations has also changed radically. With fully digital workflows, the final abutment can be placed immediately and permanently, reducing disconnections and maintaining the integrity of the biological seal (19,24). Finally, digital technologies are emerging in the surface assessment itself: Digital scanning electron microscopy, 3D profilometry, and automated image analysis now allow for extremely precise and reproducible characterisation of implant surfaces, improving the quality of research and the reliability of clinical data (40).

CONCLUSIONS

In summary, implant surfaces represent a dynamic and strategic element in modern implantology. Several physiological and pathological situations (40,41), such as smoking, osteoporosis, drug-induced osteonecrosis, diabetes, immunosuppression (42,43), cancer therapies(32), or bisphosphonate use negatively impact bone healing (45) and increase the risk of early and late implant failure promoting critical conditions that could be limited using bioactive biomaterials or digital technologies to minimize healing times and improve long-term outcomes (45) as showed in recent studies. The evolution of engineering techniques, from the first targeted approaches to roughness to nanotechnology and bioactive coatings, has profoundly transformed this field. Optimizing wettability, surface energy, and chemical composition, along with the adoption of innovative transmucosal designs such as platform switching and laser-etched microstructures (Laser-Lok), has significantly improved osseointegration and the stability of peri-implant soft tissues. In complex clinical contexts, such as low bone density or medically compromised patients (diabetes, osteoporosis, etc.), high-performance surfaces have been shown to partially compensate for biological limitations, accelerating bone neoformation and improving the predictability of immediate loading. The advent of nanotechnology and its integration with digital workflows herald a future where implant surfaces will be custom-designed to meet individual patient needs, optimizing interaction with surrounding tissues and improving long-term predictability. Future research should focus on developing multifunctional surfaces that combine osteoconductive, antibacterial (with silver, zinc, or copper ions), and immunomodulatory properties, managing the risk of mucositis and peri-implantitis. Furthermore, it is crucial to evaluate the long-term stability of bioactive coatings (calcium phosphate, biofunctional peptides), overcoming the limitations related to delamination. However, it is crucial to emphasize that clinical success does not depend solely on surface characteristics. Proper planning, atraumatic surgery, and adequate prosthetic management remain essential elements. Only through a multidisciplinary approach that integrates the latest technological innovations with a solid biological foundation

and careful clinical management will it be possible to fully harness the potential of implant surfaces to offer patients optimal and long-lasting aesthetic and functional results.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Brånemark PI, Hansson BO, Adell R, et al. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. Scand J Plast Reconstr Surg Suppl. 1977;16:1-132.
2. Albrektsson T, Brånemark PI, Hansson HA, Lindström J. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand. 1981;52(2):155-170. doi:10.3109/17453678108991776.
3. Wennerberg A, Albrektsson T. On implant surfaces: a review of current knowledge and opinions. Int J Oral Maxillofac Implants. 2010;25(1):63-74.
4. Tetè S, Mastrangelo F, Traini T, Vinci R, Sammartino G, Marenzi G, Gherlone E. A macro- and nanostructure evaluation of a novel dental implant. Implant Dent. 2008 Sep;17(3):309-20. doi: 10.1097/ID.0b013e318182d494. PMID: 18784531.
5. Wennerberg A, Hallgren C, Johansson C, Danelli S. A histomorphometric evaluation of screw-shaped implants each prepared with two surface roughnesses. Clin Oral Implants Res. 1998;9(1):11-19. doi:10.1034/j.1600-0501.1998.090102.x.
6. Cochran DL, Buser D, ten Bruggenkate CM, et al. The use of reduced healing times on ITI implants with a sandblasted and acid-etched (SLA) surface: early results from clinical trials on ITI SLA implants. Clin Oral Implants Res. 2002;13(2):144-153. doi:10.1034/j.1600-0501.2002.130204.x.
7. Piattelli A, Scarano A, Piattelli M, Vaia E. Histologic evaluation of bone reactions to implants with machined and dual acid-etched surfaces: a pilot study in the rabbit tibia. Int J Oral Maxillofac Implants. 1998;13(6):865-870.
8. Lang NP, Jepsen S; Working Group 4. Implant surfaces and design (Working Group 4). Clin Oral Implants Res. 2009;20 Suppl 4:228-231. doi:10.1111/j.1600-0501.2009.01771.x.
9. Rupp F, Scheideler L, Olshanska N, de Wild M, Wieland M, Geis-Gerstorfer J. Enhancing surface free energy and hydrophilicity through chemical modification of microstructured titanium implant surfaces. J Biomed Mater Res A. 2006;76(2):323-334. doi:10.1002/jbm.a.30518.
10. Lang NP, Salvi GE, Huynh-Ba G, Ivanovski S, Donos N, Bosshardt DD. Early osseointegration to hydrophilic and hydrophobic implant surfaces in humans. Clin Oral Implants Res. 2011;22(4):349-356. doi:10.1111/j.1600-0501.2011.02172.x.
11. Barlattani A Jr, Martelli M, Ceruso FM, Gargari M, Ottria L. Convergent implant transmucosal collar and healing abutment: aesthetics influence on soft tissues. A clinical study. J Biol Regul Homeost Agents. 2020;34(1 Suppl. 1):.
12. Zhao L, Mei S, Chu PK, Zhang Y, Wu Z. The influence of hierarchical hybrid micro/nano-textured titanium surface with titania nanotubes on osteoblast functions. Biomaterials. 2010;31(19):5072-5082. doi:10.1016/j.biomaterials.2010.03.014.
13. Bächle M, Kohal RJ. A systematic review of the influence of different titanium surfaces on proliferation, differentiation and protein synthesis of osteoblast-like MG63 cells. Clin Oral Implants Res. 2004;15(6):683-692. doi:10.1111/j.1600-0501.2004.01054.x.
14. Davies JE. Understanding peri-implant endosseous healing. J Dent Educ. 2003;67(8):932-949.
15. Ivanoff CJ, Widmark G, Johansson C, Wennerberg A. Histologic evaluation of bone integration of TiO_2-blasted and turned titanium implants: a pilot study in rabbit tibia. Biomaterials. 2001;22(15):1913-1920.
16. Hanawa T. A comprehensive review of techniques for biofunctionalization of titanium. J Periodontal Implant Sci. 2011;41(6):263-272. doi:10.5051/jpis.2011.41.6.263.
17. Sul YT, Johansson CB, Jeong Y, Albrektsson T. The electrochemical oxide growth behaviour on titanium in acid and alkaline electrolytes. Med Eng Phys. 2001;23(5):329-346. doi:10.1016/s1350-4533(01)00050-9.
18. Rossi F, Lang NP, Ricci E, Cecchinato D, Botticelli D, Salvi GE. Long-term outcomes of single implants in the esthetic area: a 10- to 12-year retrospective evaluation. Clin Oral Implants Res. 2016;27(10):1220-1226.

19. Abrahamsson I, Berglundh T, Lindhe J. The mucosal barrier following abutment dis/reconnection. An experimental study in dogs. J Clin Periodontol. 1997;24(8):568-572. doi:10.1111/j.1600-051x.1997.tb00230.x
20. Miranda M, Gianfreda F, Rosa A, et al. Treatment of Oral Mucositis Using Platelet-Rich-Fibrin: A Retrospective Study on Oncological Patients. J Craniofac Surg. 2023;34(5):1527-1529. doi:10.1097/SCS.0000000000009450.
21. Gianfreda F, Punzo A, Pistilli V, et al. Electrolytic Cleaning and Regenerative Therapy of Peri-implantitis in the Esthetic Area: A Case Report. Eur J Dent. 2022;16(4):950-956. doi:10.1055/s-0042-1750773.
22. Degidi M, Nardi D, Piattelli A. One abutment at one time: non-removal of an immediate abutment and its effect on bone healing around subcrestal tapered implants. Clin Oral Implants Res. 2011;22(11):1303-1307. doi:10.1111/j.1600-0501.2010.02111.x
23. Mastrangelo F, Quaresima R, Canullo L, Scarano A, Muzio LL, Piattelli A. Effects of Novel Laser Dental Implant Microtopography on Human Osteoblast Proliferation and Bone Deposition. Int J Oral Maxillofac Implants. 2020;35(2):320-329. doi:10.11607/jomi.7606
24. Tomasi C, Tessarolo F, Caola I, Wennström J, Nollo G, Berglundh T. Morphogenesis of peri-implant mucosa revisited: an experimental study in humans. Clin Oral Implants Res. 2014;25(9):997-1003. doi:10.1111/clr.12223.
25. Barlattani A Jr, Martelli M, Ceruso FM, Gargari M, Ottria L. Convergent implant transmucosal collar and healing abutment: aesthetics influence on soft tissues. A clinical study. J Biol Regul Homeost Agents. 2020;34(1 Suppl. 1).
26. Rasmusson L, Roos J, Bystedt H. A prospective clinical study of titanium implants with machined and anodized surfaces: 5-year data. Clin Implant Dent Relat Res. 2005;7(1):62-69.
27. Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. J Clin Periodontol. 2015;42 Suppl 16:S158-S171. doi:10.1111/jcpe.12334.
28. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. J Periodontol. 2018;89 Suppl 1:S267-S290. doi:10.1002/JPER.16-0350.
29. Grassi A, Monica D, Minetti E, et al. Innovative Alveolar Ridge Preservation Surgical Technique with Immediate Dental Implant Placement: A Retrospective Case Report of 1-Year Follow-Up. Eur J Dent. 2024 Feb;18(1):408-414. doi: 10.1055/s-0043-1772676.
30. Abrahamsson I, Berglundh T, Lindhe J. The mucosal attachment in the edentulous jaw and the effects of different implant surfaces: an experimental study in dogs. J Clin Periodontol. 2004;31(5):362-368.
31. Mastrangelo F, Gastaldi G, Vinci R, et al. Immediate Postextractive Implants With and Without Bone Graft: 3-year Follow-up Results From a Multicenter Controlled Randomized Trial. Implant Dent. 2018;27(6):638-645. doi:10.1097/ID.0000000000000816.
32. Serra E, Paolantonio M, Spoto G, Mastrangelo F, Tetè S, Dolci M. Bevacizumab-related osteneocrosis of the jaw. Int J Immunopathol Pharmacol. 2009;22(4):1121-1123. doi:10.1177/039463200902200429.
33. Alsaadi G, Quirynen M, Komárek A, van Steenberghe D. Impact of local and systemic factors on the incidence of late oral implant loss. Clin Oral Implants Res. 2008;19(7):670-676. doi:10.1111/j.1600-0501.2008.01534.x
34. Minetti E, Celko M, Contessi M, et al. Implants Survival Rate in Regenerated Sites with Innovative Graft Biomaterials: 1 Year Follow-Up. Materials (Basel). 2021;14(18):5292. doi:10.3390/ma14185292.
35. Gianfreda F, Bollero P, Muzzi M, Di Giulio A, Nicolai E, Canullo L. The Effects of Ultrasonic Scaling and Air-Abrasive Powders on the Decontamination of 9 Implant-Abutment Surfaces: Scanning Electron Analysis and In Vitro Study. Dent J (Basel). 2022;10(3):36. doi:10.3390/dj10030036.
36. Carinci F, Arcelli D, Lo Muzio L, et al. Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. Transl Res. 2007;150(4):233-245. doi:10.1016/j.trsl.2007.03.011
37. Gianfreda F, Pesce P, Marcano E, Pistilli V, Bollero P, Canullo L. Clinical Outcome of Fully Digital Workflow for Single-Implant-Supported Crowns: A Retrospective Clinical Study. Dent J (Basel). 2022;10(8):139. Published 2022 Jul 27. doi:10.3390/dj10080139.
38. Dioguardi M, Spirito F, Quarta C, et al. Guided Dental Implant Surgery: Systematic Review. J Clin Med. 2023;12(4):1490. doi:10.3390/jcm12041490
39. Raffone C, Gianfreda F, Antonacci D, Pompeo MG, Bollero P, Canullo L. Chairside virtual patient protocol. Part 3: In vitro accuracy of a digital facebow. J Dent. 2023;137:104622. doi:10.1016/j.jdent.2023.104622
40. Wennerberg A, Albrektsson T. Suggested guidelines for the topographic evaluation of implant surfaces. Int J Oral Maxillofac Implants. 2000;15(3):331-344.

