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Article

MONOPHASIC AND CONOMETRIC IMPLANTS IN COMPARISION TO OTHER IMPLANT CONNECTIONS: WHICH ONE IS BETTER?

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ABSTRACT

The volume of the maxillary sinus tends to increase in size with advancing age and with the loss of dental elements. For this reason, in some clinical situations, it is not possible to place dental implants of adequate length, mainly due to the lack of bone. The aim of this work is the evaluation of the clinical and radiographic results of the large maxillary sinus lift using the lateral window technique with Piezo Surgery and contextual GBR (Guided Bone Regeneration). Piezoelectric surgery has demonstrated the benefit of dramatically reducing the perforation rate, thus increasing the overall success rate of the sinus lift technique. Aim: The study aims to compare conometric and monophasic implant connections with other types of connections, focusing on minimizing the "pumping effect" and understanding their clinical implications. Material and methods: The study involved replacing 20 teeth in the upper and lower frontal areas with IML implants, with a 3-year follow-up period. The results showed effective osseointegration and minimal bone resorption, particularly in the interincisive papilla region. Results and conclusion: The findings emphasized the positive influence of conical connection dimensions on the marginal crest. Clinically, innovations such as tapered connections and platform switching offer strategies to reduce crestal bone resorption and improve osseointegration. These technologies eliminate the need for fixation screws, reducing micromovements and bacterial colonization. Platform switching helps

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preserve crestal bone and soft tissue, leading to improved aesthetic outcomes. However, successful implementation requires surgical precision and understanding of biomechanical principles. Further research is essential to optimize these technologies and assess their long-term effectiveness through controlled studies.

KEYWORDS: *conometric connection, platform switching, osseointegration, crestal bone resorption, monophasic implants*

INTRODUCTION

In recent decades, great progress has been made in implantology, allowing implant therapy to now become a therapeutic solution not only for total or partial edentulism but also for single-edentulism. The external hexagon was the first connection system used in implantology, created with Branemark to facilitate the insertion of the prosthetic element, subsequently expanding its functions to become an anti-rotation mechanism (1,2). In the scientific literature, several studies document the incidence of technical complications of systems equipped with an external hex connection, with percentages ranging from 6% to 45% (3). However, we must not forget the importance of the perfect fit between the implant and the hexagon of the prosthetic element. To try to overcome biomechanical complications, such as misalignment of the connection screw or breakage of the prosthetic element or tightening screw, the main implant companies with external hex connections introduced the use of dynamometers that gave the screw a calculated tightening torque (4). This did not eliminate the problem, although it led to a reduction in incidence. At the beginning of the 21st century, the theory of "platform switching" was introduced in dental implantology, based on clinical observations, to minimize crestal bone resorption. Several randomized controlled clinical studies highlight that the amount of marginal bone resorption is inversely proportional to the extent of the discrepancy between the implant and the prosthetic element. Recent studies analyze the existence of a microcrack between the implant and the prosthetic element. This microcrack represents an area of contamination for bacteria. On the contrary, in bacteria-free implants, there is a longer and wider contact with the connective tissue, therefore a reduction in epithelial growth. The presence of a microcrack in the bacteria-free system could account for the mild histological inflammation in the connective tissue. The presence of bacteria is a consequence of contact between the two connection surfaces (5). If the space is smaller than the size of the bacteria, the connection will be bacteria-free (6). The marginal connection of both surfaces is fused with the implant body (7). The cast surface with a hexagonal connection is smaller than with the conical connection (8) (Fig.1).

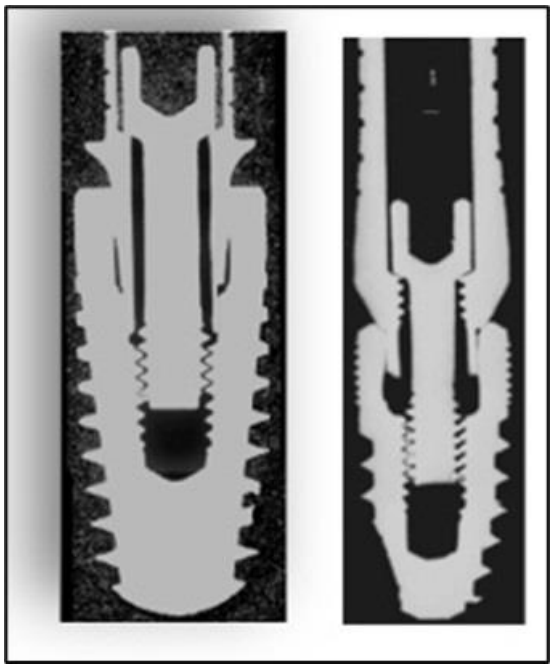

Fig. 1. *The cast surface with a hexagonal connection is smaller than with the conical connection.*

When the prosthetic element is inserted on the implant with the right tightening torque, the hexagon of the prosthetic element fits by friction into the walls of the internal hexagon of the implant. The spaces between the implant and the prosthetic element leave room for bacterial colonization. Chewing loads can generate a small displacement between components, creating a pumping effect (9). The resulting distribution of endotoxins in the tissue at the implant-prosthetic

interface causes an inflammatory reaction. Until the correct biological width is established, the bone continues to be resorbed under the implant-prosthetic element connection. Furthermore, only a bacteria-free connection prevents bone resorption, stabilizing the soft tissue. The platform-switching concept is designed to increase soft tissue volume, contributing to long-term aesthetic results. Moreover, with platform-switching, the transition area between the implant and prosthetic element is in a more central position, creating an implant/prosthetic element junction that dissipates loads internally (10,11). In this way the peri-implant tissues are free from mechanical and microbial impacts (12). Therefore, platform-switching combined with a stable, bacteria-free connection allows the stability of the peri-implant tissues to be achieved (13,14). Dibart et al. tested three single-tooth implant systems in vitro with different connection designs for anti-rotational stability, cyclic fatigue resistance, and torque. They found that the internal hexagon system offered the greatest stability of the prosthetic element and greater resistance to cyclic fatigue than the external hexagon system. In general, it can be said that the internal connection offers more advantages in terms of stability and with the prolonged application of lateral forces (14–16). A separate discussion among the internal connections deserves the purely conometric connection, which does not require the presence of screws and where the interface provides a direct junction between the surfaces of the prosthetic element and the implant (12,17). In this case, the coupling tolerances must be very precise because the torque transmission occurs by friction, the effectiveness of the system is strictly linked to the material used, the nature of the surfaces and the geometric shape. The mechanical stability of this system is guaranteed by the total elimination of all micromovements at the interface between the components (18). Numerous studies have demonstrated the effectiveness and reliability of this system, highlighting a low incidence of clinical complications (19). It has been noted, thanks to some microscopic examinations, that the discrepancies present in the interface of the components in a conometric connection amount to no more than 3 µ, compared to the 20-30 µ average distance between the prosthetic element and the implant connected with screwed and even at 70-120 µ of average discrepancy between screw thread and implant. It seems that this type of system is also very effective in counteracting the phenomenon of the pumping effect present in screwed systems (14,20,21). This conometric connection and single-phase implants provide an excellent barrier to bacterial penetration. Considering that the dimensions of a bacterium can vary from 1 to 6 µ and that, as already mentioned, the interfacial space of this system varies from 1 to 3 µ, bacterial percolation through the coupling of the components of the system becomes very difficult to achieve. Some studies have shown that the conometric connection prevents the passage of fluids and therefore also bacterial colonization. All this, translated into clinical terms, would effectively contribute to the reduction of implant failures due to infectious causes. The objective of this study is to present a series of cases of implants with monophasic connection and conometric connection (22–24).

MATERIALS AND METHODS

Since January 2019, twenty aesthetic sites (13 women and 7 men, aged 22 to 40 years) have been rehabilitated in the upper and lower frontal region (Fig.2,3).

Fig. 2. *Aesthetic site to be rehabilitated in the lower frontal region.*

Fig. 3. *Aesthetic site to be rehabilitated in the upper frontal region.*

Inclusion criteria were sufficient residual bone volume to receive implants; sufficient keratinized tissue; absence of systemic diseases and therefore all the conditions for which it is not possible to perform surgical interventions and good oral hygiene. The exclusion criteria were previous radiotherapy in the head and neck area; bruxism and/or clenching; smoking; autoimmune diseases; partial/complete dental prostheses in occlusion with implants; local inflammation and oral mucosal diseases; need for bone grafting/guided tissue regeneration (GTR) before implant placement (25,26). In these cases, we used monophasic implants (Fig.4) or implants with conometric connections (27,28) (Fig.5).

Fig. 4. *Monophasic implant positioned in the mandibular frontal sector.*

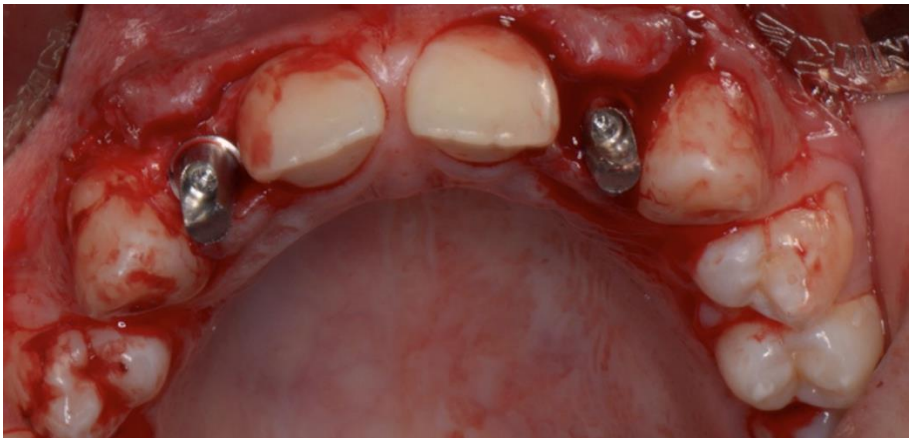

Fig. 5. *Implants with conometric connection in the maxillary frontal sector.*

The difference in their use consisted in the amount of bone available and the future inclination of the prosthetic element. When the prosthesis required an inclination of the prosthetic element, the surgeon used a 15° angled abutment (29) (Fig.6).

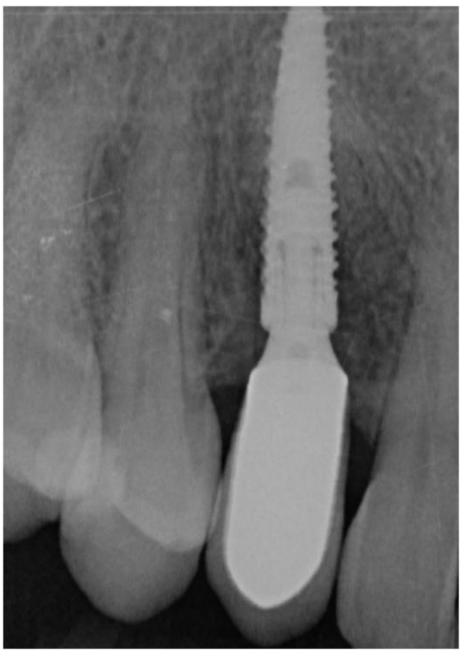

Fig. 6. *15° angled abutment in case of need for an inclined prosthetic element.*

Among these ten monophasic implants, in five cases a light filing of the prosthetic element was performed with a cylindrical diamond bur for prosthetic purposes (17). From a radiographic point of view, an orthopantomography and a cone beam CT were performed before surgery to evaluate the bone volumes (30). After surgery, control intraoral radiographs were performed to monitor the osseointegration process (31) (Fig.7).

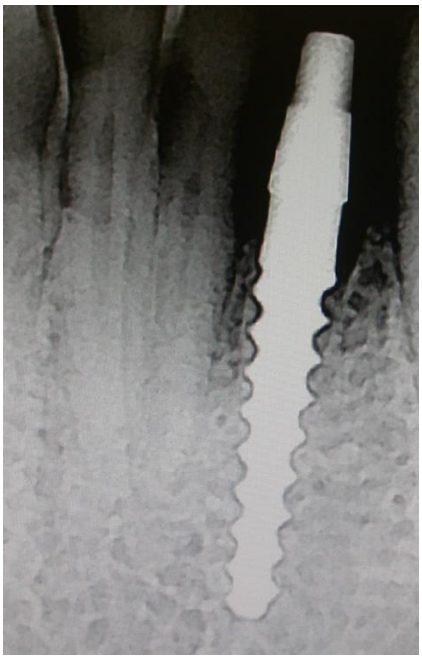

Fig. 7. *Post-surgical control intraoral x-ray.*

The prescribed post-operative therapy was as follows: 400 mg of ibuprofen 2 times a day for 2 days, 1 g of amoxicillin 2 times a day for 6 days and oral rinses with 0.12% chlorhexidine gluconate (1 minute) 2 times a day for 7 days (28,32,33). To evaluate marginal bone levels, standardized parallel intraoral radiographs (Kodak E DF; Eastman, Kodak Co, Rochester, NY) were taken at the time of final restoration placement and at subsequent annual follow-up appointments. Standardized scans were made by individualizing X-ray patterns with polyvinyl siloxane (Express; 3M ESPE, Seefeld, Germany) (32,34–37). For both the mesial and distal surfaces of each implant site, the coronal and apical measurements were averaged using a digital ruler (38). In the mandible, single crowns were placed after 10 weeks, while in the maxilla

after 20 weeks (39). Thanks to the 3-year follow-up, it is possible to note the perfect achievement of the health of the interdental papilla with minimal loss of crestal bone (40,41) (Fig.8,9).

Fig. 8. *Remote control of the health of the interdental papilla with minimal loss of low crestal bone.*

Fig. 9. *Remote control of the health of the interdental papilla with minimal loss of upper crestal bone.*

RESULTS

All cases rehabilitated in the study concluded with a perfectly functional and aesthetic result in the anterior area. Control radiographs performed up to 3 years of follow-up showed successful osseointegration, minimal resorption of the crestal bone and perfect maintenance of the inter incisive papilla. Of the 20 implants placed, all bones integrated perfectly, establishing direct contact with the bone. At 36 months, the mean peri-implant bone loss detected by radiographs was -0.41 ± 0.22 mm.

DISCUSSION

Most bone resorption occurs during the first year after placement of the prosthesis, then decreasing with occlusal load. The favorable results of mismatched abutment/implant connections are also evident in several animal studies, thanks to radiographic analysis (42). Platform switching was essential to reduce crestal bone resorption compared to diameter-matched restorations, regardless of the position of the implant on the crestal bone. Subsequently, histological samples taken from the same experiment were studied and confirmed the reduction in bone loss (43). As is known, the abutment-implant interface and the tightening screw are subjected to very high chewing loads, especially in cases of single-dentulism or partial rehabilitation of edentulous posterior teeth. It follows that a perfect fit between implant and abutment is essential for good bone preservation (44). In the conometric connection, a real "cold weld" is generated, thanks to the contact pressure between the surface of the implant cone and the internal surface of the implant abutment (45–47). The friction created between two conical-cylindrical surfaces, with a torque of 35 Ncm, is such as to generate a direct, durable and waterproof joint. In fact, this type of connection is the only one capable of approaching the ideal condition of the single-phase system. However, being able to mechanically create a perfect conometric coupling requires particular attention and skill, right from the design phase (48). Immediate load designers and engineers can identify and evaluate every critical point to produce perfect components, where the friction works not only in the design but above all in the patient's mouth (49). The resulting system is effective and reliable, as demonstrated by numerous studies conducted around the world. Some of the advantages of the conometric connection are the following:

- elimination of the passage of fluids and therefore of bacterial colonization,
- elimination of micromovements at the interface between components, resulting in greater mechanical stability,
- low incidence of clinical complications,
- reduction of peri-implantitis,
- significant reduction in plant failures.

The immediate loading implant connection is designed to not only implement the advantages of the conometric connection but also those of the one-piece system (50). The resulting benefit is a better distribution of the load, which is dispersed over 80% of the implant rather than concentrated only in the cortical area, as often happens in other implant systems (51). Monophasic implants are also a valid alternative in daily practice. They completely avoid the problem of unscrewing by eliminating the screw passing between the abutment and the implant (52,53).

CONCLUSIONS

Approaching a site in the aesthetic area with the ability to manage the treatment in a single surgical session with immediate loading, using the conometric connection or a monophasic implant, represents a benefit for both the clinician and above all for the patient. The possibility of subjecting the patient to a limited number of surgical sessions can favor better acceptance of the treatment and allow a reduction in the completion times of implant prosthetic rehabilitation, without compromising the quality of performance. The evolution of surgical techniques and the greater ability to manage the healing mechanisms of interstitial tissues, thanks to the conometric connection and monophasic implants, allow dentists to address the treatment of aesthetic sites in a more manageable way with excellent aesthetic results. Despite the results obtained, it is necessary to conduct furthermore systematic long-term studies, investigating the factors that contribute to bone resorption around the implants, after standardizing several variables such as: bone quality, bone quantity, micro/macro design and type of restoration.

Author Contributions

Conceptualization, F.I., F.F., A.D.I, A.M.I., A. M., A.P.and L.F.; methodology, A.M.I. and A.P.; software, F.I., A.D.I.; validation, F.I., G.D. and L.F.; formal analysis, A.P.; investigation, A.P. and F.F.; resources, L.F., A.M. and F.F.; data curation, G.D., A.D.I., A.M. and F.I.; writing—original draft preparation, L.F. and F.I.; writing—review and editing, A.P. and G.D.; visualization, G.D.; supervision, L.F., G.D. and F.I.; project administration, F.I. All authors have read and agreed to the published version of the manuscript.

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Consent Statement

Patients signed informed consent for publication of the manuscript and figures.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

AMCOP® ELASTODONTIC DEVICES IN ORTHODONTICS: A LITERATURE REVIEW

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ABSTRACT

Aim: This study aims to provide a comprehensive overview of the current literature on AMCOP® elastodontic devices, focusing on their applications, advantages, and limitations in contemporary orthodontic practice. *Materials and Methods:* A literature review was conducted using databases such as PubMed, and Scopus, covering studies published from 2010 to 2023. Search terms included "elastodontics," "AMCOP® devices," "orthodontic elastomers,". Inclusion criteria were studies focusing on the clinical application of AMCOP® devices, articles discussing the biomechanical principles of elastodontics, and reviews and clinical trials evaluating the effectiveness of elastodontic treatment. *Results:* The review identified five relevant studies. These studies focused on therapies with AMCOP® devices in treating various malocclusions, including Class II and Class III discrepancies, open bites, and crossbites. Notable findings included improvements in overjet, overbite, crowding, and palatal symmetry. Additionally, AMCOP® devices contributed to the correction of hyperdivergent Class II malocclusion and enhanced upper airway space. *Conclusion:* AMCOP® elastodontic devices represent a significant advancement in orthodontics, offering a less invasive, patient-friendly alternative to traditional devices. Their use of elastic materials provides continuous, gentle forces that align with physiological tooth movement, enhancing patient comfort and compliance. However, further research, including long-term clinical trials, is essential to fully establish their efficacy and explore new clinical applications.

KEYWORDS: *Elastodontic appliances, AMCOP® bio-activators, Interceptive treatment, Orthodontic elastomers, Early Treatment, Orthodontic materials, Functional Therapy, Thermoactivable materials, Orthodontic applicances*

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INTRODUCTION

Elastodontics is a branch of orthodontics that focuses on the use of elastic materials and devices to correct dental and skeletal discrepancies (1,2). Unlike traditional orthodontic treatments that rely on rigid materials such as metal brackets and wires, elastodontics employs elastomeric appliances to exert gentle, light forces on teeth and periodontal tissues and increase phosphatase alkaline (3–5). This approach capitalizes on the biomechanical properties of elastomers, which are materials known for their elasticity and ability to return to their original shape after deformation (6). These properties make elastodontic appliances (EAs) particularly suitable for applying controlled, sustained forces that facilitate desirable orthodontic movements (7,8).

The concept of elastodontics is grounded in the understanding that low-force application can be more physiologically compatible with the tissues involved in orthodontic treatment (1,9–11). It minimizes the risk of root resorption and enhances patient comfort, potentially leading to improved compliance (2). The gentle forces generated by elastomeric devices align well with the natural biological processes of bone remodeling and tooth movement, promoting efficient and effective orthodontic correction (1,12,13).

The Multifunctional Cranio-Occluso-Postural Harmonizers (AMCOP®) have emerged as a significant innovation in this field (1). These devices are designed to provide effective, patient-friendly solutions for various orthodontic issues, ranging from simple dental alignments to more complex skeletal corrections (14,15). AMCOP® devices are characterized by their use of elastomeric materials, which are both flexible and durable (16). This combination of flexibility and durability allows for a wide range of therapeutic applications, making AMCOP® devices versatile tools in the orthodontist's arsenal (17).

AMCOP® bio-activators intended to balance the dental-cranial-facial structures by addressing multiple dysfunctional disorders using a multifunctional approach. AMCOP® devices work on the link between the skull and jawbones, as well as the interaction of occlusion and posture, focusing on the first cervical vertebrae (1,18,19).

AMCOP® devices are noted for their softness, comfort, and flexibility to various arch types. They are made of an elastic and thermo-activable material produced from a polymer-elastomer combination. During treatment, the devices can be extended by immersing them in hot water at 70°C for 30 seconds, and they can also be customized with heat-appropriate tools (20–22). The transverse distance between the outermost points of the vestibular cusps of the first two upper molars is measured to determine the appropriate size of the activator, either on a plaster model or a wax bite, with the latter being especially useful for young children who dislike taking impressions (23–25).

Each AMCOP® device has two high flanges on the vestibular and lingual sides, which prevent any muscular interference with the teeth. A central section free of indentures allows for tooth mobility, while a lingual ramp and button direct the tongue onto the palate (1,26,27). The devices come in various colors, which correspond to different arch types and skeletal classes (Fig.1).

Fig. 1. *AMCOP® devices. (source: www.amcop.it/indicazioni , accessed on 20 May 2023).*

AMCOP® elastodontic devices are typically customized to fit the specific needs of each patient. They can be used to treat a variety of malocclusions, including Class II and Class III discrepancies, open bites, and crossbites (28,29). The customization aspect is crucial, as it ensures that the devices can effectively address the unique anatomical and orthodontic requirements of individual patients (30–33).

These devices often feature a combination of soft and hard elastomers, strategically arranged to provide differential force application. This design allows for targeted tooth movements, improving the precision and efficacy of the treatment. Additionally, AMCOP® devices can be designed to encourage natural jaw movements and muscle function, contributing to more stable long-term results (34,35).

The primary aim of this review is to provide a comprehensive overview of the current literature on AMCOP® elastodontic devices. By synthesizing the findings from various studies and clinical reports, this review aims to highlight the applications, advantages, and limitations of AMCOP® devices in contemporary orthodontic practice.

MATERIALS AND METHODS

A literature review was conducted to gather relevant information on AMCOP® elastodontic devices. The search strategy included terms such as "elastodontics," "AMCOP® devices," "orthodontic elastomers". The databases searched were PubMed and Scopus, covering studies published from 2010 to 2023.

Inclusion criteria were:

- Studies focusing on the clinical application of AMCOP® elastodontic devices;
- Articles discussing the biomechanical principles of elastodontics;
- Reviews and clinical trials evaluating the effectiveness of elastodontic treatment;
- English language;

Exclusion criteria included:

- Studies not related to elastodontics or AMCOP® devices;
- Articles published before 2010.

RESULTS

The research strategy identified five relevant articles that were included in the analysis. These articles provide valuable insights into the clinical applications and effectiveness of AMCOP® elastodontic devices in various orthodontic treatments (Table I).

Table I. *Selected items.*

Authors	Publication year	Materials and Methods	Outcomes
Lo Giudice et al. (36)	2022	Class II AMCOP® bio-activator for one hour each day for a year, as well as at night.	AMCOP® treatment resulted in an improvement in anterior dental crowding as well as a decrease in overjet and overbite.
Lo Giudice et al.(37)	2023	AMCOP® Integral/Basic activator for two hours each day and at night for a year.	AMCOP® tratment resulted in a reduction of palate asymmetry and an increase in palate size in children with crossbite.
Fichera et al. (38)	2021	AMCOP® second class, one hour each day for a year, and at night. Patients were required to bite the device during the day while maintaining lip contact.	Crowding, overjet, and overbite were reduced as a result of AMCOP®. The number of Class I relationships increased.
Inchingolo et al. (26)	2022	AMCOP® in 16–18-month-old hyperdivergent children. For 6 to 8 months, AMCOP® was taken only at night and for an hour each day.	The overbite and hyperdivergence were reduced as a result of the device. Additionally, the breadth of the upper ways was improved.
Patano et al. (39)	2023	AMCOP® treatment for 3 years.	AMCOP® resulted in an enhancement in the upper way dimensions.

DISCUSSION

Recent studies have highlighted the effectiveness of elastodontic devices in various orthodontic treatments, demonstrating their potential to address malocclusions and promote harmonious craniofacial development.

The prospective clinical study conducted by Lo Giudice et al. (36) evaluated the effectiveness of elastodontic devices in treating subjects with Class II sagittal discrepancy in mixed dentition. A treatment group of 19 subjects received elastodontic devices for one year, while a control group of 17 subjects remained untreated. The results demonstrated a significant reduction in overjet and improvement in overbite in the treated group, whereas the control group exhibited a

slight, non-significant increase in these parameters. Additionally, the number of subjects with anterior crowding decreased in the treated group, in contrast to a slight increase observed in the control group. 3D analysis of intraoral scans revealed pre-treatment palatal asymmetry that partially improved in the treated group compared to controls. In conclusion, elastodontic devices proved effective in mitigating early signs of malocclusion in Class II subjects and promoting harmonious palatal development (7,36,40).

Building on these findings, Lo Giudice et al. conducted another study (37) to evaluate the palatal dimensional and morphological changes following the treatment of functional posterior crossbite (FPXB) using EAs. A treatment group (TG) of 25 subjects received EA treatment for one year, while a control group (CG) of 14 subjects remained untreated. Results demonstrated a significant increase in inter-canine and inter-molar widths in the TG, along with a reduction in the asymmetry between the crossbite and non-crossbite sides. 3D deviation analysis showed a significant improvement in palatal symmetry in the TG, with the matching percentage between original and mirrored models increasing from 81.12% to 92.32%. Conversely, the CG showed no significant changes. The study concluded that EAs effectively correct FPXB and promote the harmonious development of the palate in children (41–43).

Furthermore, the retrospective study by Fichera et al. (38) assessed the skeletal and dentoalveolar changes following one year of treatment with elastodontic appliances (EAs) in children showing early signs of malocclusion. The study included 20 treated subjects and 20 control subjects. Digital impressions and lateral cephalograms were taken before treatment (T0) and after one year (T1). In the treated group, significant improvements were noted in overjet, overbite, crowding, and sagittal molar relationships. Cephalometric analysis showed no significant changes in SNA (sella-nasion-A point) angle values, but significant increases in SNB (sella-nasion-B point) angle, ANB (A point-nasion-B point) angle values. Conversely, the control group showed a slight increase in overjet and overbite without significant improvement in other parameters. The study concluded that EAs effectively improve malocclusion indicators and promote harmonious dentoalveolar development, offering a viable interceptive treatment option, especially for patients with limited financial resources (44–46).

In a different but related investigation, the retrospective study by Inchingolo et al. (26) evaluated the effectiveness of elastodontic therapy using AMCOP® devices in treating hyperdivergent Class II malocclusion in children and its impact on upper airway patency. The study included 21 patients with hyperdivergent growth patterns and Class II malocclusion. Cephalometric analysis before and after treatment showed correction of the Class II malocclusion, a reduction in divergence, and improvement in upper airway space. Significant skeletal changes included mandibular advancement and reduction in the ANB angle. The AMCOP® devices effectively corrected hyperdivergent Class II malocclusion and enhanced upper airway space, indicating their potential in interceptive orthodontics for growing patients (1,46,47).

Finally, Patano et al. (39) investigated the impact of EAs on the pharyngeal airway space and hyoid bone position in patients with skeletal Class II malocclusion. The findings demonstrated that treatment with the AMCOP® SC elastodontic device resulted in significant clinical improvements. Specifically, there was a notable enhancement in the superior upper airway space (SPAS) and the vertical position of the hyoid bone (39,48–50). These changes suggest that elastodontic therapy can effectively increase airway dimensions, potentially alleviating breathing issues associated with Class II malocclusion. The study underscores the utility of elastodontic devices in promoting favorable orthopedic and functional modifications, contributing to better respiratory function and overall craniofacial harmony in growing patients (39,51,52).