41. Lauritano D, Mastrangelo F, D'Ovidio C, et al. Activation of Mast Cells by Neuropeptides: The Role of Pro-Inflammatory and Anti-Inflammatory Cytokines. Int J Mol Sci. 2023;24(5):4811. doi: 10.3390/ijms24054811.
42. Sammartino G, Marenzi G, Tammaro L, et al. Anti-inflammatory drug incorporation into polymeric nano-hybrids for local controlled release. Int J Immunopathol Pharmacol. 2005;18(3 Suppl):55-62.
43. Tettamanti L, Kritas SK, Gallenga CE, et al. IL-33 mediates allergy through mast cell activation: Potential inhibitory effect of certain cytokines. J Biol Regul Homeost Agents. 2018;32(5):1061-1065.
44. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in mucosal immunity of intestinal inflammation: Inhibitory effect of IL-37. Eur J Pharmacol. 2018;818:294-299. doi:10.1016/j.ejphar.2017.09.044
45. Conti P, Caraffa A, Ronconi G, et al. Mast cells participate in allograft rejection: can IL-37 play an inhibitory role? Inflamm Res. 2018;67(9):747-755. doi:10.1007/s00011-018-1166-3
46. Lo Muzio L, Tetè S, Mastrangelo F, et al. A novel mutation of gene CBFA1/RUNX2 in cleidocranial dysplasia. Ann Clin Lab Sci. 2007;37(2):115-20.
47. Mastrangelo F, Dedola A, Cattoni F, et al. Etiological periodontal treatment with and without low-level laser therapy on IL-1β level in gingival crevicular fluid: an in vivo multicentric pilot study. J Biol Regul Homeost Agents. 2018;32(2):425-431.
48. Tranasi M, Sberna MT, Zizzari V, et al. Microarray evaluation of age-related changes in human dental pulp. J Endod. 2009;35(9):1211-7. doi: 10.1016/j.joen.2009.05.026.

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Case Report

HYALURONIC ACID RELIEVES PAIN IN A SORE KNEE BUT NOT IN ANTERIOR TALOFIBULAR LIGAMENT INJURY: CASE REPORT

F. Pandolfi[1*], M.J. Conti[2], M. Di Emidio[3], A. Coppola[4], F. Mastrangelo[5] A. Younes[6], G. Marinelli[7], A.M. Inchingolo[7], A.D. Inchingolo[7] and G. Dipalma[7]

[1] Immunology and Allergy, Internal Medicine Department, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy;
[2] S. Andrea University "La Sapienza", Rome, Italy;
[3] University of L'Aquila, L'Aquila, Italy;
[4] Private Practice, Studio Armando Coppola, Naples, Italy;
[5] Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy;
[6] Medical Center "Mai più Dolore", Pescara, Italy;
[7] Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy.

**Correspondence to*:
Prof. Franco Pandolfi,
Immunology and Allergy,
Internal Medicine Department,
Fondazione Policlinico Universitario A. Gemelli IRCCS,
Università Cattolica del Sacro Cuore,
Rome, Italy.
e-mail: pandolfi@rm.unicatt.it

ABSTRACT

Hyaluronic acid (HA) is effective in reducing knee pain in several inflammatory diseases (particularly in osteoarthritis). In this case report, we show that a single dose of 30 mg/2 ml HA injection eliminated pain in the knee but not in the painful anterior talofibular ligament. In the knee, the pain was eliminated after about 20 minutes, while in the torn ligament, the pain persisted. These results are probably due to the different nature of the tissue, and show that HA is more appropriate for synovial pain than tendon pain.

KEYWORDS: *hyaluronic acid, injection, inflammation, knee pain, anterior talofibular ligament*

INTRODUCTION

Hyaluronic acid (HA) is a glycosaminoglycan that is naturally present in the synovial fluid of the knee, which lubricates and cushions the joint (1) (Fig.1). Various knee conditions can cause a decrease in HA concentration, resulting in fluid loss in the joint, causing dysfunction and pain. The exogenous supply of HA aims to restore viscosity and improve joint motion, unfortunately without causing cartilage recovery. Knee viscosupplementation is a therapy that involves injecting HA directly into the joint to relieve osteoarthritis symptoms, such as pain and stiffness, and improve the lubrication and viscoelasticity of the synovial fluid (2) (Table I).

Received: 29 August, 2025
Accepted: 29 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

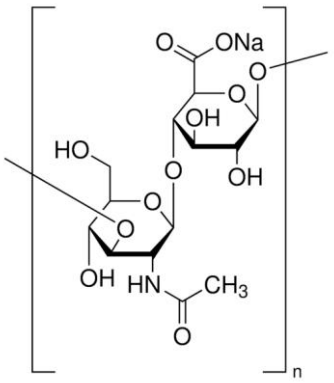

Fig. 1. *Generic chemical formula \([(C_{14}H_{21}NO_{11})_{n}\cdot Na_{n}]_{m}\) or \([(C_{16}H_{27}NO_{11})_{n}\cdot Na_{n}]\), where the subscript "\(n\)" indicates the number of monomer units that make up the polymer chain.*

Table I. *Effect of Hyaluronic acid (HA) on knee pain.*

Viscoelastic mechanical effect:	Increased viscosity and elasticity of the synovial fluid, reducing friction on the cartilage and nerve endings.
Anti-inflammatory effects:	Decreased pro-inflammatory cytokines and suppression of catabolic enzymes that degrade cartilage. Increased endogenous matrix metalloproteinase (MMP) inhibitors and protective TGF-β.
Homeostatic effect:	Stimulation of type B synovial fluid to produce endogenous HA.
Protection of the cartilage:	Formation of a protective film on the surface of the chondrocyte and the synovial membrane.
Pain modulation:	Reduction of nociceptor sensitivity and inhibition of Toll-like receptor 4 (TLR4).

HA acts not only as a mechanical lubricant, but also through biochemical and cellular effects on the joint environment (3). It also slows the penetration of free radicals and oxidants. Injecting HA into the knee can reduce pain in some people, but effectiveness varies greatly from case to case. The treatment is not effective in very advanced osteoarthritis, where a prosthesis is often considered (4).

In addition, in ligaments, as in tendon tissue, HA contributes to interfibrillar lubrication, reducing friction between collagen fibers, promotes the diffusion of nutrients, participates in tissue repair processes, and is expected to modulate the inflammatory response.

MATERIAL AND METHODS

First treatment

An 80-year-old male patient suffering from left knee pain visited a private medical practice in Pescara, Italy, directed by Dr. A. Younes (anaesthesiologist). The physician examined the patient and assessed his pain and knee joint tightness. After lying on a stretcher, the area of pain in the knee was disinfected and a 30 mg/2 ml solution of HA sodium salt (Hyalubrix, Fidia, Italy) was injected into the knee using a prefilled syringe (Fig.2a). In this case, a single course of HA sodium salt solution (30 mg/2 ml) for intra-articular injection was sufficient to eliminate pain after about 20 minutes and restore proper joint function.

Second treatment

The same patient also had a torn anterior talofibular ligament in his right limb due to a car accident. Here too, 30 mg/ 2 ml of HA was injected into the site of pain using the same method as the knee treatment; figure 2c shows a radiograph of the foot (Fig.2b,2c).

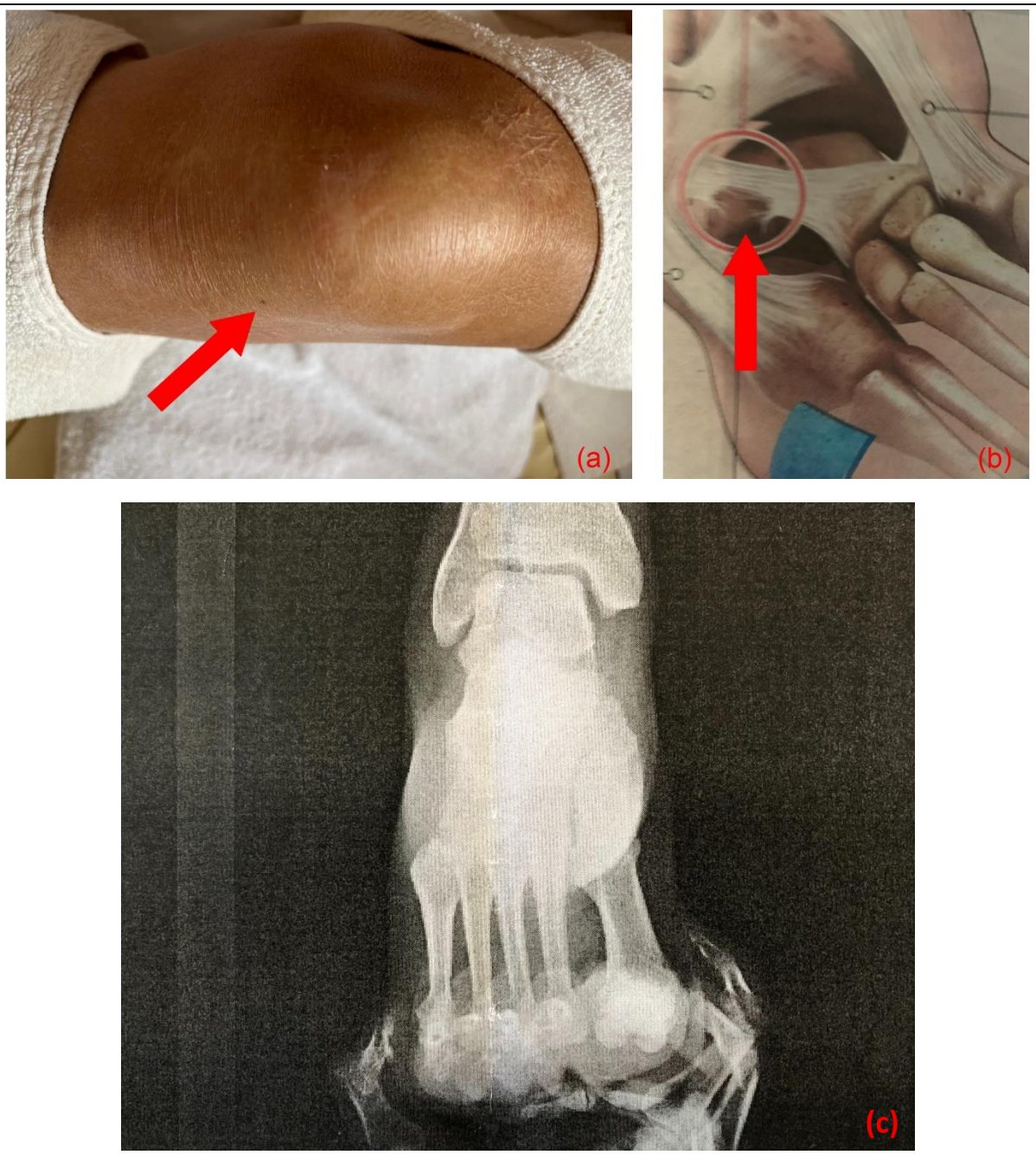

Fig. 2. (a) *30 mg/ 2 ml of HA was injected into the site of pain of the knee.* **(b)** *30 mg/ 2 ml of HA was injected into the site of pain of the torn anterior talofibular ligament. After the injections, the patient was discharged from the clinic.* **(c)** *Radiograph of the foot affected by anterior talofibular ligament.*

RESULTS AND DISCUSSION

Following the two HA injections, one in the left knee and the other in the torn anterior talofibular ligament, the patient found relief in the knee after approximately 20 minutes, and the pain was completely gone after about 1 hour. However, treatment to the ligament showed no improvement in terms of pain, which remained similar to before the HA treatment.

The ligament pain was not reduced because tendon or ligament pain is often linked to microlesions, collagen degeneration such as tendinosis, and local mechanical alterations where it is necessary to stimulate collagen repair and vascularization, not just reduce friction.

Knee viscosupplementation is a therapy that involves injecting HA directly into the joint to relieve the symptoms of osteoarthritis, which causes pain and stiffness, and improve the lubrication and viscoelasticity of the synovial fluid (5). This procedure can be performed on an outpatient basis, and the benefits can last from several months to a couple of years, depending on the pathological state of the affected knee (6). Intra-articular injection of HA significantly improves

knee pain and joint function, substantially reducing the need for painkillers (7). This harmless treatment often avoids the use of immunosuppressive corticosteroids.

The HA injection is most effective when joint damage is mild or moderate. HA treatment is generally safe, but the variability of response has led to the cautious recommendation of viscosupplementation (8). In rare cases, the therapy may cause temporary pain or swelling and inflammatory reactions, after the injection of the HA sodium salt solution (9).

HA interacts with specific receptors on the surface of synovial and immune cells, such as CD44, receptor for hyaluronan-mediated motility (RHAMM), and intercellular adhesion molecule 1 (ICAM-1), modulating various inflammatory pathways and reducing the expression of pro-inflammatory cytokines such as IL-1β, TNF, and IL-6. It also inhibits the Toll-like receptor 4 (TLR4) pathway, which is involved in the transmission of inflammatory pain (10,11). Furthermore, HA reduces the expression of catabolic enzymes, such as matrix metalloproteinase (MMPs), which degrade cartilage (12). HA increases the production of endogenous MMP inhibitors and protective trophic factors such as TGF-β and forms a protective film on the chondrocyte surface and the synovial membrane (13,14). It stimulates chondrocytes to produce new endogenous HA and proteoglycans, restoring a more physiological environment (15). HA inhibits the TLR4 pathway, which is involved in the biochemical cascade for inflammatory cytokine production (16). It also has a homeostatic effect on the synovial membrane where it stimulates type B synoviocytes to produce more endogenous HA (17).

CONCLUSIONS

This paper reports an interesting case in which HA was effective in treating knee pain, but not the talofibular ligament. As far as we know, this is the first case describing the different effects of HA injected into the knee and the ligament.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Wang JY, Roehrl MH. Glycosaminoglycans are a potential cause of rheumatoid arthritis. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(22):14362-14367. doi:https://doi.org/10.1073/pnas.222536599
2. Peck J, Slovek A, Miro P, et al. A Comprehensive Review of Viscosupplementation in Osteoarthritis of the Knee. *Orthopedic Reviews*. 2021;13(2). doi:https://doi.org/10.52965/001c.25549
3. Cole BJ, Karas V, Hussey K, Merkow DB, Pilz K, Fortier LA. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. *The American Journal of Sports Medicine*. 2016;45(2):339-346. doi:https://doi.org/10.1177/0363546516665809
4. Liu L, He G, Li Y, et al. Hyaluronic Acid-Based Microparticles with Lubrication and Anti-Inflammation for Alleviating Temporomandibular Joint Osteoarthritis. *Biomaterials Research*. 2024;28. doi:https://doi.org/10.34133/bmr.0073
5. Glinkowski W, Śladowski D, Tomaszewski W. Molecular Mechanisms and Therapeutic Role of Intra-Articular Hyaluronic Acid in Osteoarthritis: A Precision Medicine Perspective. *Journal of Clinical Medicine*. 2025;14(8):2547-2547. doi:https://doi.org/10.3390/jcm14082547
6. Corvelli M, Che B, Saeui C, Singh A, Elisseeff J. Biodynamic performance of hyaluronic acid versus synovial fluid of the knee in osteoarthritis. *Methods (San Diego, Calif)*. 2015;84:90-98. doi:https://doi.org/10.1016/j.ymeth.2015.03.019
7. Zhou F, Chen M, Qian Y, et al. Enhancing Endogenous Hyaluronic Acid in Osteoarthritic Joints with an Anti-Inflammatory Supramolecular Nanofiber Hydrogel Delivering HAS2 Lentivirus. *Small*. 2024;20(40):e2400542. doi:https://doi.org/10.1002/smll.202400542
8. Beer K, Kaufman-Janette J, Bank D, et al. Safe and Effective Chin Augmentation With the Hyaluronic Acid Injectable Filler, VYC-20L. *Dermatologic Surgery*. 2021;47(1):80-85. doi:https://doi.org/10.1097/DSS.0000000000002795
9. Yau LK, Henry F, Man Hong C, et al. Swelling assessment after total knee arthroplasty. *Journal of Orthopaedic Surgery*. 2022;30(3):102255362211276. doi:https://doi.org/10.1177/10225536221127668

10. Ebbesen MF, Olesen MT, Gjelstrup MC, et al. Tunable CD44-Specific Cellular Retargeting with Hyaluronic Acid Nanoshells. *Pharmaceutical Research*. 2014;32(4):1462-1474. doi:https://doi.org/10.1007/s11095-014-1552-7
11. Kosovrasti VY, Nechev LV, Amiji MM. Peritoneal Macrophage-Specific TNF-α Gene Silencing in LPS-Induced Acute Inflammation Model Using CD44 Targeting Hyaluronic Acid Nanoparticles. *Molecular Pharmaceutics*. 2016;13(10):3404-3416. doi:https://doi.org/10.1021/acs.molpharmaceut.6b00398
12. Hashizume M, Mihara M. High molecular weight hyaluronic acid inhibits IL-6-induced MMP production from human chondrocytes by up-regulating the ERK inhibitor, MKP-1. *Biochemical and Biophysical Research Communications*. 2010;403(2):184-189. doi:https://doi.org/10.1016/j.bbrc.2010.10.135
13. Knight PG, Glister C. Local roles of TGF-β superfamily members in the control of ovarian follicle development. *Animal Reproduction Science*. 2003;78(3-4):165-183. doi:https://doi.org/10.1016/s0378-4320(03)00089-7
14. Wan H, Ren K, Kaper HJ, Sharma PK. Cartilage lamina splendens inspired nanostructured coating for biomaterial lubrication. *Journal of Colloid and Interface Science*. 2021;594:435-445. doi:https://doi.org/10.1016/j.jcis.2021.03.052
15. Kang JY, Chung CW, Sung JH, et al. Novel porous matrix of hyaluronic acid for the three-dimensional culture of chondrocytes. *International Journal of Pharmaceutics*. 2009;369(1-2):114-120. doi:https://doi.org/10.1016/j.ijpharm.2008.11.008
16. Lee S, Seo J, Kim YH, et al. Enhanced intra-articular therapy for rheumatoid arthritis using click-crosslinked hyaluronic acid hydrogels loaded with toll-like receptor antagonizing peptides. *Acta Biomaterialia*. 2023;172:188-205. doi:https://doi.org/10.1016/j.actbio.2023.10.023
17. Schmidt TA, Gastelum NS, Nguyen QT, Schumacher BL, Sah RL. Boundary lubrication of articular cartilage: Role of synovial fluid constituents. *Arthritis & Rheumatism*. 2007;56(3):882-891. doi:https://doi.org/10.1002/art.22446

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Observational Study

WATER-BASED BIODANZA AS A MULTISENSORY STIMULATION IN THE MANAGEMENT OF CHRONIC PAIN: A PILOT OBSERVATIONAL STUDY

G. Barassi[1], V. De Carolis[1], A. Younes[1], L. Prosperi[1], C. Di Matteo[1], C. Mariani[1], G. Pasetti[2], L. Buzzelli[2], C. Candita[3] and P.E. Gallenga[1]

[1] Center for Physiotherapy, Rehabilitation and Re-Education (Ce.Fi.R.R.), Venue "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy;
[2] Social Promotion Association "Spazio Donna Abruzzo", Pescara, Italy;
[3] Department of Innovative Technologies in Medicine & Dentistry, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy.