Collectively, these studies underscore the efficacy of elastodontic devices in addressing various orthodontic issues, promoting favorable orthopedic and functional modifications, and contributing to better respiratory and craniofacial outcomes in children.

LIMITATIONS

Despite the promising results obtained, these studies present several limitations. Firstly, much of the research is retrospective in nature, which can introduce selection bias and limit the ability to establish direct causality. Additionally, the sample size in some studies is relatively small, reducing the generalizability of the findings. The reliance on patient compliance with therapeutic guidelines represents another limitation, as non-adherence can negatively influence outcomes. Finally, most studies utilize two-dimensional cephalometric analyses, which may not fully capture the complex three-dimensional dynamics of structural changes. Future research with larger sample sizes, prospective designs, and three-dimensional analyses could provide a more comprehensive and robust understanding of the long-term efficacy of elastodontic devices.

CONCLUSIONS

AMCOP® elastodontic devices represent a valuable addition to the field of orthodontics, offering a comfortable and effective alternative to traditional braces. Their innovative use of elastic materials to provide gentle forces aligns well with the principles of physiological tooth movement, potentially leading to better patient experiences and outcomes. The flexibility and resilience of the elastomers used in these devices contribute to effective treatment while minimizing discomfort and adverse effects commonly associated with conventional orthodontic methods.

The design and functionality of AMCOP® devices promote natural jaw movements and muscle function, enhancing treatment stability and long-term results. Furthermore, their aesthetic appeal, being less noticeable than traditional metal braces, makes them an attractive option for patients concerned about the visual impact of orthodontic appliances. This is particularly advantageous for adults seeking discreet orthodontic treatment.

Further research is essential to fully establish the benefits and potential drawbacks of AMCOP® elastodontic devices in various orthodontic scenarios. Long-term clinical trials are particularly needed to provide comprehensive data on the durability, effectiveness, and stability of results achieved with these devices over extended periods. Such studies would also help in refining treatment protocols, identifying potential complications, and optimizing patient selection criteria.

Additionally, future research should explore the integration of AMCOP® devices with other orthodontic and dental technologies. For example, combining EAs with digital orthodontic planning tools or advanced imaging techniques could enhance treatment precision and predictability. Investigating the potential of AMCOP® devices in interdisciplinary treatment approaches, such as in conjunction with maxillofacial surgery or periodontal therapy, could further expand their clinical applications and benefits.

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Conflict of interest
The authors declare that they have no conflict of interest.

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Case Study

NON-HODGKIN'S LYMPHOMA: AN OVERVIEW AND CASE STUDY

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ABSTRACT

Since non-Hodgkin lymphoma (NHL) has a great histological variability and tends to afflict organs and tissues that do not normally contain lymphoid cells, it is used to refer to a broad category of lymphoid neoplasias unrelated to Hodgkin's disease. The intraoral site is uncommon (3–5% of cases), and it is rarely where the disease first manifests itself. We present the case of a 73-year-old male Italian Caucasian patient who presented to us with a tongue lesion. Hemorrhage and macroglossia were the clinical findings, which were probably caused by the tongue-bite wounds. For 48 hours, the patient had been complaining of dyspnea. In conclusion, tongue involvement is not common in NHLs. However, when making a differential diagnosis between benign and malignant lesions affecting the same location, this potential should always be taken into account. To improve the prognosis and therapy of this disease, a timely diagnostic diagnosis in conjunction with sufficient histopathologic confirmation is necessary.

KEYWORDS: *Non-Hodgkin lymphoma; Reed-Sternberg cells; owl's eyes; immunodeficiency; extranodal sites*

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INTRODUCTION

Lymphomas account for approximately 3% of all malignant tumors, making them the third most common type of neoplasm globally (1). The incidence of lymphomas is gradually increasing at a rate of 3% per year. Tumors originating from hematopoietic and lymphoid tissues are classified by the World Health Organization (WHO) into various categories based on cell differentiation and lineage (2). These categories include Hodgkin's lymphoma, peripheral B-cell neoplasia, T-cell neoplasia, peripheral T/NK-cell neoplasia, B-cell neoplasia, and B-cell proliferations with uncertain malignant potential (3).

Hodgkin's lymphoma is primarily characterized histopathologically by the presence of Reed-Sternberg cells. These cells can be either binucleated or multinucleated and have large, transparent nuclei with prominent nucleoli resembling "owl's eyes." In contrast, non-Hodgkin's lymphoma (NHL), which encompasses all other histopathologic entities unrelated to Hodgkin's disease, does not contain Reed-Sternberg cells (2). Due to considerable histological variation, NHL is further categorized into two primary types based on morphology: nodular (or follicular) types, which display a regular pattern of nodules, and diffuse types, in which neoplastic cells are uniformly dispersed throughout the affected tissue (4).

From a clinical perspective, NHL often begins in extranodal sites, whereas Hodgkin's lymphoma typically presents as a nodular lesion, rarely involving extranodal areas (5,6). Additionally, the spread of NHL is non-contiguous and unpredictable, unlike Hodgkin's disease, which spreads in an orderly, contiguous manner through nodal groups. This distinction has significant therapeutic implications (7–9). The incidence of NHL shows notable geographic variability within Italy, with a 2:1 ratio favoring northern regions over southern regions. Several risk factors are associated with NHL, including immunodeficiency (either primary or acquired), autoimmune diseases (such as Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and celiac disease), and certain infections (10,11). Infectious agents linked to NHL include herpesviruses (HHV8, associated with Kaposi's sarcoma; EBV, associated with the African form of Burkitt's lymphoma; and HCV, which is strongly associated with NHL in some European countries with high HCV prevalence) and Helicobacter pylori, which is associated with peptic ulcer disease and gastric MALT lymphoma (12–14). Additional risk factors include exposure to harmful chemicals and hereditary factors (15,16). Chromosomal translocations play a crucial role in the pathophysiology of NHL by activating oncogenes or inactivating tumor suppressor genes, leading to the disruption of normal lymphoid cell genomic rearrangement processes (17). The most commonly affected nodal sites include supraclavicular and laterocervical lymph nodes, while extranodal involvement occurs in 20–30% of cases and can affect the skin, subcutaneous tissue, gastrointestinal tract, and Waldeyer's ring (18). Splenomegaly is almost always present in the immunoblastic type due to frequent spleen and bone marrow involvement in advanced stages. Severe splenomegaly often indicates leukemic progression (19,20). Infiltration of non-lymphoid tissues, such as the oral cavity, is another presentation of NHL (21). The most commonly affected sites in the oral cavity are the tonsils (55% of cases), palate (30%), and gingival mucosa (2%) (22–24). Less commonly affected sites include the tongue, buccal floor, and retromolar trigone (each representing 2% of cases) (25–27). These presentations are typically asymptomatic but may be associated with mucosal ulcers. In the head and neck region, the large cell type of NHL is the most prevalent (28–30).

CASE PRESENTATION

The following case illustrates the clinical presentation and diagnostic challenges associated with NHL in the oral cavity. During an emergency first aid procedure, a 73-year-old Caucasian male presented with a history of hypertension treated with ACE inhibitors, chronic atrial fibrillation managed with oral anticoagulants, and diabetes mellitus controlled with biguanides. The patient exhibited macroglossia and had been experiencing dyspnea for 48 hours, likely due to tongue-bite injuries causing bleeding. A review of the patient's clinical documentation revealed that a month prior, a neck CT scan with contrast agents had identified a solid lesion approximately 6 cm in diameter on the tongue, contiguous with the muscles of the oral floor, along with a few enlarged lymph nodes (up to 15 mm in diameter) in the submandibular and laterocervical regions. The patient had previously undergone surgery organized by a different healthcare provider, during which a losangic biopsy (4 × 4 cm) and immediate histological examination were performed under general anesthesia and local anesthetic infiltration. The intraoperative examination indicated widespread proliferation of lymphoid cells, consisting of large and medium-sized cells infiltrating the skeletal muscle, suggesting an extensive NHL.

Subsequent diagnostic procedures included CT scans of the thorax, abdomen, and pelvis, which revealed enlarged lymph nodes in the subcarinal area and the right pulmonary hilum (measuring 10 mm in diameter). The patient also underwent a hematologic consultation and an osteomedullary biopsy. Approximately thirty days after the initial surgical

excision of the tongue lesion, the patient returned to the clinic with significant dyspnea, prompting immediate evaluation by the authors due to concerns of lesion recurrence. Extraoral examination revealed a firm tumor of normal color in the left submandibular region. Intraoral examination showed significant reddish-violet enlargement of the tongue, with well-defined necrotic-ulcerative regions on the left margin and left region, and bleeding likely caused by tongue-bite injuries. The tongue felt woody and uncomfortable to touch.

A fiberoptic examination of the larynx conducted 72 hours later revealed a reduction in the tracheal lumen and extrinsic compression of the posterior tracheal wall. An emergency inferior tracheostomy was performed by colleagues when the patient's breathing worsened, along with providing necessary medical guidance (Fig.1).

Fig. 1. *A picture showing the entire involvement of the emi-tongue on the left side.*

The mucosa is infiltrated by small/medium B lymphocytes in the upper and middle layer of the subepithelial stroma (figures A and B - hematoxylin and eosin; low and high magnification respectively), diffusely immunoreactive for CD20 (figures C and D - immunohistochemistry; low and high magnification respectively) (Fig.2). Overall, histological analysis shows an extranodal marginal zone NHL.

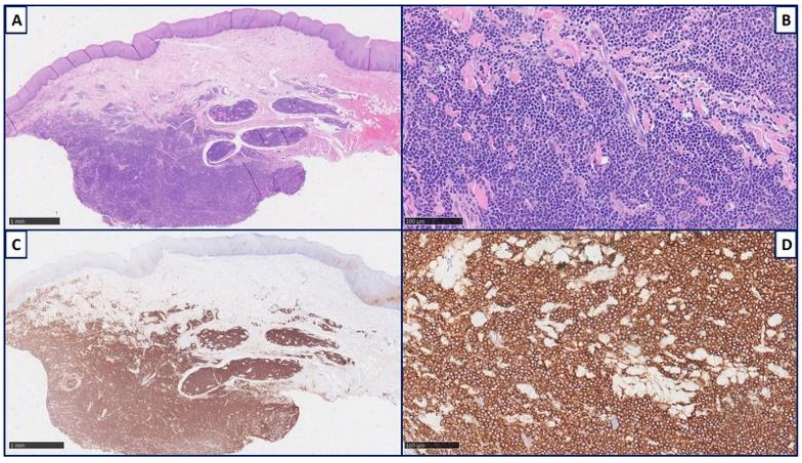

Fig. 2. *Histological and immunohistochemical analysis reveals mucosal infiltration by small/medium B lymphocytes in the subepithelial stroma, diffusely CD20-positive, consistent with extranodal marginal zone NHL. Hematoxylin and eosin staining* ***(A, B)*** *and CD20 immunohistochemistry* ***(C, D)*** *shown at low and high magnification.*

DISCUSSION

NHL encompasses a wide range of lymphoid neoplasias unrelated to Hodgkin's disease, characterized by significant histological variation and a propensity to involve organs and tissues not typically containing lymphoid cells. Extranodal involvement is the predominant site of disease in 20–30% of cases, with the head and neck region and gastrointestinal

tract being the most commonly affected sites with increase the alkaline phosphatase (31–33). Early signs of NHL rarely occur in the intraoral region, accounting for only 3-5% of patients (34,35).

In the oral cavity, the most commonly affected sites are the tonsils (55% of cases), palate (30%), and gingival mucosa (2%) (36). Less common sites include the tongue, buccal floor, and retromolar trigone (each representing 2% of cases) (37–40). These rare presentations typically manifest as asymptomatic swellings, often associated with mucosal ulcers (41,42). The limited signs and symptoms, along with the potential for misdiagnosis as benign orodental conditions, underscore the importance of considering NHL in differential diagnoses to avoid delayed diagnosis and treatment.

The prognosis of NHL is directly tied to the histopathologic type and is significantly improved by early diagnosis and appropriate management. Given the vast histological variation and clinical presentations of NHL, a thorough diagnostic evaluation and histopathologic confirmation are essential to optimize treatment outcomes.

CONCLUSIONS

NHL rarely affects the tongue, yet it remains a critical consideration in the differential diagnosis of lesions in this region. Recognizing the potential for NHL involvement is essential for timely and accurate diagnosis, which significantly impacts prognosis and treatment. Clinicians must maintain a high index of suspicion and ensure adequate histopathologic evaluation to improve patient outcomes in cases of suspected NHL in the oral cavity.

Author Contributions

Conceptualization, F.I., A.L., A.D.I, A.M.I., A. M., A.P. and S.R.T.; methodology, A.M.I. and A.P.; software, F.I., A.D.I.; validation, F.I., G.D. and G.P.; formal analysis, A.P.; investigation, A.P. and F.C.T.; resources, A.L., A.M., G.I., R.S. and I.R.B.; data curation, G.D., A.D.I., A.M. and F.I.; writing—original draft preparation, G.D, I.R.B , A.M. and F.I.; writing—review and editing, A.P. , A.M., A.M.I. and G.D.; visualization, G.D.; supervision, A.L., M.C., G.D. and F.I.; project administration, F.I. All authors have read and agreed to the published version of the manuscript.