**Correspondence to*:
Loris Prosperi,
Center for Physiotherapy, Rehabilitation and Re-Education (Ce.Fi.R.R.) venue "G. d'Annunzio" University of Chieti-Pescara,
Chieti 66013, Italy.
e-mail: cefirr.ricerca@gmail.com

ABSTRACT

Chronic pain (CP) is a condition characterized by persistent pain in one or more parts of the body, which can take on very disabling characteristics of intensity and intrusiveness. Its management is multidisciplinary, and among the various therapeutic and re-educational tools, adapted physical activity, including artistic forms such as dance, appears to yield positive results for CP. However, research in this area is still limited, and the most appropriate forms of therapeutic dance for this condition need to be identified. This single-arm pilot study aims to preliminary evaluate the effectiveness of water-based Biodanza (BD), a dance approach that integrates multisensory stimulations of a motor and psycho-emotional nature in an aquatic environment, in the management of CP. A group of 10 CP women (mean age 58 ± 12 years) was enrolled after medical examination and observed while undergoing treatment with water-based BD. Practitioners underwent water-based BD sessions 1 time a week for 10 weeks, with each session lasting around 1 hour and 30 minutes. They were evaluated before the start of the protocol (T0) and after the end of it (T1) through the Numeric Pain Rating Scale, Digitized Bio-Metric Assessment and Safe Bead Balance postural assessment. The statistical analysis, in relation to the observed variations in the parameters considered, highlighted mixed levels of statistical significance, varying from high to null, but generally characterized by a high clinical relevance by virtue of moderate to large effect sizes. The water-based BD approach might be a safe and valid support for women affected by CP but further studies are necessary to deepen the validity of the approach.

KEYWORDS: *Chronic pain, posture, proprioception, dancing, dance therapy, rehabilitation*

INTRODUCTION

Chronic pain (CP) is a condition characterized by the persistence of pain in one or more parts of the body for months or years, which over time causes interference with daily life, often associated with the presence of depression and anxiety (1). Prevalence rates of CP are estimated to be between 11% and 40%, also varying depending on the severity of the condition considered (1). The annual incidence rate for CP seems to be around 8%, with a recovery rate of about 5% (1).

Received: 16 September, 2025
Accepted: 31 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

It mainly occurs in the spine and shoulder girdle, often associated with symptoms of motor limitation and, above all, postural alteration (2,3).

Given the multifactorial nature of CP, over time, multiple forms of treatment have been identified that act more or less directly on the condition (4). The typical treatment is in fact based on pharmacological, neurocognitive, sensorimotor and invasive instrumental interventions (4). In general, it is believed that the management of CP should be predominantly person-centered, so as to allow the patient to self-manage the problem, as well as provide broader and more comprehensive professional treatment (5). In fact, activities based on an occupational and motor-recreational vision of the problem would appear to be very useful for managing CP (6,7). Among the most frequently proposed motor and recreational activities for the management of CP, we certainly find dance, which seems to guarantee excellent outcomes in terms of musculoskeletal pain and coping strategies for the pathology (8). Dance is particularly suitable in the presence of CP when based on typologies exploiting the integration of mindfulness with the motor component of the activity (9).

Biodanza (BD) is a therapeutic approach based on dance and applied in multiple treatment fields, especially neuro-psychiatric (10). BD is a bionatural discipline defined as a system of affective-motor integration for the development of human vital potential (10). It can be viewed as a holistic activity based on psychological concepts promoted by Chilean psychologist Rolando Toro Araneda, conducted in groups using music and dance (10). The goal of BD is to enable practitioners to awaken intrinsic human qualities, such as vitality, creativity, sexuality, affectivity, and transcendence, in relation to one's natural instincts, all through movement integrated with music (10). This discipline has proven useful in improving the well-being of people affected by various pathological conditions associated with symptoms such as depression, anxiety, reduced quality of sleep, or altered emotional intelligence (10). Therefore, it is possible that BD could also bring benefits to people with CP, who often present the same symptoms in terms of psycho-physical well-being, especially when performed in a water-based environment.

To date, however, research into the therapeutic role of artistic disciplines, including BD, is still relatively lacking and it would be desirable to conduct studies on the possible implications of these therapeutic approaches at the psychological and musculoskeletal levels (11). This is especially true for water-based BD.

The present observational study aims to preliminarily describe the effects that a BD protocol, applied in a water-based environment, can induce in women affected by CP.

MATERIALS AND METHODS

This research is a single-arm pilot retrospective analytical observational study carried out at the Center for Physiotherapy Rehabilitation and Re-Education (Ce.Fi.R.R.) of Chieti (Italy), from April to July 2025.

All the procedures applied follow the Italian safety regulations. The main major contraindications to access the protocol were acute infectious disease, severe neurological disease, feeling of instability or dizziness, epilepsy, electrical implants, and general contraindications to practicing water-based exercises (such as allergy to chlorine, intolerance to temperatures above 32°C, inability to swim, etc.). The protocol was not an experimental practice and fell within the re-educational context of non-sanitary adapted physical activity, in accordance with the definitions and indications of Italian laws. 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).

During the reference period, a total of 10 women (mean age 58 ± 12 years), affected by CP, spontaneously approached the study center to undertake an aquatic physical activity program consisting of 10 water-based BD sessions, to be performed 1 time per week. Water-based BD sessions were conducted in small groups of no more than 4-5 people, and not all practitioners began the 10-session process at the same time. Before starting the water-based BD program (time T0), the practitioners underwent an admission rheumatological medical examination, aimed at ascertaining the absence of contraindications to the specific activity, as well as confirming the diagnosis of CP and collecting data relating to pain intensity and static postural alignment. At the end of the water-based BD program (time T1), the practitioners were reevaluated by the same medical doctors to verify the status of the CP after performing the aquatic physical activity protocol.

Specifically, the evaluations were based on the rapid and non-invasive collection of the following parameters:

- *Numeric Pain Rating Scale (NPRS)*: it is one of the most used tools in clinical practice for assessing the subjective pain perceived by an individual. It derives from the Visual Analogue Scale (VAS) and is divided into ten pain levels, distributed equidistant on a 10 cm long strip. A value of 0 represents the total absence of pain, a value between 1

and 3 corresponds to mild pain, a value between 4 and 6 corresponds to moderate pain and a value between 7 and 10 corresponds to severe pain, where a score of 10 represents the maximum level of pain imaginable and/or ever experienced by the patient (14).

- *Digitized Biometric Assessment (DBA)*: assessed through a high-resolution 2D platform which captures plantar pressure distribution changes with 4 sensors per cm2 (Diasu Health Technologies, Rome, Italy) (15). 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 Postural Biometric Index (PBI), which is an index calculated by the software of the platform combining the parameters of Center of Pressure, Symmetry of Bipodalic Load, Symmetry of Retro-Forefoot Load, Angle of Centers of Pressure, Podalic Angle, Location of Maximum Pressure Point, Symmetry of Support Surface and Center of Gravity Deviation - Center of Pressure (15). The PBI value is considered healthy from 0 to 10 and dysfunctional if >10.

- *Safe Bead Balance (Sa.B.B.)*: it is a postural markers-free assessment tool exploiting the Microsoft Kinect (Microsoft Corporation, Redmond, Washington, U.S.A.) camera combined with a proprietary software able to reconstruct a 3D-avatar called “Skeletal View. The software has a capture frequency of 30 frames per second and each single analysis lasts about 5 seconds, capturing on average 150 frames in a single evaluation. The avatar obtained through the combination of all the frames captured is formed by a frontal and a sagittal projection, which shows different postural setting parameters both of a single body district and of multiple districts in relationship with each other, such as the spine, the shoulders, the hips and various other bodyparts (16). For this study, in particular, the symmetry values of the shoulders (Sa.B.B. – SS), for the upper body, and of the knees (Sa.B.B. -KS), for the lower body, were considered. The value was indicated in degress of the angle formed between the ideal horizon line and the actual line passing through the two acromial margins and the centre of the two patellas respectively.

The water-based BD protocol, guided by a qualified instructor in each of the 10 sessions, was developed in two macro-phases. Each session lasted approximately 1 hour and 30 minutes, varying slightly depending on the progress of the session and the personalization of the work for the individual participants in the small group.

In the first "introductory" macro-phase, corresponding to the first 2 sessions, the participants performed motor work guided by the instructor outside the pool; they were taught and performed the BD movements which were then carried out in subsequent sessions within the water-based work.

From sessions 3 to 10, the actual water-based BD work macro-phase was carried out inside a pool measuring approximately 10 m in length and 5 m in width, with 3 levels of depth (1,1 m, 1,3 m and 1,8 m) and chlorinated water (± 1,2 mg/l) heated to 33 °C with an average pH value of ± 7. For ease of execution and safety of the practitioners, the water-based BD sessions were carried out in water at a depth of 1.3 m. This water-based BD work macro-phase was divided into sub-phases as follows:

- *“welcome” phase*: it consists of verbally sharing and exchanging feelings and emotions relating to the previous lesson and the past week, as well as in the presentation of the new session. This phase lasted approximately 20 minutes;

- *“activation” phase*: during this phase, active-playful exercises were proposed, such as various forms of walking (starting from rhythmic, physiological and synergistic ones), motor integration movements and spontaneous dances to the notes of cheerful and lively musical pieces, to be performed alone or in pairs, usually with eyes open. This phase lasted approximately 20 minutes;

- *“harmonization” phase*: in this phase, through the slowing down of movements, a progressive state of regression is reached, by performing semi-guided exercises to stimulate kinesthetic pleasure, characterized by slow, fluid and harmonious movements, and mobilization exercises of different body areas such as the ocular, oral, cervical, thoracic, diaphragmatic, abdominal and pelvic segments. These exercises, preferably performed with eyes closed, are inspired by the mobilizations and movements of Thai Chi techniques and are performed respecting the mobility and fluidity of each practitioner. Furthermore, in this phase part of the work is focused on a form of floating supported by the instructor, which aims to induce total relaxation in the practitioners by causing a state defined as "waking trance". This phase lasted approximately 30 minutes;

- *“reactivation” phase*: in this final stage, there is a gradual return from the state of regression to that of identity. Music plays an extremely important role in this phase; the use of songs with a fast tempo, which can be hummed if desired, encourages a return to identity and reactivation after a moment of intense relaxation. All this occurs while respecting the individual timing and progressiveness of reactivation for each practitioner. In the end, holding each other by the waist or by the hand, practitioners slowly move in a circle to the right, opening their eyes when desired and gradually increasing the intensity and speed of the movement, until stopping at the end of the music. This phase

lasted approximately 20 minutes.

Due to the relatively small size of the observed group, 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

Of the 10 participants who began the water-based BD adapted physical activity program, 2 did not complete all 10 planned sessions, stopping early due to personal reasons related to the difficulty of scheduling their family and work lives around the session appointments. Therefore, data analysis was conducted taking into account the T0 and T1 values collected for the 8 participants who completed the entire protocol.

Statistical analysis showed that the execution of the water-based BD protocol is associated with more or less significant, but generally always clinically relevant, variations in the pain and postural quality of the practitioners.

In particular, statistically significant changes with a large effect size were detected in terms of pain assessed with the NPRS (Table I). The difference in foot load assessed with the SPT and in knee symmetry assessed with the Sa.B.B. also showed slightly non-significant changes, but with a large effect size (Table I). More uncertain results were detected regarding the PBI and shoulder symmetry values, which improved non-significantly and with only a moderate to low effect size (Table I).

Table I. *Results of the data analysis.*

Variable	Count	Mean ± SD	*p*	r	% variation
NPRS (T0)	8	6.4 ± 2.0	0.02	-0.8687	-32.2 %
NPRS (T1)	8	4.0 ± 2.8			
SPT (T0)	8	16.5 ± 8.5 %	0.08	-0.6228	-37.3 %
SPT (T1)	8	10.4 ± 9.4 %			
PBI (T0)	8	12.0 ± 5.2	0.40	-0.3206	-12.5 %
PBI (T1)	8	10.5 ± 2.6			
Sa.B.B - SS (T0)	8	1.2 ± 1.2 °	0.93	-0.0320	+0.8 %
Sa.B.B - SS (T1)	8	1.2 ± 1.1 °			
Sa.B.B - KS (T0)	8	3.3 ± 1.5 °	0.11	-0.5660	-36.9 %
Sa.B.B - KS (T1)	8	2.1 ± 2.0 °			

No reports of discomfort, adverse events or side effects were recorded in any of the treatment sessions of each practitioner who completed the protocol in whole or in part.

DISCUSSION

The present study confirmed that adapted physical activity through a water-based BD protocol is associated with a general improvement in the health status of practitioners with CP. In particular, excellent results were observed in terms of pain reduction (NPRS variation = -32.2%, p = 0.02, r = -0.8687). Positive and relevant results, although not fully significant, were also observed in relation to foot load symmetry (SPT variation = -37.3%, p = 0.08, r = -0.6228) and knee symmetry (Sa.B.B - KS variation = -36.9 %, p = 0.11, r = -0.5660). However, in terms of general postural quality, the improvement observed was apparently insignificant, although still moderately clinically relevant (PBI variation = -12.5%, p = 0.40, r = -0.3206), with a tendency to approach the PBI normality cut-off value, equivalent to a score of 10. At the same time, the symmetry of the shoulders of the practitioners remained essentially unchanged (Sa.B.B - SS variation = +0.8 %, p = 0.93, r = -0.0320).

CP is characterized by an extremely complex etiology, as it loses its function as a signal of physical damage, typical of acute inflammatory or nociceptive pain, to take on the characteristics of a phenomenon involving neuropathic, nociplastic-dysfunctional and psycho-emotional factors (17). Indeed, chronicity, through complex mechanisms, brings into play psychological, behavioral, cognitive, and social factors, which require a multidimensional assessment and, at times, the use of specialized pain management facilities and techniques (18). Management often involves the combination of exercise reconditioning, an exercise program, and cognitive and behavioral psychoeducation. In all cases,

multidisciplinary management ensures consistency and effectiveness (5). Multidisciplinary management of CP cannot ignore the use of adapted physical activity protocols, especially those based on activities such as dance (19).

In fact, dance, due to its unique nature as an activity that engages both the motor and psycho-emotional aspects of the human being, can provide significant benefits in the presence of CP (19). It is no coincidence that group dance protocols based on mindful approaches appear to yield excellent results in the management of some forms of CP, such as fibromyalgia or chronic headaches (20,21). It is highly likely that these positive effects of dance are the result of a rebalancing of the viscero-somatic and somato-visceral integration circuits that occur in the human body, particularly at the level of the posterior horn of the spinal cord at various metameric levels (22). The alteration of this feedback circuit, based on motor and emotional responses to afferent inputs from the external environment, can in fact determine the onset of multiple pathological symptoms, such as musculoskeletal pain, postural alterations, neurovegetative phenomena, and psycho-emotional changes (23).

The positive effects of water-based BD we observed, in addition to leveraging the neurophysiological mechanisms described, may have been amplified by the fact that it was performed, from the third session onward, in an aquatic environment. Indeed, pool exercise has consistently proven to be an extremely useful tool in managing CP, especially given its ability to control the pain experienced by patients (24). It is believed that the positive effect of water exercise on pain is due to a combination of thermal and mechanical stimuli, particularly those related to hydrostatic pressure, which induce an increase in the serotoninergic and beta-endorphin systems at the central nervous level, as well as modulation of the activation of nociceptive fibers at the peripheral level (24), probably activating the “gate control” mechanism (25). Furthermore, water allows for physical exercises and movements to be performed in a less impactful way on the physique of practitioners, by virtue of its anti-gravity effect in reducing body weight, as well as the more gradual speed-dependent and surface-dependent modulation of the resistance offered to movements by the medium (26).

Furthermore, considering that BD in general is also characterized by phases of work that converge in the psychological field, particularly through moments of dialogue and sharing of emotions and experiences that take place during the sessions, it also embraces the management of psycho-emotional aspects typically related to CP (27).

It follows that the positive effects we observed in association with the water-based BD protocol in practitioners affected by CP could likely be due to an ideal combination of factors that compose it, such as dance (motor and artistic work aspect), water (favorable environmental aspect) and moments of sharing and dialogue (psycho-emotional support aspect).

It must be considered that the present study is characterized by a series of limitations that keep from making clear generalizations of the results. First, the observed sample is quite small. Second, the observational single-arm nature of the study does not allow to make comparison between the observed sample and a sample of subjects undergoing a different exercise approach for CP. Lastly, the assessments, being based on routine, rapid, and minimally invasive methods, were probably not sufficiently thorough. Therefore, deeper studies on the topic should consider larger and better stratified samples, combined with the presence of a control group and the use of more accurate assessment systems.

CONCLUSIONS

The results of this multisensory stimulation experience through water-based BD demonstrate that well-modulated and integrated somatic, sensorial, and emotional inputs can have a positive impact on pain perception, posture, and the quality of life of individuals suffering from CP. Furthermore, because the water-based BD approach is pleasant, non-invasive, and integrates aspects ranging from physical activity to psycho-emotional support in the same session, this system of adapted physical activity could offer significant long-term benefits in terms of time, cost of care, and quality of life for people with CP. However, new and more extensive studies will be needed to not only confirm the validity of the water-based BD approach in this context, but also to better define the ideal methodology for its application to ensure greater replicability of its effects.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Cohen SP, Vase L, Hooten WM, et al. Chronic pain: an update on burden, best practices, and new advances. The Lancet. 2021; 397(10289):2082-2097.