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Consent Statement

The patient gave written informed consent for the publication of this case study and the photos that go with it. The chief editor of this journal can evaluate a copy of the written consent.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

INFLUENCE OF PROBIOTIC SUPPLEMENTATION ON NUTRIENT ASSIMILATION IN HEALTHY PEDIATRIC POPULATIONS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EXPLORATORY STUDY

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ABSTRACT

The rise in global use of dietary supplements, especially probiotics, necessitates assessing their effectiveness. Probiotics, beneficial microorganisms like lactic acid bacteria, improve health by modifying the gut microbiota. They are effective in treating gastrointestinal and allergy disorders, obesity, diabetes, and boosting immunity. This study evaluates the impact of a specific probiotic formulation on children's health and nutrient absorption. In a randomized, double-blind, placebo-controlled trial, 40 pediatric patients aged 14 to 18 were divided into active treatment and placebo groups. The active group received Hyperbiotics PRO-Kids, a symbiotic containing four proprietary probiotic strains and a prebiotic. Clinical outcomes, including blood levels of vitamins, calcium, iron, and zinc, were monitored over 10 weeks. The probiotic group showed significant improvements in weight, BMI, and nutrient absorption, with no adverse effects reported, suggesting probiotics enhance children's immune and nutritional health. However, further research is needed due to limitations like the small sample size and lack of fecal microbiota analysis. Future studies should focus on understanding probiotics' mechanisms and optimizing protocols for pediatric use, emphasizing the need for customized probiotic delivery and recognizing the variability in strain efficacy.

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INTRODUCTION

The use of dietary supplements, such as probiotics, has increased globally. Probiotics, derived from the Greek term meaning "for life," are non-pathogenic organisms (yeast or bacteria, particularly lactic acid bacteria) in foods that positively influence health. Modulating the gut microbiota can involve using probiotics, indigestible carbohydrates (prebiotics), or combinations of both (symbiotic) (1,2).

Clinical studies have shown that probiotics positively affect gastrointestinal diseases (like irritable bowel syndrome, Helicobacter elimination, inflammatory bowel disease, and diarrheas) and allergic diseases (such as atopic dermatitis) (3–5). Probiotics have also been effective in treating obesity, insulin resistance syndrome, type 2 diabetes, and non-alcoholic fatty liver disease, and in enhancing immunity (6). Probiotics and prebiotics have been shown to enhance nutritional status by reducing gastrointestinal disorders and to enhance the absorption of micronutrients (such as iron and calcium) from diet (7,8). The primary bacterial stimulation of gut-associated immune cells is crucial for developing and maturing the immune response in children. However, this has been impacted by fewer vaginal births, less breastfeeding, increased use of antibiotics, and more stringent hygiene and pasteurization practices (9–11).

Consuming certain probiotics benefits gut barrier function and immune response, enhancing host-microbe interactions, nutrient harvesting, and production of substances like short-chain fatty acids, vitamins, amino acids, polyamines, growth factors, and antioxidants (Fig.1). This helps manage various illnesses (12–14).

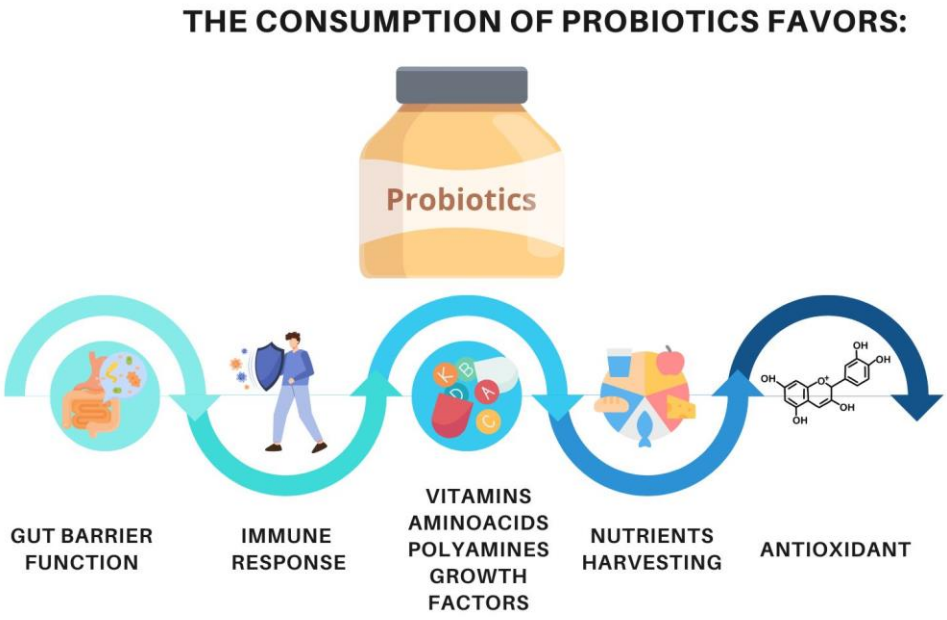

Fig. 1. *The consumption of probiotics favors gut barrier function, immune responses, vitamins, aminoacids, polyamines, growth factors, nutrients harvesting, and antioxidants.*

Current studies focus on understanding the in vivo mechanisms and challenges in translational research on probiotics (15). The application of immunological tests for probiotic selection may become clearer with a deeper understanding of the clinical and molecular mechanisms of probiotics, the effects of probiotic mixes vs single strains, probiotic composition, and the destiny of ingested probiotics (16–18).

This translational study aims to evaluate the efficiency of specific probiotics customized for children to improve nutritional absorption and enhance overall health and immunity.

MATERIALS AND METHODS

This study, titled "Probiotics Efficacy and Safety in Humans," was a collaborative effort between Elbasan University in Albania and the University of Bari Aldo Moro. Conducted as a randomized, double-blinded, placebo-controlled trial,

it received approval from the Institutional Ethics Committee of the Faculty of Technical Medical Sciences of Elbasan. The protocol identification was INTL_ALITCOOP/Probiotics/INRES2019_w/a/c.

Subjects Recruited

A total of 40 pediatric patients, aged between 14 and 18 years, were enrolled in the study and divided into two groups (Fig.2). Prior to participation, all patients' parents or guardians were required to read, understand, and sign an informed consent form, in accordance with the ethical principles outlined in the Helsinki Declaration. The clinical protocol was verbally explained to the parents or guardians of the patients. Eligible participants were randomly assigned to either a placebo group (n = 20) or an active treatment group (n = 20), ensuring that the allocation remained blinded to the investigators (Figure 2). The study involved healthy pediatric patients with similar body mass index (BMI) and age, who were randomly assigned to receive either a placebo or a symbiotic containing a specific probiotic formulation (Hyperbiotics PRO-Kids). This formulation consisted of four patented probiotic strains (Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacter infantis, Bifidobacter lactis), along with a prebiotic (fructo-oligosaccharides), and was manufactured using the LiveBac® process and BIO-tract® technology for protection and time-release delivery. 3 billion colony-forming units (CFUs) per BIO-tract® pearl were present in the studied recipe, which is equal to 45 billion CFUs of conventional probiotic capsules. The main inclusion criteria were healthy individuals with similar BMI and age, while exclusion criteria included recent antibiotic or drug use, malnutrition, or use of nutritional supplements (19).

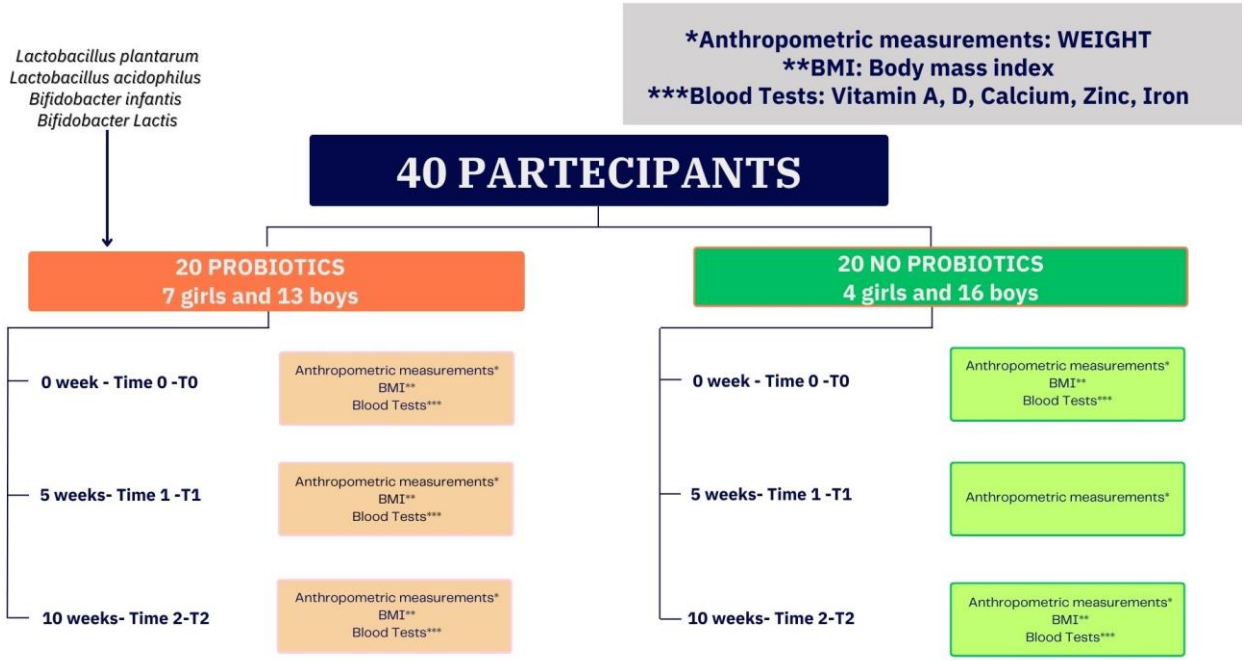

Fig. 2. *Participants in the study.*

Randomization

Enrolling patients and classifying treatments were done using a double-blind procedure to guarantee objective and reliable clinical data. Envelopes with sequential numbers were made using a computer-generated list of random numbers, and inside were assignments to receive probiotics or a placebo. The immunologist investigator oversaw the distribution of blinded supplements, whilst the clinical biochemistry investigator was in charge of randomization in the study. The supplements were the same save for their letter A or B labels. Participants, investigators, outcome assessors, and data analysts were all blinded to treatment allocations once they were assigned to interventions.

Clinical Outcomes

The primary objective of the study was to evaluate the impact of supplementing digestive probiotics, specifically Hyperbiotics PRO-Kids, on enhancing the nutritional absorption capacity in children, thereby promoting overall health and immunity. Secondary outcomes included assessing the levels of blood biomarkers such as Vitamins D and A, Calcium, and mineral absorption (iron and zinc) over a 10-week period. Blood samples were collected from participants via vein puncture, with approximately 5 ml of blood collected during laboratory sampling between 7:00 and 9:00 am.

These blood samples were then centrifuged at 2500×g for 10 minutes, and the serum was separated for serum biochemical analysis (20).

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) and GraphPad Prism (version 6.01, La Jolla, CA, USA) were used to analyze the mean values for the Treaded and Control groups software (Inc., Version 16.0, Chicago, IL, USA).

The Statistical Product and Service Solution (SPSS) Statistics 21 program (IBM Corp., Armonk, NY, USA) was used to conduct statistical analyses. ANOVA tests were used to analyze data.

A significance level of $p<0.05$ was deemed to be statistically significant.

RESULTS

This study aimed to assess the efficacy of specific probiotics tailored for pediatric use in enhancing nutritional absorption capacity among adolescents aged 14 to 18 years. The research, conducted as a randomized clinical trial, involved collaboration between Elbasan University in Albania and the University of Bari Aldo Moro. Approval from the Institutional Ethics Committee was obtained, and the study adhered to the Helsinki Declaration's ethical principles.

Forty pediatric patients were enrolled, with parents or guardians providing informed consent. Participants were randomly assigned to either a probiotic (n = 20) or placebo (n = 20) group. The probiotic used, Hyperbiotics PRO-Kids, contained patented strains of Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacter infantis, and Bifidobacter lactis, along with prebiotic fructo-oligosaccharides (FOS) and patented delivery mechanisms.

Criteria for inclusion encompassed healthy individuals with similar body mass index (BMI) and age, while exclusion criteria included recent antibiotic use, malnutrition, and active drug treatments. Randomization ensured unbiased allocation to treatment groups.

Clinical outcomes focused on assessing nutritional absorption capacity through blood biomarker levels of Vitamin D, Vitamin A, calcium, iron, and zinc at baseline (T0) and 10 weeks (T2). Statistical analysis involved comparing mean values between treatment and control groups using ANOVA tests (21,22) (Table I).

Table I. *Table showing how the Active/Treated (A) and Placebo (B) groups compare: weight increase, BMI, Vitamin D, Vitamin A, Calcium, Zinc, and Iron measured at baseline (T0) and ten weeks (T2) after probiotic/placebo administration. These results indicate that probiotic supplementation led to significant improvements in several nutritional biomarkers compared to the placebo group.*

Parameter	Treated group (T0-T2) (probiotic)	Placebo group (T0-T2)	p-value
Weight increase	+1.5%	+1.5%	<0.001
BMI	Unchanged	Unchanged	<0.001
Vitamin A	+9%	+1%	<0.001
Vitamin D	+3.2%	-3%	<0.001
Calcium	+4%	-7%	<0.001
Zinc	+1.7%	-3.5%	<0.001
Iron	+2%	-1%	<0.001

Results revealed significant differences between the probiotic and placebo groups, indicating the probiotics' positive impact. Patients receiving probiotics demonstrated improvements in weight, BMI, and blood biomarker levels compared to those in the placebo group. Notably, no adverse events were reported during the study (Fig.3,4).