2. Viseux FJF, Simoneau M, Billot M. A Comprehensive Review of Pain Interference on Postural Control: From Experimental to Chronic Pain. Medicina. 2022; 58(6):812.
3. Cramer H, Mehling WE, Saha FJ, Dobos G, Lauche R. Postural awareness and its relation to pain: validation of an innovative instrument measuring awareness of body posture in patients with chronic pain. BMC musculoskeletal disorders. 2018; 19(1):109.
4. Rahman S, Kidwai A, Rakhamimova E, Elias M, Caldwell W, Bergese SD. Clinical Diagnosis and Treatment of Chronic Pain. Diagnostics. 2023; 13(24):3689.
5. Themelis K, Tang NKY. The Management of Chronic Pain: Re-Centring Person-Centred Care. Journal of Clinical Medicine. 2023; 12(22):6957.
6. Lagueux É, Masse J, Pagé R, Marin B, Tousignant-Laflamme Y. Management of Chronic Pain by Occupational Therapist: A Description of Practice Profile. Canadian Journal of Occupational Therapy. 2023; 90(4):384-394.
7. Nielsen SS, Skou ST, Larsen AE, Bricca A, Søndergaard J, Christensen JR. The Effect of Occupational Engagement on Lifestyle in Adults Living with Chronic Pain: A Systematic Review and Meta-analysis. Occupational Therapy International. 2022; 2022(1):7082159.
8. Hickman B, Pourkazemi F, Pebdani RN, Hiller CE, Fong Yan A. Dance for chronic pain conditions: a systematic review. Pain Medicine. 2022;23(12):2022-2041.
9. Shim M, Gaydos M, Goldstein-Levitas N, et al. Development and feasibility of a mindfulness-based dance/movement therapy intervention for chronic low back pain. Frontiers in Pain Research. 2024; 5:1281085.
10. Quevedo CA, Viera EC, Pascual IR. Biodanza: systematic review of the benefits of an emerging practice in the promotion of health and well-being. Retos. 2021; 39:844-848.
11. Raudenska J, Šteinerová V, Vodičková Š, et al. Arts therapy and its implications in chronic pain management: a narrative review. Pain and Therapy. 2023; 12(6):1309-1337.
12. De Sanctis V, Soliman AT, Daar S, et al. Retrospective observational studies: Lights and shadows for medical writers. Acta Bio Medica Atenei Parmensis. 2022; 93:e2022319.
13. Winter EM, Maughan RJ. Requirements for ethics approvals. Journal of Sports Sciences. 2009; 27:985.
14. Cheatham SW, Kolber MJ, Mokha M, Hanney WJ. Concurrent validity of pain scales in individuals with myofascial pain and fibromyalgia. Journal of Bodywork and Movement Therapies. 2018; 22:355–360
15. Barassi G, Di Simone E, Galasso P, et al. Posture and health: are the biomechanical postural evaluation and the postural evaluation questionnaire comparable to and predictive of the digitized biometrics examination? International Journal of Environmental Research and Public Health. 2021; 18(7):3507.
16. Barassi G, Bellomo RG, Carmignano SM, et al. Flexible software for the elimination of the markers used in the analysis of human posture through kinect® sensor. Archives of Physiotherapy & Global Researches. 2016; 20(1).
17. Nijs J, Malfliet A, Nishigami T. Nociplastic pain and central sensitization in patients with chronic pain conditions: a terminology update for clinicians. Brazilian Journal of Physical Therapy. 2023 May-Jun;27(3):100518.
18. Harris RE, Clauw DJ. Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy. Neuroscience letters. 2012; 520:192–196.
19. Shim M, Johnson RB, Gasson S, Goodill S, Jermyn R, Bradt J. A model of dance/movement therapy for resilience-building in people living with chronic pain. European Journal of Integrative Medicine. 2017; 9:27-40.
20. Murillo-Garcia A, Villafaina S, Adsuar JC, Gusi N, Collado-Mateo D. Effects of Dance on Pain in Patients With Fibromyalgia: A Systematic Review and Meta-Analysis. Evidence-Based Complementary and Alternative Medicine. 2018; 2018(1):8709748.
21. Majore-Dusele I, Karkou V, Millere I. The development of mindful-based dance movement therapy intervention for chronic pain: a pilot study with chronic headache patients. Frontiers in psychology. 2021; 12:587923.
22. Mørch CD, Hu JW, Arendt-Nielsen L, et al. Convergence of cutaneous, musculoskeletal, dural and visceral afferents onto nociceptive neurons in the first cervical dorsal horn. European Journal of Neuroscience. 2007; 26(1):142-154.
23. Barassi G, Pellegrino R, Di Matteo C, et al. Bio-physico-metric approach: assessment and treatment of key myofascial trigger points through an adaptive neuromodulation device. Journal of Biological Regulators and Homeostatic Agents. 2023; 37(1):25-29.

24. Wang T, Wang J, Chen Y, Ruan Y, Dai S. Efficacy of aquatic exercise in chronic musculoskeletal disorders: a systematic review and meta-analysis of randomized controlled trials. Journal of Orthopaedic Surgery and Research. 2023; 18(1):942.
25. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. The Journal of Pain. 2015; 16(9):807-813.
26. Torres-Ronda L, i del Alcázar, X.S. The properties of water and their applications for training. Journal of human kinetics. 2014; 44:237.
27. Driscoll MA, Edwards RR, Becker WC, Kaptchuk TJ, Kerns RD. Psychological interventions for the treatment of chronic pain in adults. Psychological Science in the Public Interest. 2021; 22(2):52-95.

European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Article

MATERIALS SELECTION AND EVALUATION OF OUTCOMES IN ENDODONTIC SURGERY: AN UPDATE

S. Ceraulo[1,2*], H.Z. Hao[1] and A. Barbarisi[1]

[1] Department of Medicine and Surgery, University of Milano-Bicocca, 20100 Monza, Italy;
[2] Fondazione IRCCS San Gerardo dei Tintori, 20900 Monza, Italy.

Correspondence to:
Saverio Ceraulo,
Department of Medicine and Surgery,
University of Milano-Bicocca,
20100 Monza, Italy.
e-mail: saverio.ceraulo@unimib.it

ABSTRACT

Purpose: Endodontic surgery is a reliable procedure for the treatment of teeth with persistent periradicular lesions. The aim of this study is to identify and summarise the cases in which retrograde endodontic surgery is indicated and the materials for performing it, with the aim of providing simple and predictable guidelines for daily clinical practice to achieve the best possible results. *Methods:* An electronic search of the Cochrane, PubMed (MEDLINE) and ScienceDirect databases was conducted between January and December 2024. Inclusion criteria were randomised clinical trials, prospective or retrospective cohort studies and cross-sectional studies in humans with at least 1 year of follow-up, published within the last 15 years. Two researchers independently screened the title and abstract of each article identified in the search to determine eligibility. *Results:* Ten articles were selected and compared with the Matrix method, as the other publications were used for background writing. The indications for retrograde surgery are persistent or refractory endodontic lesions, perforations of the apical third, intraradicular infections that cannot be treated with orthodontic root canal therapy, obstruction or obliteration of the root canal lumen, extraradicular infections, well-executed root canal treatments where it is difficult to obtain a better result with orthodontic therapy. *Conclusions:* With regard to materials, Super-EBA, MTA and BD when used according to the indications, reported superimposable results. The use of magnifying equipment and ultrasonic inserts facilitates the execution of treatment and increases the quality of work.

KEYWORDS: *Endodontic surgery, retrofilling material, MTA, SuperEba, periradicular lesion, retrograde endodontics*

INTRODUCTION

Endodontic surgery is a reliable procedure for the treatment of teeth with persistent periradicular lesions that did not respond to initial primary or secondary canal treatment (1). The main aim of apical surgery is to achieve the cleaning, shaping, and three-dimensional filling of the apical portion of the root canal system, which is not treatable through an access cavity, but through a surgical flap (2). So, prevention of the bacterial leakage from the root canal system into the periradicular tissues is given by placing a tight root canal filling after root-end resection.

Recent studies have shown a 93% success rate for endodontic retrograde therapy after 1-10 years of follow-up (3,4), based on clinical and radiological principles.

The materials used for retrograde filling (5) must be easily manipulated and rapidly positioned with adequate timing, dimensionally stable after insertion, capable of hermetically sealing the retrograde cavity preparation and the entire bevel surface (if desired), easily adaptable to the various shapes and contours of the preparation, biocompatible and capable of

Received: 04 September, 2025
Accepted: 21 October, 2025

ISSN 2038-4106 print
ISSN 2975-044X online

promoting cementogenesis, non-porous and impermeable to all periapical tissues and fluids, insoluble in tissue fluids, non-corrosive and non-oxidizable, non-resorbable, not affected by humidity, bacteriostatic or that do not favor bacterial growth, radiopaque or easily recognizable on radiographs, not discolor the tooth structure or surrounding tissues, sterile or easily sterilized before their using, easily removable, non-carcinogenic and non-irritating to periapical tissues.

Nowadays, there are many materials that can be used for endodontic surgery, including IRM, SuperEBA (SEBA), Optibond, Geristore, Mineral Trioxide Aggregate (MTA) and BC-RRM (6).

One study stated that the main differences between periapical tissue responses to amalgam, SuperEBA, and MTA as root filling materials are the degree of inflammation and the type of inflammatory cells infiltrated, the frequency of fibrous capsules, cement formation over these materials, and the thickness of the periodontal ligament (7). MTA was found to be the best material overall, although SuperEBA was better than amalgam as a root filling material.

Indications for surgical endodontics include (8):

i. Radiographic evidence of apical periodontitis and/or symptoms associated with an obstructed canal (the obstruction proved not to be removable, displacement did not seem feasible, or the risk of damage was too great);
ii. Extruded material with clinical or radiographic evidence of apical periodontitis and/or symptoms persisting over a prolonged period;
iii. Persistent or new disease following root canal treatment when root canal retreatment is inappropriate;
iv. Perforation of the root or pulp chamber floor where treatment from within the pulp chamber is not possible.

Contraindications to surgical endodontics include (8):

i. Local anatomical factors such as inaccessible root end;
ii. Tooth with inadequate periodontal support;
iii. Uncooperative patient;
iv. Patients with compromised medical history.

To sum up, according to the literature the cases solvable by endodontic surgery include (8,9):

i. Infections or injures, such as persistent or refractory endodontic lesions, intraradicular infections that cannot be treated with orthograde canal therapy, extraradicular infections (the root surface cementum is colonised by bacteria), and foreign body or periradicular cyst reactions.
ii. Factors related to the morphology and content of the endodontium, such as apical third perforations, blockage or obliteration of the canal lumen, well-executed root canal treatments where a better result is difficult to achieve by orthograde.
iii. Factors associated with tooth reconstruction, such as recently made crowns or bridges or intracanal pins (10).

Over the years, international literature has produced numerous studies on endodontic surgery from various perspectives. However, there is also a great deal of conflicting data in the literature.

Our aim is to provide simple and predictable guidelines on the materials used for endodontic surgery and the protocols to be followed to achieve the highest success rate.

MATERIALS AND METHODS

An electronic search was conducted in the Cochrane, PubMed (MEDLINE), and ScienceDirect databases between January and December 2024. Boolean operators were then used to create a syntax to search for topics as precisely as possible: "Endodontic surgery AND retrofilling materials", “Endodontic surgery AND retrograde endodontics”.

Papers were considered admissible only if they met the following inclusion criteria: definition of a specific systematic search strategy, use of internationally recognized databases for their references, analysis of data obtained from descriptive studies, randomized clinical trials and observational studies (cross-sectional, case-control, cohort studies cohort studies) cited and expressly indicated in the document performed on humans with at least 1 year of follow-up and published within the last 15 years. These are recent studies with the aim of providing as current and reliable as possible impression on the subject.

The exclusion criteria were in silica studies, not on human studies, not in English, not accessible title or abstract, not enough information about the main question of the review.

Titles and abstracts were independently screened by two authors (AB and ZH). If both authors were confident that a study was unsuitable, based on the titles and abstracts, this study was excluded. Any disagreements were resolved by the third author (SC).