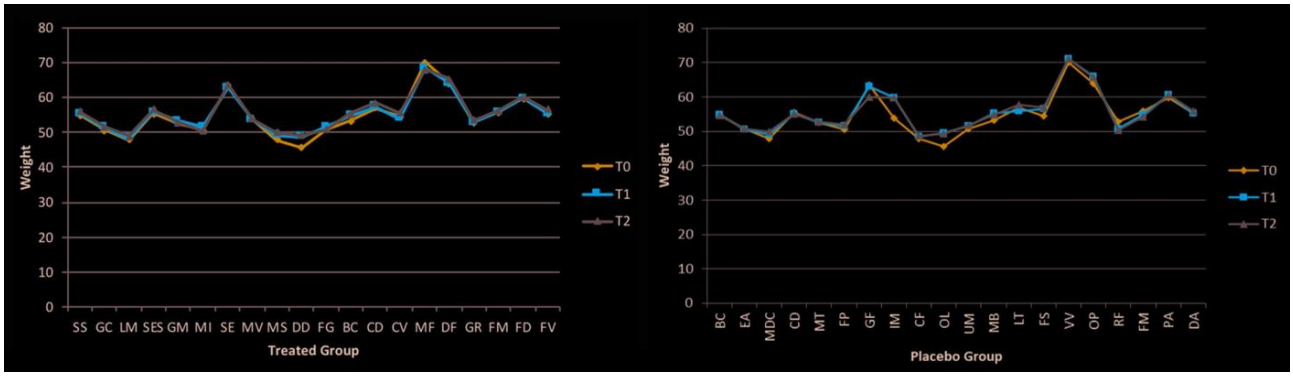

Fig. 3. *Charts show how the Active/Treated (A) and Placebo (B) groups compare: Anthropometric measurements, or body weight, were taken at baseline (T0), five weeks (T1), and ten weeks (T2) following probiotic/placebo administration. These data are of nutritional importance. The abscissa axis displayed the patient's initials (full name, family name), while the ordinate axis displayed the body weight value as the consequence.*

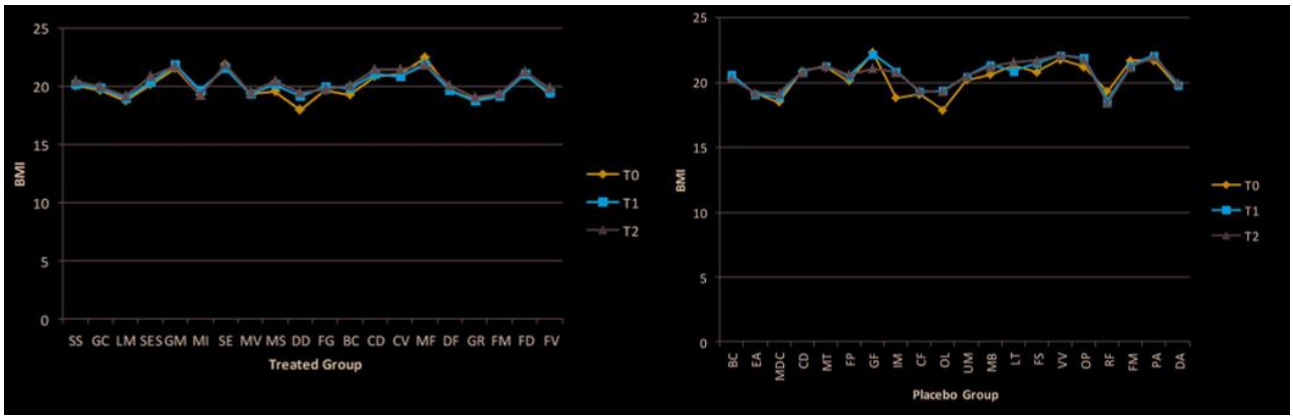

Fig. 4. *Charts show how the Active/Treated (A) and Placebo (B) groups compare: Body mass index (BMI) and other nutritionally significant data were measured at baseline (T0), five weeks (T1), and ten weeks (T2) after probiotic/placebo administration. The patient's initials (full name, family name) were given in the abscissa axis, and the outcome (BMI) value was reported in the ordinate axis.*

Discussion of previous literature highlighted the varying efficacy of probiotics in managing conditions like antibiotic-associated diarrhea (AAD) in children. Studies demonstrated mixed outcomes, emphasizing the importance of selecting appropriate probiotic strains tailored to desired clinical outcomes (23–25).

Despite limitations, including a small sample size and lack of fecal microbiome analysis, the study underscores the potential benefits of probiotics in enhancing nutritional absorption in pediatric populations. Further research is warranted to elucidate probiotics' mechanisms and optimize treatment protocols for pediatric patients (26–28).

DISCUSSION

The meta-analysis conducted in 2015 encompassed 23 studies up to 2014, evaluating the efficacy and safety of probiotics in preventing antibiotic-associated diarrhea (AAD) in pediatric populations. These studies examined various probiotic strains, including Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., and others, administered in different doses and durations. The majority of these studies reported improvements in the average duration of diarrhea with probiotic treatment, especially when administered concurrently with antibiotics. Notably, serious side effects were not observed, though minor adverse events like skin rash, vomiting, and phlegm were reported in some cases (29–32).

An earlier study from 2002 demonstrated the efficacy of probiotics in reducing the frequency of diarrhea in children (32). However, subsequent research, such as the 2018 study, found that Lactobacillus reuteri did not prevent diarrhea in children taking antibiotics. This underscores the variability in the effectiveness of different probiotic strains in this context (33–36).

In 2015, a study compared five different probiotics and found that not all were effective against antibiotic-induced diarrhea. Lactobacillus rhamnosus GG showed promise in reducing the duration of diarrhea, while Streptococcus faecium SF68 improved clinical outcomes in children with diarrhea associated with respiratory infections (23,37,38).

Further investigations evaluated probiotic yogurt containing Lactobacillus rhamnosus GG, Bifidobacterium lactis, and Lactobacillus acidophilus. This yogurt demonstrated a reduction in both the incidence and severity of diarrhea caused by antibiotics in children compared to a placebo yogurt (4,39,40).

The combination of Bifidobacterium lactis and Streptococcus thermophilus also exhibited positive effects in decreasing the frequency of diarrhea in children undergoing various antibiotic treatments (3,41–43).

The rationale behind using probiotics to mitigate antibiotic-induced diarrhea lies in their ability to restore the balance of intestinal microbiota disrupted by antibiotics. However, not all probiotic strains exhibit equal efficacy, and the parameters used to evaluate their effectiveness vary among studies. Some strains, such as LGG and S. boulardii, have consistently shown efficacy in reducing the risk of antibiotic-associated diarrhea in children (1,44–46).

Despite these findings, certain limitations need to be considered, including the variability of the intestinal microbiota among individuals and the absence of fecal microbiome analysis in some studies. Overall, while certain probiotic strains hold promise in preventing antibiotic-associated diarrhea in children, further research is necessary to refine recommendations and gain a comprehensive understanding of their mechanisms of action (31,32,47).

Moreover, recent studies have focused on exploring different types of probiotics and their efficacy in preventing antibiotic-associated diarrhea. For example, a study in 2018, still ongoing, is testing various probiotics in children undergoing antibiotic treatment. This study aims to evaluate the consistency and frequency of stools daily, both during and after antibiotic use, to assess the effectiveness of probiotics in preventing diarrhea (34,37,48).

Articles addressing the prevention and treatment of diarrhea caused by antibiotic use are increasing. In 2017, guidelines were established for the combined use of probiotics with antibiotics to prevent diarrhea in children. This systematic review identified two probiotic strains, LGG and S. boulardii, with sufficient evidence of efficacy in reducing the risk of antibiotic-associated diarrhea in children, based on data from well-designed randomized trials (1).

However, this study has several limitations. Firstly, the number of cases analysed was limited, with more robust outcomes needed for conclusive results. Secondly, the lack of fecal microbiome analysis is a significant gap, as the variability of gut microbiota among individuals may impact the response to probiotics. However, the study's strength is that it chose a probiotic supplement that contains strains that other research has shown to have a beneficial impact on general health (49,50).

CONCLUSIONS

The findings of this preliminary study indicate that administering a specific combination of probiotics as a preventive measure could benefit pediatric patients by enhancing their overall health and immunity. This intervention not only improves serum biochemical parameters but also enhances nutritional absorption capacity. The study suggests that for optimal results, probiotics should be taken for a minimum of five weeks. However, additional research is needed to refine recommendations for patient prevention and treatment strategies.

Author Contributions

Conceptualization, F.I., L.C., I.R.B., G.D., P.N. A.P., M.G. and A.D.I.; methodology, F.I., G.D., A.P., L.C., L.B, A.M. and A.M.I.; software, A.D.I., A.P., and G.D.; F.C.T.; validation, A.M.I., F.I., G.D., A.D.I., and F.I.; formal analysis, A.D.I., F.I., A.M., P.M., P.N., A.M.I., A.P., and G.D.; resources, A.D.I., A.M.I., A.P., F.I, L.C., and G.D.; data curation, A.M.I., F.I., A.M.I., A.D.I., L.C.; P.N., and G.D.; writing—original draft preparation, F.I., A.D.I., A.M.I., M.P., L.C., P.N.; F.C.T., and G.D.; writing—review and editing, A.P., A.M., I.P., M.G., L.C., P.N., F.I., G.D., A.M.I., and A.D.I.; visualization, A.M.I., F.I., A.D.I., P.M., D.C., G.D., and A.P.; supervision, G.D., F.T. L.C., P.N., A.D.I., A.M.I., A.P., and F.I.; project administration, G.D., A.M.I., A.D.I., and F.I. All authors have read and agreed to the published version of the manuscript.

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Data are contained within the article.

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The authors declare that they have no conflict of interest.

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Review

USE OF DIODE LASER TECHNIQUES IN LABIAL FRENULECTOMY. SYSTEMATIC REVIEW

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ABSTRACT

Introduction: In addition to diastemas, gingival recession, eruption abnormalities, the beginning of carious and periodontal problems in the upper central incisors, and functional and cosmetic disorders of the top lip, an aberrant and hypertrophied upper labial frenulum (ULF) can also result in these conditions. The purpose of this study is to evaluate the available data on surgical methods for treating ULF in order to determine which is the most effective. *Material and Methods:* Using the Boolean keywords "frenulum" and "surgery" we searched PubMed, Scopus, Cochrane Library, and Embase from December 1, 2012, to December 31, 2023, for papers that matched our topic. In all, eight articles were chosen for the review's purposes. *Discussion:* Laser surgery or conventional scalpel surgery can be used to surgically treat ULF. Due to its advantages before and after surgery for patients as well as physicians, including quicker recovery, less discomfort and side effects, and higher patient compliance, the latter is preferable. But this method has a steeper learning curve, particularly in terms of calibrating the laser's power. *Conclusions:* It is now impossible to determine which kind of laser produces the best therapeutic outcomes while treating ULF.

KEYWORDS: *Oral surgery, frenectomy, laser, upper labial frenulum*

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INTRODUCTION

A soft tissue called the upper labial frenulum (ULF) runs from the maxillary gingiva's center to the upper lip's center (1). The tectolabial bands that join the upper lip to the tectolabial papilla, which begins in the peri-fourth month of intrauterine life, form the insertion height, which varies (2). From birth until the central maxillae erupts, the frenulum is steady (3). The development of the permanent teeth and the expansion of the alveolar process are associated with atrophy and relocation of the insertion in the apical direction (4).

Collagen constitutes most of the frenulum, although elastic and lax reticulars are also present. The liner is composed of laminated polyethylene pavement (5). Although the presence of 1 muscular tissue in the frenum is unknown, it is currently accepted that musclular tissue is not a necessary part of the frenulum (6).

Based on implant location and insertion site, multiple ULF classifications have been suggested. Placek (1974) distinguished between mucosal attachment (frenulum), gingival attachment (frenulum), attached to the papilla, and penetrating papillary attachment (frenulum) when classifying the different kinds of ULF according to the site of the implant (7,8). According to the insertion place, Popovich et al. (1977) divided the frenulum into two main morphotypes: transpapillary and alveolar, gingival, interdental, and alveolar. Ischemia of the palatine's papilla and mesial gingival margins of the upper central incisors following traction of the upper lip is referred to as an aberrant ULF, also called "traction syndrome"(9). The tectolabial frenulum, which has an expanded upper triangle, is the subject of other investigations more frequently. It is the tense, fibrous, papillary or transpapillary interincisional frenulum (10). This type of ULF is considered like a genuine dysontogenic sign of the fetal frenulum's postnatal persistence (11).

Traditional surgery

There are two common surgical methods: laser surgery and traditional cold blade (CVA) surgery. With the traditional cold blade, the frenulum's edges are cut in a V-shape, the coronal insertion is retracted, and the apical region is realigned (12). Because the latter method causes periosteal fibers to form and become tangled and chipped, it has greater adverse effects (13).

To sum up, ULF is a complicated and multidimensional illness that can be managed using several surgical methods.

Laser Surgery

At the moment, many kinds of lasers are employed in oral surgery, making laser surgery a widespread procedure. These consist of neodymium-doped yttrium-aluminum garnet (Nd:YAG) (1064 nm), diodes (810-930 nm), titanium oxide (KTP) potassium lasers (532 nm) and erbium family lasers (Er;Cr;YSGG or Er:YAG) (2780-2940 nm) (Fig.1). The capacity to only operate on teeth, gums, or both is the primary distinction between them (15). Compared to traditional dental procedures, laser surgery has the following benefits: less bacterial development, faster healing, decreased post-operative pain, and greater coagulation and effusion (16). Due to their compact size, affordability, and convenience of use for minor dental surgery, diode lasers have gained popularity in the dental field. They also have advantages in coagulation and the decrease of post-operative pain (17). Due to the great biological memory of the pulmonary frenules, surgery must address both the frenulum's edge and its deep insertion in the muco-gingival line with a view to stop regrowth (18). In cases of maxillary labial type IV with palatine insertion, fibrotomy of the circular and transatlantal fibers must be extended to the level of the oral palatal bone. There is less data regarding the surgical treatment of the lingual frenulum despite the abundance of articles on the condition's resolution in the literature (19). The aim of this study is to evaluate the existing surgical methods for treating lingual frenulum and to weigh the advantages and disadvantages of each strategy (20) (Fig.2).

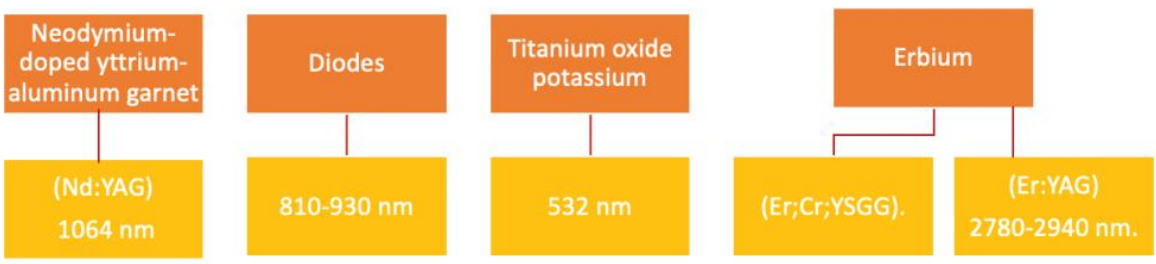

Fig. 1. *Types of lasers applied in oral surgery.*

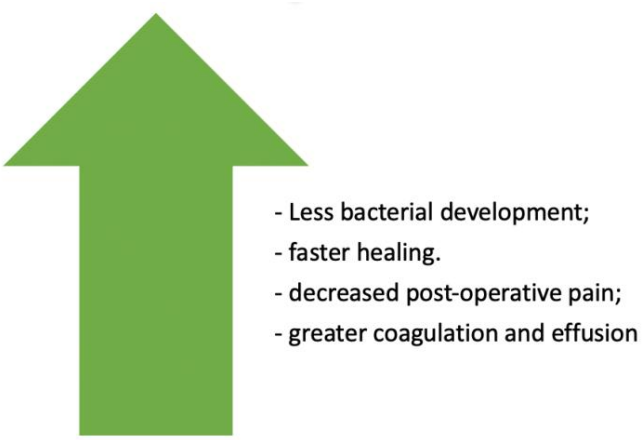

Fig. 2. *Benefits of Using Laser in Surgery*.

MATERIAL AND METHODS

Recording and Protocol

Under PROSPERO number 549366, this systematic review was registered and carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (21).

Research strategy and data sources

The demographic, intervention, comparison, results, and study design components of the PICOS framework were used to build the data sources and search method. Table I describes PICOS criteria in detail (Table I). Using the phrases "frenulum" and "surgery," the analysis was carried out from December 2012 to December 2023 on databases like Pubmed, Cochrane, Scopus, and Embase. The writers looked up whole article titles and analysis of papers that might be pertinent. Table II summarizes the research strategy in detail (Table II).

Table I. *PICOS criteria (population, intervention, comparison, outcome, study design), which include population, intervention, comparison, outcome, and research design, as well as their use in this evaluation*.

Population	• Patients with lingual and/or ULF requiring surgical treatment.
Intervention	• Laser surgery (various laser types such as neodymium-dopedyttriumaluminumgarnet laser (Nd:YAG), diode, Potassium titanylphosphate laser (KTP), Erbiumchromiumyttriumscandiumgallium-garnet laser (Er,Cr:YSGG) or erbium-dopedyttriumaluminumgarnet laser (Er:YAG) • traditional scalpel surgery (CVA)
Comparison	• Laser surgery vs. traditional scalpel surgery.
Outcome	• Healing time • Post-operative pain • Coagulation and bleeding • Post-operative side effects and complications
Study design	• Randomised controlled trials (RCTs) • Retrospective studies • Observational studies • Case reports

Table II. *Screening strategy.*

Article screening strategy:	
Keywords:	• A: “frenulum” • B: “surgery”
Boolean indicators:	• (“A” AND “B”)
Timespan:	• from 1 December, 2012 to 31 December, 2023
Electronic Databases:	• Pubmed • Cochrane • Scopus • Embase

Criteria for inclusion and exclusion

Articles that fulfilled the following criteria were included in the analysis: only human studies, open access, randomized, retrospective, observational, and treatment of the surgical approach of the ULF, along with comparisons of different procedures. Reviews, editor's letters, studies on closed skulls, and animal models were not included in the study.

Information collection

Analyzing the design, field size, control group, intervention type, follow-up, and outcome allowed for the collection of study data.

Data processing

Two reviewers (R.V.G. and B.F.P.P.) searched databases to find relevant studies and evaluated them separately based on predetermined inclusion and exclusion criteria. During the screening process, articles that didn't fit the specifications for the manuscript and abstract were disqualified. We performed an eligibility analysis by reading the complete texts of the remaining articles. Mendeley (version 2.112.2) published the chosen articles.

Quality assessment

The quality of the included papers was assessed by two reviewers, A.M.I. and A.D.I., using the ROBINS is a tool developed to assess risk of bias in the results of non-randomized studies that compare health effects of two or more interventions. Seven points were evaluated, and each was assigned a degree of bias. A third reviewer (F.I.) was consulted in the event of a disagreement until an agreement was reached. The question in the domains evaluated in the ROBINS is the following:

-Bias due to confounding
-Bias arising from measurement of exposure
-Bias in the selection of participants into the study
-Bias due to post-exposure intervention
-Bias due to missing data
-Bias arising from measurement of the outcome
-Bias in the selection of the reported results.

Risk of Bias of Included Articles

Figure 3 reports the risk of bias in the included studies (Fig.3). Confounding bias is a major source of bias in most studies. One parameter that has little chance of bias is measurement bias. A low risk of bias in much research can be attributed to participant selection bias. The significant heterogeneity makes it impossible to calculate bias resulting from post-exposure. Many studies have low bias rates because of missing data. There is little bias resulting from outcome measurement. In most studies, there is a significant bias in the selection of the published results. As per the final results, there is a low risk of bias in 5 studies, a very high risk of bias in 12 studies, and a high risk of bias in 9 research.

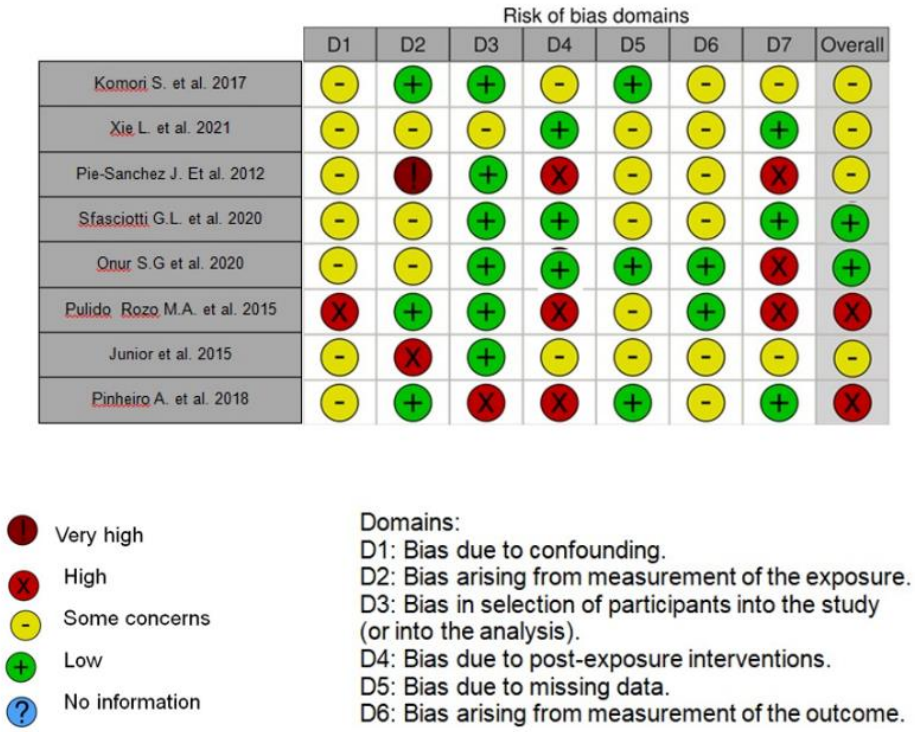

Fig. 3. *Bias assessment.*

RESULTS

274 post-duplication checks were conducted on 334 studies that were found in the electronic database. 56 publications were chosen for approval consideration after 274 papers were deemed duplicates. 48 articles were eliminated following full-text review; they included 42 papers that were not related to the issue, 5 that had incorrect taxation, and 1 that lacked interest. Eight articles were ultimately chosen for thorough editing (Table III). Figure 4 provides an illustration of the selection procedure (Fig.4).

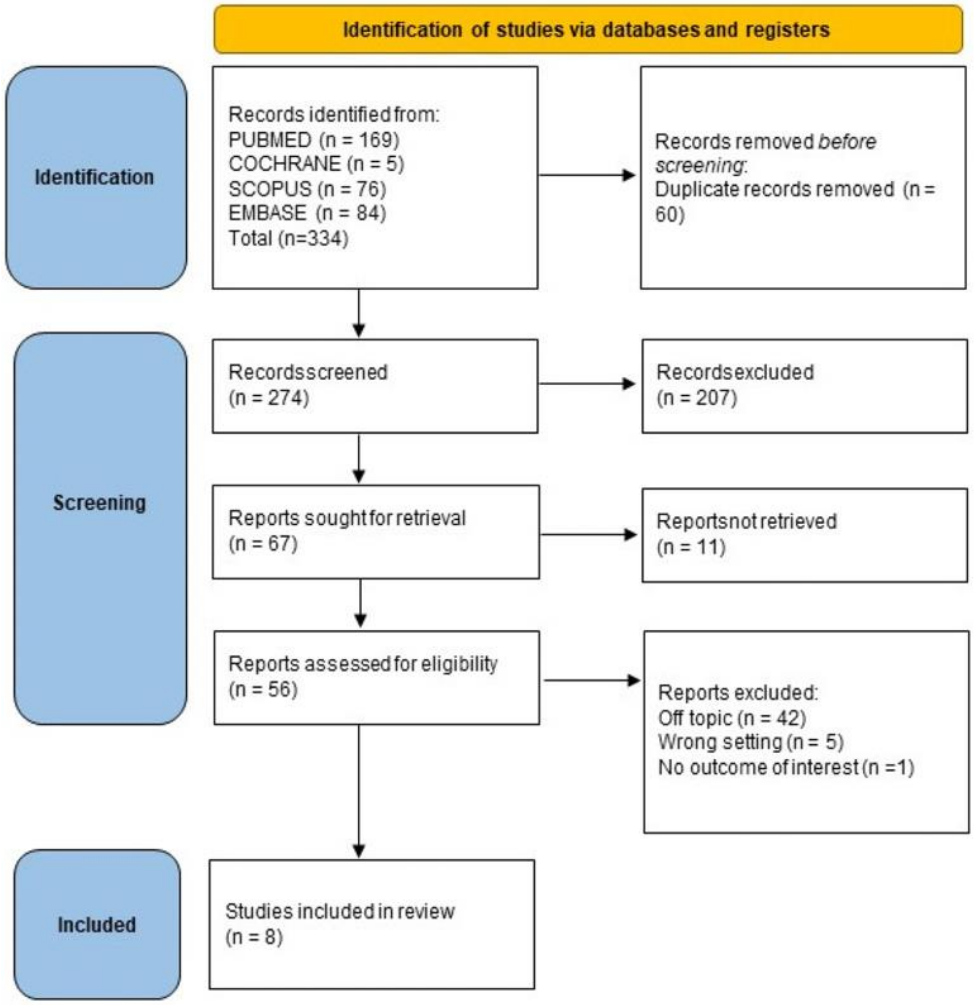

Fig. 4. *Literature search preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.*

Table III. *Characteristics of the included studies.*

Authors	Study Design	Sample Size	Average Age at Intervention (Years)	Type of Surgery	Follow-Up
Komori S. et al., 2017	Retrospective	21 total laser surgery, 15 lingual, 6 labial	6.0 Lingual: 5.2 Labial: 8.2	3 Carbon dioxide laserCO2 laser operating continuously for around 60 seconds at 2 to 5 W.	*4.6 months.* Re-adhesion in 1 patient of the lingual frenulum.
Xie L. et al., 2021 (31)	Double bind-randomized controlled trial (DB-RCT)	34 patients, 17 laser surgery, 17 scalpel surgery	5–10	First, a 1.80 W Er:YAG laser with a wavelength of 2940 nm and a short pulse (SP) of 60 MJ of energy and 30 Hz of frequency is used for laser surgery. The Nd:YAG laser was then configured with an extremely long pulse width, frequency of 20 Hz, and power of 4.00 W. sterilized scalpels were used during the procedure, #11. and 4–0 absorbable suture.	*1 month.* Wound healing and no re-adhesion in every group Scar in 1 case of scalpel surgical technique.
Pie-Sanchez J. et al.,	RCT	50 total patients, 25 CO_2laser surgery,	11.3	A 5 W CO2 laser with a wavelength of 10,600 nm is employed in the focused	*4 months.* No variations in the post-operative

2012		25 Er,Cr:YSGG laser surgery		continuous wave mode. Er,Cr:YSGG laser with a wavelength of 2780 nm, a frequency of 20 Hz, and a pulse length of 140 to 200 µs. 1.5 W of power with 12% water and 8% air.	Faster operation times and a bloodless, intraoperative environment with the CO2 laser group YSGG laser group promotes quicker wound healing in Er,Cr.
Sfasciotti G.L. et al., 2020	DB-RCT	25 total patients, 13 Diode laser surgery, 13 CO_2laser surgery	9	The diode laser has a wavelength of 980 nm, a continuous pulse mode, and a 2.5 W setting. The CO2 laser, operating at 4.5 W in super pulse wave mode at 10.600 nm.	*14 days.* In the Diode laser group, improved biological outcomes and fewer intraoperative mistakes.
Onur S.G et al., 2020	Retrospective	22 total patients, 11 Er,Cr:YSGG laser surgery 11 diode laser surgery	8–13	2780 nm Er,Cr:YSGG laser: 2.75 W of power, 50 Hz of frequency, 60 ls of pulse length, 55 mJ of energy per pulse, 22 J/cm^2 of energy density per pulse, 20% air, 40% water. 940 nm diode laser running in continuous wave mode at 1.5 W of power.	*2 weeks.* Improved wound healing in the laser group Er,Cr:YSGG.
Pulido Rozo M.A. et al., 2015	Case report	1	16	High-intensity laser not specified.	*15 days.* Resolved post-operative edema and excellent healing.
Junior et al., 2015	Prospective	40 total patients, 22 scalpel surgery, 18 Nd:YAG laser surgery	20.9 ± 10.3	No. 15 scalpel blade with a basic silk thread stitch 4-0. Nd:YAG laser with the following specifications (λ = 1064 nm): 40 J of energy at 40 Hz frequency, 4 W of power, and a brief pulse width were used for 10 s (power density = 5 W/cm2 and energy density = 50 J/cm2).	Shortened surgical time and suture-free in the Nd:YAG laser group.
Pinheiro A. et al., 2018	Case series	1 scalpel surgery, 1 diode laser surgery	28	A 15-scalpel incision and a 5-nylon-thread suture were made using a diode laser with an infrared wavelength of 808 nm, a power of 2 W, an energy of 120 J, a pulsed mode, and a repetition frequency of 20 pps.	*7 days.* Less bleeding during and after surgery and increased efficiency in terms of time with laser surgery Consumption of drugs after surgery, pain, and swelling during scalpel surgery

DISCUSSION

In addition to diastemas, gingival recessions, eruption abnormalities, and the beginning of carious and periodontal problems of the upper central incisors, the existence of an interdental abnormality and hypertrophy can also result in

esthetic and functional disorders of the top lip (22). The condition can be surgically solved by using a traditional scalpel, electrosurgery, several high-intensity laser equipment or atmospheric plasma (23-26).