Relevant articles were obtained in full-text form, and raw data were extracted independently by each reviewer.

The selected articles were classified into different levels of evidence by means of the Strength of Recommendation Taxonomy criteria. A literature review was performed, following the Matrix method of Judith Garrard (1999). Review articles and relevant articles were searched for cross-references. Twelve articles were selected and compared with the Matrix method, as the other publications were used for background writing (Fig.1).

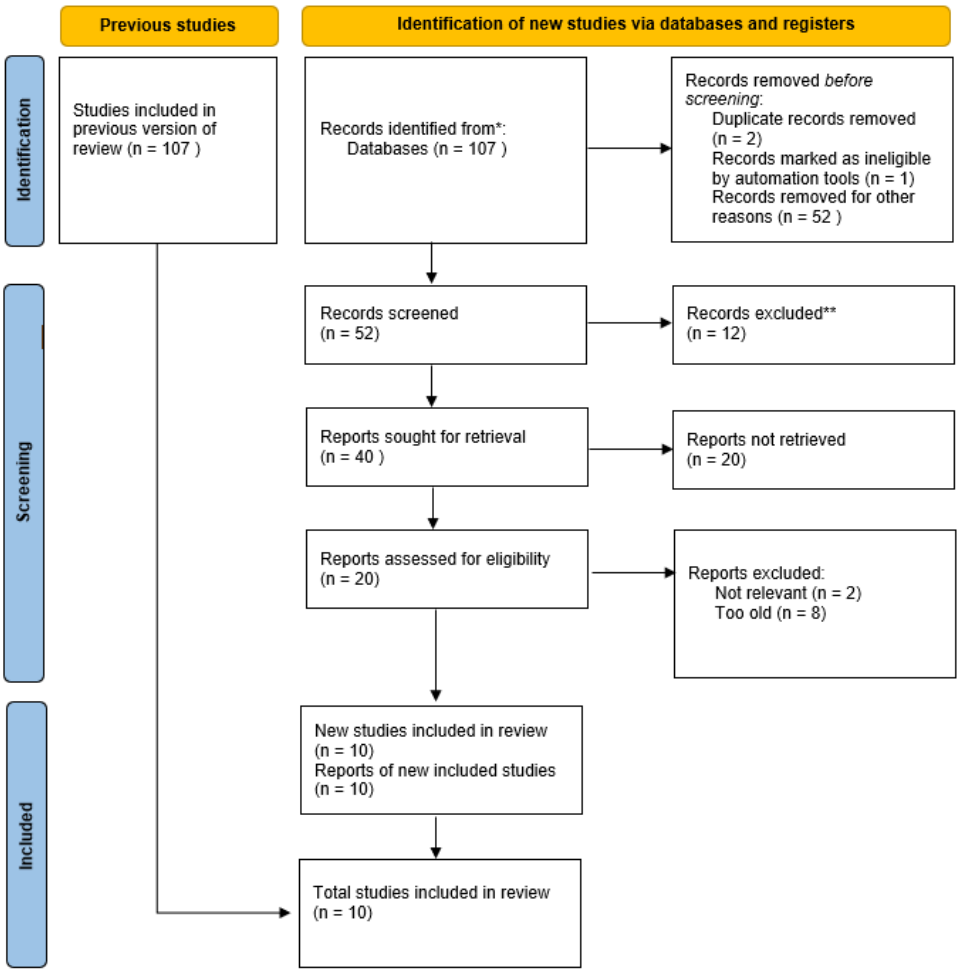

Fig. 1. *Flowchart of the article selection method according to The PRISMA Statement. PRISMA: Preferred Reporting Items for Systematic Reviews.*

The Matrix method is a fundamental method for conducting a literature review; it consists of reading, analyzing and writing a summary of scientific publications on a specific topic and then comparing them. The focus is on the authors' hypotheses, scientific methods, results, interpretations and conclusions.

Once the research was completed, the results obtained were analyzed and discussed in the following chapters.

RESULTS

There were 107 articles identified after database searching. Cross-references of these articles revealed one additional article that was relevant. A total of 52 records were selected after title reading was performed. Following abstract and full-text reading, a total of 42 articles were excluded according to the exclusion criteria previously established. The most frequent cause of exclusion was a not recent and a not relevant study for the aim of this article. All reviewed articles selected are shown below (Table I).

Table I. *Articles selected for this work.*

N° article	Authors, title, journal, year of publication	Objective	Conclusions
1	M K Çalışkan U Tekin M E Kaval M C Solmaz,The outcome of apical microsurgery using MTA as the root-end filling material: 2- to 6-year follow-up study, *International Endodontic Journal,* March 2016 (11).	Evaluate the influence of various predictors on healing outcomes after apical microsurgery (AMS) using MTA as root-end filling material	Using MTA as a root-end filling material for apical microsurgery resulted in an 80% favorable outcome, with no significant impact from the investigated predictors on healing.
2	S. Taschieri, M. Del Fabbro, T. Testori, R. Weinstein, Endoscopic periradicular surgery: A prospective clinical study, *British Journal of Oral and Maxillofacial Surgery*, 2007 (12).	Assess the outcome of periradicular surgery with endoscopy for improved illumination and magnification	Endoscopy allowed good field control but increased surgical time due to the need for frequent lens cleaning.
3	EJerome A. H. Lindeboom, Joost W. F. H. Frenken, Frans H. M. Kroon and Hans P. van den Akker, A comparative prospective randomized clinical study of MTA and IRM as root-end filling materials in single-rooted teeth in endodontic surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005 (13).	Compare MTA and IRM as retrograde sealers in endodontic surgery	No statistically significant differences in success rates between MTA and IRM as retrograde sealers were observed.
4	Gowri, Sree[1]; Jayasheelan, Nishi[1]; Kutty, Shakkira Moosa[1]; Kumar, Pradeep[1,]; Shetty, Divya[2]; Banu, Kausar[3.] An *in vitro* Investigation of the Sealing Ability of Biodentine and Mineral Trioxide Aggregate as Retrofilling Materials after the use of Various Irrigating Solutions. *Journal of Pharmacy And Bioallied Sciences* , July 2022. (14).	Assess the sealing ability of Biodentine (BD) and MTA as retrofilling materials after irrigation with different solutions	Biodentine exhibited better sealing ability than MTA after irrigation with QMix.
5	Yeon-Jee Yoo, Eun-Bee Cho, Hiran Perinpanayagam, Yu Gu, Qiang Zhu, W. Craig Noblett, Kee-Yeon Kum, Endodontic Microsurgery Outcomes over 10 Years and Associated Prognostic Factors: A Retrospective Cohort Study, *Journal of Endodontics*, Volume 50, Issue 7, 2024 (15).	Evaluate long-term outcomes (10–17.5 years) of endodontic microsurgery and identify associated prognostic factors	Long-term success depends on the preoperative condition of the tooth, alveolar bone support, and full-crown restorations.
6	Thomas von Arx, Apical surgery: A review of current techniques and outcome, The Saudi Dental Journal, Volume 23, Issue 1, 2011 (16).	Provide an update on apical surgery techniques and outcomes	Apical surgery is now a predictable treatment for teeth with apical pathology not manageable by conventional endodontics.
7	Seung-Ho Baek, Hanns Plenk, Syngcuk Kim, Periapical Tissue Responses and Cementum Regeneration with Amalgam, SuperEBA, and MTA as Root-End Filling Materials, Journal of Endodontics, Volume 31, Issue 6, 2005 (17).	Compare periapical tissue responses and cementum regeneration with three root-end filling materials: amalgam, SuperEBA, and MTA	MTA showed the most favorable periapical tissue response with cementum neoformation; SuperEBA was superior to amalgam.
8	Pinto D, Marques A, Pereira JF, Palma PJ, Santos JM. Long-Term Prognosis of Endodontic Microsurgery-A Systematic Review and Meta-Analysis. *Medicina (Kaunas).* 2020 September (18).	Evaluate long-term outcomes of endodontic microsurgery (follow-up ≥ 2 years)	Long-term success rates ranged from 78% to 91%, with better outcomes associated with biocompatible filling materials like ProRoot MTA.

9	Kohli MR, Berenji H, Setzer FC, Lee SM, Karabucak B. Outcome of Endodontic Surgery: A Meta-analysis of the Literature-Part 3: Comparison of Endodontic Microsurgical Techniques with 2 Different Root-end Filling Materials. J Endod. 2018 Jun (19).	Compare outcomes of endodontic microsurgery (EMS) and root-end surgery (RES) using different filling materials	EMS showed a significantly higher success rate than RES, with MTA and SuperEBA being the most effective root-end filling materials.
10	Von Arx T, Janner SF, Hänni S, Bornstein MM. Evaluation of New Cone-beam Computed Tomographic Criteria for Radiographic Healing Evaluation after Apical Surgery: Assessment of Repeatability and Reproducibility. J Endod. 2016 Feb (20).	Assess the repeatability and reproducibility of new CBCT-based healing criteria for radiographic evaluation of periapical healing after apical surgery	The B and R indices for healing were highly repeatable and reproducible and should be recommended for future radiographic outcome assessments using CBCT.

DISCUSSION

As Thomas von Arx indicates, retrograde endodontics is to date a predictable technique for treating a peri-apical lesion that cannot otherwise be treated with orthodontic therapy (16). Certainly, the use of a correct magnification and illumination system is the basis for successful treatment. Taschieri et al. claim using an endoscope for illumination and magnification (12). The perception of the depth of field however remains similar to what a surgeon would have with the naked eye. On the other hand, it was necessary to repeatedly clean the lenses in the event of bleeding in the surgical field, which can increase the time required to complete the operation by a few minutes.

Regarding the materials indicated for endodontic surgery, several studies have been analyzed including that of M K Çalışkan (11). In this clinical study, the results showed that apical microsurgery using MTA as a coating material for the radicular end resulted in an 80% favorable clinical outcome and that none of the various predictors studied significantly influenced post-surgical healing. According to the study by Kohli MR, the probability of success for EMS proved to be significantly higher than the probability of success for RES, providing the best available evidence on the influence of cavity preparation with ultrasonic tips and/or SuperEBA, IRM, MTA or silicate cements as root filling material instead of superficial cavity preparation and placement of a resin-based material (19). On the other hand, with regard to root filling material, in the study by Pinto D, ProRoot MTA showed a tendency to better results (18).