Although electrosurgery is a well-known surgical procedure for ULF, only papers on laser and conventional surgery have made it beyond the screening phase in this study (27). The various surgical approaches are examined and contrasted, and it is widely accepted in the literature that when a patient has a small lip and a fornix, conventional surgery is not recommended unless it is paired with Z-plasty (28,29).

While electrosurgery has excellent hemostatic properties and can produce significant scarring and postoperative discomfort, suturing is usually necessary. Contrarily, laser irradiation draws exact, non-bleeding surgical margins without penetrating deeply into the tissue, enhancing patient comfort and compliance as well as visibility of the surgical site (30).

Research contrasting diode laser surgery with conventional surgical methods demonstrates the advantages of the laser technique in terms of wound healing time, discomfort, oedema, haemostasis, and post-operative inflammation (31). Komori et al. conducted a retrospective clinical investigation to analyze the application of a 10.6 μm CO 2 laser on six pediatric patients, two of whom had a Type II frenulum and four of whom had a Type III frenulum based on Rui's classification (32).

Of the six patients treated, only one required suturing because of the excellent haemostatic activity and precise excision and vaporization of the oral cavity's soft tissues produced by high-frequency laser irradiation (33,34). Not a single patient reported experiencing any postoperative complications, including pain, difficulty chewing, bleeding, or recurrence with fiber reattachment. Compared to traditional surgery, the approach is simpler, and the operative time is shorter (35).

Pie-Sanchez et al. evaluated the effectiveness of two different types of laser devices-CO 2 and Er,Cr:YSGG in a prospective study involving 50 patients (36). They came to the conclusion that while the CO 2 laser allows the surgeon to perform surgery more quickly and with a bloodless surgical field, the Er,Cr:YSGG laser promotes faster wound healing (37).

The Rozo case served as an example of the laser surgical technique's adaptability (38). In the same procedure, the 16-year-old patient had an anterior gingivoplasty and a frenolectomy-the latter for aesthetic purposes and the former for practical ones (39). Patients will experience fewer visits and less discomfort as a result of the simultaneous use of two treatments with laser surgery (40).

The therapy of frenectomy in pediatric patients who were at risk of developing gingival recessions made worse by the existence of the frenulum was examined by Sfasciotti et al. While the latter provides better control over bleeding, the former is more effective in managing pain and accelerating the healing of wounds (24,41).

There were no statistically significant differences in safety and efficacy between laser diode surgery and Er,Cr:YSGG treatment, according to Onur et al.'s study on pain perception and healing time. It is important to calibrate the laser's power appropriately and to shield the patient's and operator's eyes when utilizing one (43). Overpowering can result in damage to the surface (44). To avoid localized and reversible tissue necrosis and patient suffering, diode, Nd:YAG, and CO2 lasers specifically suppress adjacent tissues and any fiber interaction with the periosteum. The primary research constraint is that, despite examining identical clinical parameters, the studies employ distinct categorization schemes and juxtapose a single laser type against conventional surgery or two types of laser devices against one another (15,45). Consequently, it is unfeasible to conduct a comparable analysis between traditional surgery and the diverse laser methodologies (46).

CONCLUSIONS

ULF can induce anomalies that result in diastemas, recessions, gingival anomalies, eruptive lesions, carious lesions, and periodontal lesions of the upper central incisors. Studies investigating the surgical methods that can be used for therapy, such as conventional and laser surgery, are included in a systematic review. While traditional scalpel surgery is less expensive and has a shorter learning curve, it has disadvantages such as longer operating times, blood loss, decreased field visibility, tissue suturing requirements, longer healing times, and the possibility of plaque accumulation on the sutures. With clean margins and little blood loss, laser surgery offers far less discomfort both during and after the procedure. In comparison to traditional surgery, the outcomes of laser surgery are superior in terms of hemostasis, surgical time, discomfort, oedema, post-operative infection, and healing time. Nevertheless, it is impossible to identify the laser source that produces the greatest clinical outcomes. It is necessary to conduct randomized, controlled trials in order to compare the benefits and drawbacks of the various laser surgical instruments on the market.

Author contributions

Conceptualization, A.L., A.D.I., F.I., A.M.I., G.D., I.R.B. and A.P.; methodology, A.D.N., B.F.P.P., R.V.G., F.C.T. and A.P. software, B.F.P.P., G.P., A.D.I., R.V.G. and A.L.; validation, F.I., A.M., A.M.I., G.D., M.C. and B.F.P.P.; formal analysis, A.D.I., A.M.I., A.L., B.F.P.P. and R.V.G.; investigation, G.D., A.P., M.C., F.l. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.l. and G.D.; data curation, G.P., B.F.P.P., R.V.G., A.P. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., B.F.P.P. and R.V.G.; writing-review and editing, F.I., A.P., A.L., A.D.N. and G.P.; visualization, B.F.P.P., R.V.G., A.D.N., A.P., I.R.B. and A.D.I.; supervision, G.D, F.I., A.D.I.,A.D.N. and F.C.T.; project administration, M.C., G.P., B.F.P.P., A.M.I. and R.V.G.. All authors have read and agreed to the published version of the manuscript.

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Informed consent

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Conflict of interest

The authors declare that they have no conflict of interest.

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Review

OCCLUSAL TRAUMA AND ORAL MICROBIOTA CORRELATION: A MICROBIOLOGICAL STUDY

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ABSTRACT

Aim: This study is to assess the effects of treating occlusal stress on the bacterial flora subgingival to the gingiva and periodontal health, with a focus on changes in clinical parameters such pus presence, bleeding on probing, etc. *Materials and Methods:* There were fifteen nonsmoking adults with adult periodontitis who were free of systemic illnesses and recent antibiotic use. At least three of the upper anterior teeth in each showed occlusal damage and a pocket depth of three millimeters. Five patients received a temporary resin bridge, and ten patients underwent intracoronal splinting. Using real-time Polymerase Chain Reaction (PCR) to evaluate bacterial loads, including particular pathogens like Porphyromonas gingivalis (Pg) and Actinobacillus actinomycetemcomitans (Aa) , clinical parameters and subgingival flora samples were measured at baseline (T0), 20 days (T1), and 60 days (T2). *Results:* After 60 days, there were notable improvements in bleeding on probing ($p<0.001$), pus present ($p<0.002$), and probing depth (mean decrease of 3.13 mm, $p<0.001$). Notable decreases were observed in the overall bacterial load and in the following pathogens: Tannerella forsythensis (Tf) (87.5%, p=0.007), Treponema denticola (Td) (92.6%, p=0.001), Fusobacterium nucleatum (Fn) (83.4%, p=0.008), Porphyromonas gingivalis (Pg) (59.5%, p=0.046), and Prevotella intermedia (Pi) (92.6%, p=0.001). *Conclusion:* Without the need for medicine or surgery, treating occlusal trauma improves clinical parameters and reduces pathogenic bacterial loads, hence improving periodontal health. The significance of treating occlusal variables in periodontal therapy is underscored by these findings.

KEYWORDS: *Occlusal Trauma, Periodontal Disease, Subgingival Bacterial Flora, Probing Depth, Bleeding on Probing, Real-time PCR*

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INTRODUCTION

Subgingival bacteria are the source of periodontal disease because they cause deep periodontal tissues to deteriorate. Given their diversity and difficulties in culturing, pathogenic periodontal bacteria can be difficult to identify (1–4). Periodontal pockets can be used to cultivate more than 400 species, of which 30–100 have the ability to spread disease in a single location (5,6). The physical constraints of periodontal pockets and sampling irregularities make it more difficult to accurately identify these microbes (1,7). Furthermore, rather than being the source of disease, opportunistic organisms may multiply as a result, making it more difficult to distinguish between primary infections and secondary invaders (8,9).

Because many bacteria cannot live in ordinary transport media and cannot flourish in laboratory settings, traditional culture methods have proven ineffective for identifying the gingival microflora (10,11). The strains' unique metabolic requirements and oxygen tolerance are the main causes of this restriction (6,12). Moreover, distinct strains of the same species may display differing degrees of virulence and pathogenicity, and culture techniques are unable to distinguish between them (13–15).

Molecular biology innovations like real-time Polymerase Chain Reaction (PCR) have greatly increased the sensitivity and specificity of diagnosing periodontal infections (7,16). These days, consistent measurement and identification of these pathogens are made possible by advanced techniques, which also shed light on their involvement in periodontal disease (17,18).

Unexpectedly, periodontal pathogens are frequently found in places where there is no visible periodontal injury, which raises the possibility that they are saprophytes coexisting peacefully with the oral microbial ecology (19,20).

Despite extensive plaque and tartar deposits, the site-specific character of periodontal disease suggests the potential impact of environmental factors (21,22). These variables may cause pathogenic traits to be expressed in microbes or favor more pathogenic strains (23,24). Because occlusal trauma produces traumatic pressures that alter tooth stability and dental alignment, they can worsen periodontal diseases (25,26). In order to examine changes in clinical parameters including probing depth, bleeding on probing, and pus presence after occlusal trauma treatment—without the use of medication or surgery—this study focuses on analyzing the effect of occlusal trauma on subgingival bacterial flora (27–29).

MATERIALS AND METHODS

In this trial 15 nonsmoking patients with adult periodontitis (aged 41-62) who did not smoke were included; patients with systemic diseases or recent antibiotic usage were not included. At least three upper anterior teeth with a 3 mm pocket depth and evidence of occlusal damage were present in every patient. Without the use of medication or surgery, the occlusal trauma was conservatively treated in 10 patients with intracoronal splinting and in 5 patients with a temporary resin bridge.

In addition to measuring clinical characteristics such pus presence, bleeding on probing (BOP), and probing depth (PD), samples of subgingival flora were taken at baseline (T0), 20 days (T1), and 60 days (T2). Using real-time PCR, the microbiological analysis covered the total number of bacteria as well as particular pathogens such as *Porphyromonas gingivalis (Pg)* and *Actinobacillus actinomycetemcomitans (Aa).*

Teeth mobility was eliminated following treatment for occlusal injuries (mobility 0 on Miller's scale). The results of the investigation showed that there were notable post-treatment modifications in both bacterial profiles and clinical indicators. Significant differences in PD, BOP, and pus were revealed by statistical analysis employing ANOVA and Tukey post-hoc testing. The baseline and post-60-day bacterial quotas were compared using the 2-sample T-test. This study emphasizes the significance of treating occlusal variables in the management of periodontal disease and the effect of occlusal trauma treatment on periodontal health (Table I).

Table I. *Changes of clinical parameters recorded (PD, BOP, pus) during the observation period in the tooth studied for each patient.*

	PD	BOP	Pus	Time
Patient 1	7 mm	+	+	T0
	4 mm	-	+	T1
	3 mm	-	-	T2
Patient 2	7 mm	+	+	T0
	3 mm	-	-	T1
	3 mm	-	-	T2
Patient 3	4 mm	+	-	T0
	3 mm	+	-	T1
	2 mm	-	-	T2
Patient 4	4 mm	+	+	T0
	2 mm	-	-	T1
	2 mm	-	-	T2
Patient 5	3 mm	-	+	T0
	2 mm	-	-	T1
	1 mm	-	-	T2
Patient 6	10 mm	+	+	T0
	6 mm	-	-	T1
	4 mm	-	-	T2
Patient 7	5 mm	+	-	T0
	3 mm	-	-	T1
	2 mm	-	-	T2
Patient 8	3 mm	+	-	T0
	2 mm	-	-	T1
	1 mm	-	-	T2
Patient 9	4 mm	+	-	T0
	3 mm	-	-	T1
	2 mm	-	-	T2
Patient 10	3 mm	+	-	T0
	2 mm	-	-	T1
	2 mm	-	-	T2
Patient 11	8 mm	+	+	T0
	4 mm	-	-	T1
	3 mm	-	-	T2
Patient 12	3 mm	+	-	T0
	2 mm	-	-	T1
	2 mm	-	-	T2
Patient 13	10 mm	+	+	T0
	7 mm	-	+	T1
	5 mm	-	-	T2
Patient 14	9 mm	+	+	T0
	6 mm	-	-	T1
	4 mm	-	-	T2
Patient 15	5 mm	+	+	T0
	3 mm	-	-	T1
	2 mm	-	-	T2

RESULTS

This study assessed the impact of treatment on periodontal health, observing significant improvements in PD, BOP and pus presence across all patients. The mean PD decreased by 3.13 mm from baseline to 60 days ($p<0.001$). BOP and

pus were negative at 60 days ($p<0.001$ and $p<0.002$, respectively). Subgingival flora load was significantly reduced over the same period, highlighting the treatment's efficacy in enhancing clinical and microbiological periodontal parameters. Among fifteen patients, eleven with severe periodontal disease (BOP+, Pus+, PD >4mm) experienced significant reductions in periodontal bacterial flora. Four patients showed a variable, non-significant decrease in bacterial load, which was minimal and consistent with healthy sites at baseline. The therapy significantly improved clinical conditions, but did not substantially reduce the already low bacterial load, which was within physiological norms (Fig.1). Significant reductions were observed in pathogens: Pg (59.5%, p=0.046), *Tannerella forsythensis* (Tf) (87.5%, p=0.007), *Treponema denticola* (Td) (92.6%, p=0.001), and *Fusobacterium nucleatum* (Fn) (83.4%, p=0.008). The results highlight substantial decreases in bacterial loads.