In a 2005 study by E. Jerome et al., it is claimed that there are no statistically significant differences in success rates between MTA and IRM (13).

In the study by Seung-Ho Baek et al., the conclusions were that the main differences in tissue responses to retrofilling materials were the degree of inflammation and types of inflammatory cells, the number of fibrous capsule formations, cement neoformation on these materials, bone healing and the thickness of the resulting periodontal ligament (17). Therefore, it is crucial to maintain low levels of inflammation in oral pathologies, both endodontic and periodontal, as chronic oral inflammation has been shown to contribute to systemic diseases such as Alzheimer's disease (21).

The MTA showed the most favorable periapical response, with cementum neoformation on the MTA. SuperEBA was superior to amalgam as a root filling material. In addition, in an article from 2022, it was claimed that BioDentine shows better sealing ability than MTA as posterior filling material after irrigation with QMix (14). Finally, the article of Yeon-Jee Yoo, et al. states that the preoperative state and condition of the tooth, including alveolar bone support and adequate restoration with a full crown, can be prognostic determinants of success and survival over time after EMS (15). Furthermore, the same article states that the long-term outcome of EMS showed high pooled success rates of 78 to 91 per cent at follow-ups of 2 to 13 years.

This therapeutic approach is predictable when performed with modern surgical techniques and associated with biocompatible and bioactive root filling materials, allowing a tooth survival of 79 to 100 per cent, 2 to 13 years after treatment. EMS can be influenced by the following potential prognostic factors: smoking habit, tooth position and type, absence/presence of dentinal defect, interproximal bone level and root filling material.

For the evaluation of the radiographic outcome of retrograde endodontic treatment, the authors Von Arx T et al. state that all indices showed excellent intra-observational concordance (repeatability) (20). Regarding the inter-observational concordance (reproducibility), the B-index (healing of apical and cortical defects combined) and the R-index (healing on the resection plane) showed substantial congruence and thus are to be recommended in future studies when using buccolingual CBCT sections for the evaluation of the radiographic outcome of apical surgery.

Table II summarizes the factors attributable to a significant increase in the healing rate and a better ability to assess the results of therapy (Table II).

Table II. *Factors associated with a significant increase in healing rates and better evaluation of outcomes.*

Absence of pre-operative pain	(22)
Good material density or lesion size less than or equal to 5 mm	(23)
Absence of periapical lesions or lesion size less than or equal to 5 mm	(24)
Use of magnifying equipment	They improve vision of the surgical field. They facilitate the recognition of the root canal system, possible fracture rims, accessory systems (25).
Filling materials	Super-EBA, MTA and BD when used according to the indications, reported superimposable results that were far better than those obtained with other filling materials (amalgam, glass ionomer cements…) (11, 14, 17, 26, 27, 22).
Evaluation of the radiographic outcome of retrograde endodontic treatment	Buccolingual CBCT sections (20).

CONCLUSIONS

This review summarizes both the cases in which retrograde surgery is indicated as a clinical solution and the materials that have been used for better outcomes in retrograde endodontics. The indications for retrograde surgery are persistent or refractory endodontic lesions, perforations of the apical third, intraradicular infections that cannot be treated with orthodontic root canal therapy, obstruction or obliteration of the root canal lumen, extraradicular infections (the root surface cement is colonized by bacteria), well-executed root canal treatments where it is difficult to obtain a better result with orthodontic therapy. With regard to materials, Super-EBA, MTA and BD when used according to the indications, reported superimposable results. The use of magnifying equipment and ultrasonic inserts facilitates the execution of treatment and increases the quality of work. Further studies are necessary in order to have even stronger evidence and to perform clinical trials on patients to confirm or refute the indications found in this literature review.

Author Contributions

Writing-original draft preparation, S.C. end A.B.; Conceptualization, S.C. end A.B.; Supervision, S.C.; Writing-review and editing, Z.H.; Data curation, A.B.; Formal analysis, Z.H end A.B. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Gutmann JL, Harrison JW. Posterior endodontic surgery: anatomical considerations and clinical techniques. *Int Endod J.*1985;18(1):8-34. doi:10.1111/j.1365-2591.1985.tb00415.x.
2. Castellucci A. Why microsurgical endodontics? In: Castellucci A, ed. *MicrosurgicalEndodontics.* Milano: Edra; 2019:1-9.
3. Çalışkan MK, Tekin U, Kaval ME, Solmaz MC. The outcome of apical microsurgery using MTA as the root-end filling material: 2- to 6-year follow-up study. *Int Endod J.* 2016;49(3):245-254.

4. Taschieri S, Del Fabbro M, Testori T, Weinstein R. Endoscopic periradicular surgery: a prospective clinical study. *Br J Oral Maxillofac Surg.* 2007;45(3):242-244.
5. Carr GB, Bentkover SK. Surgical endodontics. In: *Pathways of the Pulp.* 7th ed. St. Louis: Mosby; 1998:636.
6. Castellucci A, ed. *Endodonzia.* Milano: Edra; 2022:1538-1539.
7. Baek SH, Plenk H, Kim S. Periapical tissue responses and cementum regeneration with amalgam, SuperEBA, and MTA as root-end filling materials. *J Endod.* 2005;31(6):444-449. doi:10.1097/01.don.0000148145.81366.a5.
8. European Society of Endodontology. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. *Int Endod J.* 2006;39(12):921-930.
9. Serrano-Giménez M, Sánchez-Torres A, Gay-Escoda C. Prognostic factors on periapical surgery: a systematic review. *MedOralPatolOralCirBucal.* 2015;20(6):e715-e722. doi:10.4317/medoral.20613.
10. Song M, Jung IY, Lee SJ, Lee CY, Kim E. Prognostic factors for clinical outcomes in endodontic microsurgery: a retrospective study. *J Endod.* 2011;37(7):927-933. doi:10.1016/j.joen.2011.04.005. Erratum in: *J Endod.*2011;37(11):1595.
11. Çalışkan MK, Tekin U, Kaval ME, Solmaz MC. The outcome of apical microsurgery using MTA as the root-end filling material: 2- to 6-year follow-up study. *Int Endod J.* 2016;49(3):245-254.
12. Taschieri S, Del Fabbro M, Testori T, Weinstein R. Endoscopic periradicular surgery: a prospective clinical study. *Br J Oral Maxillofac Surg.* 2007;45(3):242-244.
13. Lindeboom JAH, Frenken JW, Kroon FHM, van den Akker HP. A comparative prospective randomized clinical study of MTA and IRM as root-end filling materials in single-rooted teeth in endodontic surgery. *Oral Surg Oral Med Oral Pathol Oral RadiolEndod.* 2005;100:495-500.
14. Gowri S, Jayasheelan N, Kutty SM, Kumar P, Shetty D, Banu K. An in vitro investigation of the sealing ability of Biodentine and mineral trioxide aggregate as retrofilling materials after the use of various irrigating solutions. *J Pharm Bioallied Sci.* 2022;14(Suppl 1):S563-S567.
15. Yoo YJ, Cho EB, Perinpanayagam H, Gu Y, Zhu Q, Noblett WC, Kum KY. Endodontic microsurgery outcomes over 10 years and associated prognostic factors: a retrospective cohort study. *J Endod.* 2024;50(7):934-943.
16. von Arx T. Apical surgery: a review of current techniques and outcome. *Saudi Dent J.* 2011;23(1):9-15. doi:10.1016/j.sdentj.2010.10.004.
17. Baek SH, Plenk H, Kim S. Periapical tissue responses and cementum regeneration with amalgam, SuperEBA, and MTA as root-end filling materials. *J Endod.* 2005;31(6):444-449. doi:10.1097/01.don.0000148145.81366.a5.
18. Pinto D, Marques A, Pereira JF, Palma PJ, Santos JM. Long-term prognosis of endodontic microsurgery—a systematic review and meta-analysis. *Medicina (Kaunas).* 2020;56(9):447. doi:10.3390/medicina56090447.
19. Kohli MR, Berenji H, Setzer FC, Lee SM, Karabucak B. Outcome of endodontic surgery: a meta-analysis of the literature—part 3: comparison of endodontic microsurgical techniques with 2 different root-end filling materials. *J Endod.*2018;44(6):923-931. doi:10.1016/j.joen.2018.02.021.
20. von Arx T, Janner SF, Hänni S, Bornstein MM. Evaluation of new cone-beam computed tomographic criteria for radiographic healing evaluation after apical surgery: assessment of repeatability and reproducibility. *J Endod.*2016;42(2):236-242. doi:10.1016/j.joen.2015.11.018.
21. Barbarisi A, Visconti V, Lauritano D, Cremonini F, Caccianiga G, Ceraulo S. Correlation between periodontitis and onset of Alzheimer's disease: a literature review. *Dent J (Basel).* 2024;12:331. doi:10.3390/dj12100331.
22. von Arx T, Jensen SS, Hänni S. Clinical and radiographic assessment of various predictors for healing outcome 1 year after periapical surgery. *J Endod.* 2007;33(2):123-128. doi:10.1016/j.joen.2006.10.001.
23. von Arx T, Hänni S, Jensen SS. Correlation of bone defect dimensions with healing outcome one year after apical surgery. *J Endod.* 2007;33(9):1044-1048. doi:10.1016/j.joen.2007.06.010.
24. Peñarrocha M, Martí E, García B, Gay C. Relationship of periapical lesion radiologic size, apical resection, and retrograde filling with the prognosis of periapical surgery. *J Oral Maxillofac Surg.* 2007;65(8):1526-1529. doi:10.1016/j.joms.2006.10.058.

25. Setzer FC, Kohli MR, Shah SB, Karabucak B, Kim S. Outcome of endodontic surgery: a meta-analysis of the literature—part 2: comparison of endodontic microsurgical techniques with and without the use of higher magnification. *J Endod.*2012;38(1):1-10. doi:10.1016/j.joen.2011.09.021.
26. Ceraulo S. Modifica della dimensione verticale: caso clinico. *Protech.* 21AD:15-21.
27. Song M, Kim SG, Lee SJ, Kim B, Kim E. Prognostic factors of clinical outcomes in endodontic microsurgery: a prospective study. *J Endod.* 2013;39(12):1491-1497. doi:10.1016/j.joen.2013.08.026.