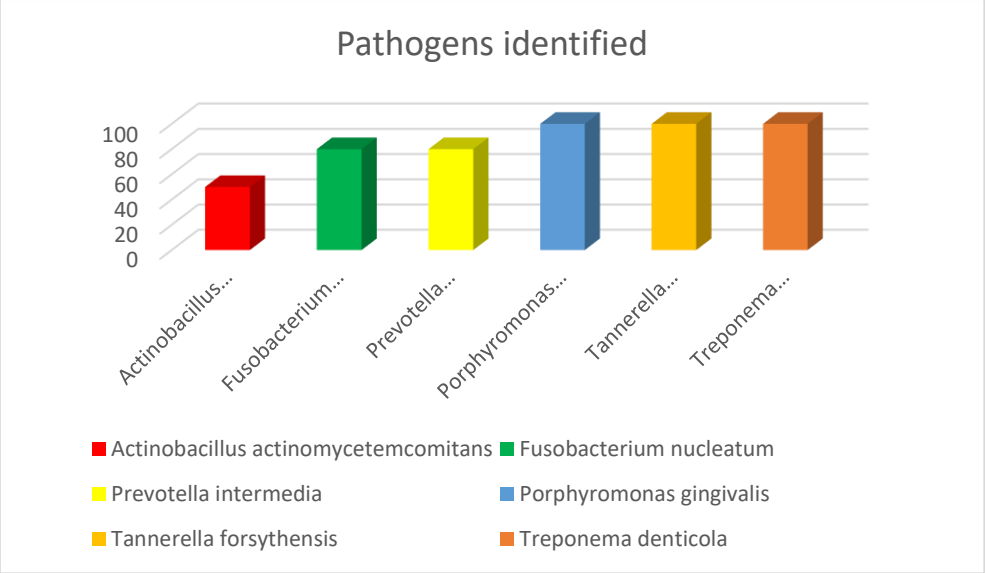

Fig. 1. *Microbiological findings in periodontal specimens: frequency with which pathogens were identified.*

DISCUSSION

This study evaluated the impact of 60-day occlusal trauma treatment on periodontal health, noting significant reductions in bacterial flora *(Aa, Pg, Tf, Td, Fn, Pi)* and improvements in PD, BOP, and pus (30). Severe cases necessitated surgical intervention, preventing microbial normalization (31,32). Although clinical indicators improved early on, pocket microbiota changes were inconsistent after 20 days, likely due to complex agonist-antagonist relationships between bacterial species. Treatment for occlusal trauma significantly reduced bacterial load without the need for medication or surgery (33). *Tf* and *Td* were the most significant bacterial species in distinguishing between periodontitis and healthy subjects, with an average reduction in bacterial load of 87.5% and 92.6% respectively (34,35).

Changes in temperature, osmotic pressure, and metabolite concentration in periodontal tissues can influence bacterial flora (36). The study by Grant et al. analyzed subgingival microbiota in patients with untreated periodontitis and those on maintenance therapy (13,37). The reorganization of microcirculation and removal of environmental stress can affect the pathogenicity of subgingival species (38,39). Increased growth in periodontal tissues activates the local immune system, potentially driving bacterial flora into dormancy (40,41). Dental mobility is linked to higher levels of bacteria associated with periodontal disease, such as *Campylobacter rectus* and *Peptostreptococcus micros*. Studies show that these bacteria are prevalent in individuals from a young age, regardless of their oral health (42,43). While periodontal disease is typically localized, the presence of specific bacteria and inflammation in the periodontal tissues can lead to more serious complications (39,44). The periodontal ligament space can expand due to occlusal trauma, impacting the movement and growth of bacteria (45,46). *Aa* was found in 53.3% of analyzed sites. While considered a primary periodontal infection, recent studies suggest it may not always be harmful. More advanced detection methods may change its role in periodontal disease (47,48). Some experts suggest that probiotics may not be effective in preventing periodontal disease without addressing environmental disturbances that allow pathogenic bacteria to thrive. Treating occlusal trauma could prevent these disruptions and inhibit aggressive pathogenic species (49,50).

CONCLUSIONS

This study showed that by lowering PD, BOP and pus presence, addressing occlusal trauma greatly enhances periodontal health. Real-time PCR analysis revealed that the interventions, which comprised temporary resin bridges and intracoronal splinting, markedly reduced pathogenic bacterial loads and decreased tooth mobility. The findings emphasize that non-surgical and non-pharmacological treatments can successfully lower clinical and microbiological indicators of periodontal disease, underscoring the significance of treating occlusal trauma in the management of periodontal disease. These results support the notion that an important part of periodontal therapy should be occlusal factor-focused.

Author Contributions

Conceptualization, A.D.I., F.I., A.M.I., G.P. and A.P. ; methodology, A.D.N., L.B., A.F., F.C.T. and A.P. software, F.I., G.D., A.D.I.,L.B. and A.L.; validation, F.I., A.M.I., G.D.,M.C. and A.F. formal analysis, A.D.I., A.M.I., A.L..,L.B. and A.F.; investigation, G.D., A.P., M.C., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I. and G.D.; data curation, G.P., L.B.,A.F., A.P. and F.C.T.; writing—original draft preparation, A.D.I., A.M.I., G.D., L.B. and A.F.; writing—review and editing, F.I., A.P., A.L., A.D.N. and A.F.; visualization, L.B., A.F., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T.; project administration, M.C., G.P., L.B, A.M.I. and A.F. All authors have read and agreed to the published version of the manuscript

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Data Availability Statement

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

RECURRENCE OF RELAPSE AFTER ORTHOGNATHIC SURGERY TREATMENT: A SYSTEMATIC REVIEW

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ABSTRACT

The purpose of this review is to look into the outcomes that recur after orthognathic surgery. Between January, 2012, and December, 2022, we looked for pertinent publications published in PubMed, Scopus, and Web of Science. The included studies had to fulfill three requirements: 1) use human subjects; 2) be open access; 3) look at the connection between orthognathic surgery and recurrence. In vitro or animal studies, off-topic studies, reviews and non-English papers published, were the exclusion criteria. After deletion of 158 duplicates, 324 items were found. 198 papers that were eliminated. We finally included 9 articles in the review after retrieving and evaluating the remaining 126 manuscripts for eligibility. The included studies show that most cases have recurrence after orthognathic surgery, as evidenced by digital study models and cephalometric tests. Research is limited by small sample sizes and retrospective study designs. Future research should focus on long- term clinical studies with larger sample sizes.

KEYWORDS: *orthognathic surgery, Le Fort I, Le Fort II, class III skeletal, mandible relocation, class II skeletal, surgical treatment*

INTRODUCTION

Orthognathic surgery is the field of dentistry and maxillofacial surgery that deals with occlusion- related asymmetries and severe maxillofacial abnormalities that might result from trauma, disease, or heredity (1-3). Class III malocclusions, which affect about 7.04% of the population, are very difficult to correct and include mandibular prognathism and maxillary retrognathism (4,5). These disorders frequently result in notable differences in maxilla-mandible connections and jaw size, which can have negative functional and cosmetic effects (6,7).

The most common congenital facial deformity is skeletal class III malocclusion, which is often associated with cleft lip and palate (CL/P) (8-10). Because of midface hypoplasia, 20-40% of these instances require surgical repair (11,12).

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The psychological and social well-being of affected persons can be greatly impacted by cosmetic issues, breathing and speaking difficulties, poor masticatory function, and facial abnormalities (13,14).

Mandibular prognathism is frequently corrected with orthognathic surgeries such osteotomy (15,16). The goal of these procedures is to enhance the appearance and functionality of the face; stable and appealing long-term results depend on precise maxillary advancement (17,18). When there is too much horizontal difference for a single jaw correction, maxillary surgery is the preferable option (19,20) (Fig.1).

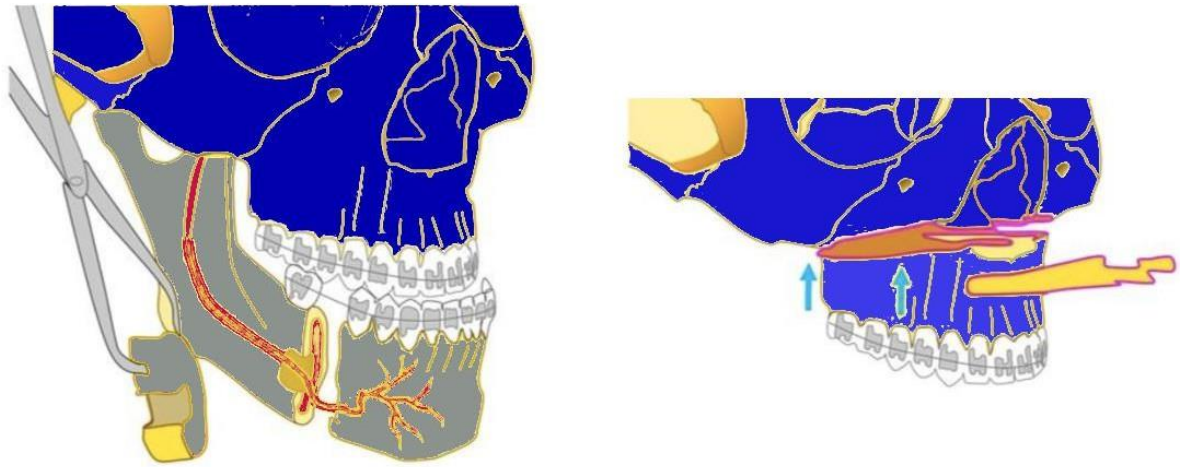

Fig. 1. *Orthognathic surgery. Correction of a class III malocclusion.*

Surgery is necessary to balance the skeletal and soft tissue components of severe skeletal Class II malocclusions, particularly in those with substantial maxillary projection (21,22) (Fig.2). Despite being less common, anterior subapical osteotomy (ASO) is useful in some situations and is frequently used in conjunction with other osteotomies (23,24). Mandibular skeletal abnormalities are often managed using bilateral sagittal split ramus osteotomy (BSSRO) in conjunction with mandibular surgery, with consistent long-term results being a critical indicator of success (25,26).

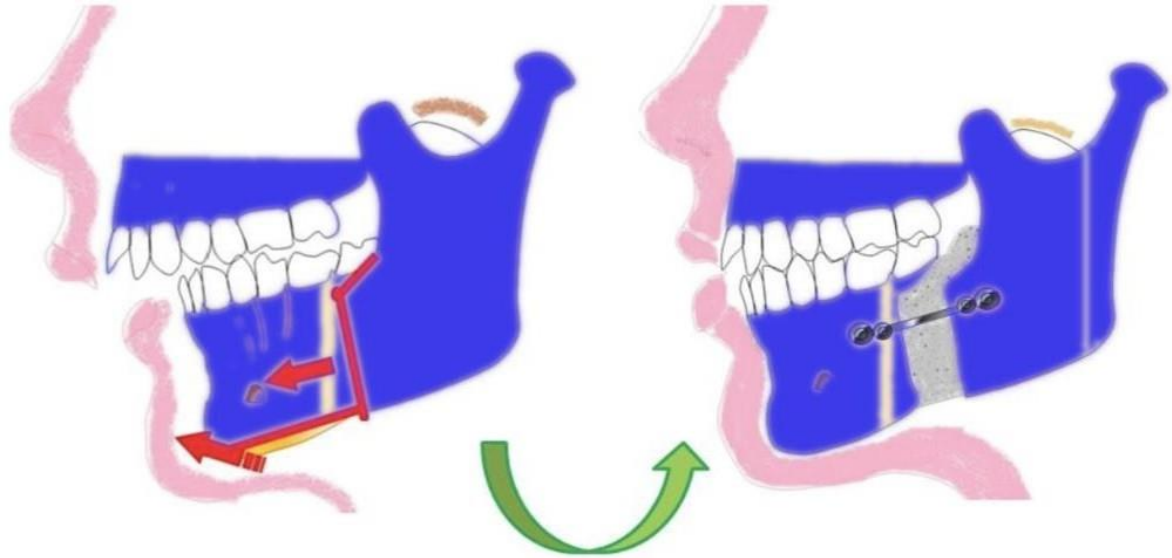

Fig. 2. *Orthognathic surgery. Correction of a class II malocclusion.*

The intricacy of maxillary movements affects relapse, which is the loss of teeth or skeleton alterations after treatment, especially in CL/P patients (27,28). Neural damage, infections, bleeding, and skeletal recurrence are among the postoperative problems that might occur; the latter is the most common (29,30). Adverse condylar morphology, muscle strain during surgery, condyle placement, and long- term progressive alterations and condyle resorption are all factors that contribute to relapse (31,32). The frequency, timing, and percentage of relapses after different orthognathic surgery procedures are investigated in this study (33-35).

MATERIALS AND METHODS

Search processing

This systematic review was conducted in accordance with PRISMA standards and has been registered on PROSPERO with ID 552857. A language restriction on English was applied when searching PubMed, Scopus, and Web of Science for studies on this topic from January 2012 to December 2022. Since the use of orthognathic surgery and the possibility of recurrence are the main foci of this research, a search strategy was created utilizing a combination of phrases that matched those goals ("Relapse" AND "Orthognathic Surgery").

Our review focuses on the qualitative analysis of the literature on orthognathic surgery and recurrence, even though the inclusion of NNT (number required to treat), 95% CIs (confidence intervals), risk analysis, and NNH (number needed to harm) in the study is valuable. Thus, our primary objective was to examine the postoperative phase in which the relapse occurred, the proportion of relapses, and the relapses linked with the different orthognathic surgical approaches qualitatively rather than statistically (Table I).

Table I. *The qualitative analysis encompasses the attributes of the in vivo research.*

Authors and Year	Type	Aim	Materials and Methods	Results
Al-Delayme et al., 2018 (37)	Prospective comparative clinical trial	Examine the stability of double-jaw surgery and contrasting mandibular techniques for class III.	This study analyzed 12 class III malocclusion patients undergoing double-jaw surgery with BSSO or intraoral vertical ramus osteotomy (IVRO), using cephalograms.	BSSO group showed 2.93 mm mandibular setback, 6.22 mm maxillary advancement, with 24.9% and 26.6% relapse rates.
Antonarakis. et al., 2019 (38)	Case report	To offer first documented combined orthognathic and orthodontic surgery with extended radiographic follow-up.	17-year-old male with myotonic dystrophy (MD) type 1 underwent combined orthodontic and orthognathic surgery.	The article discusses long-term stability in MD patient post-orthodontic and orthognathic surgery for open bite.
da Costa Senior et al., 2021 (39)	Study *in vivo*	This study aimed to evaluate the efficacy of a surgical technique in treating condylar recurrence.	Seven patients had BSSO, plus two Le Fort I and temporomandibular joint (TMJ) procedures.	The modified C-osteotomy effectively corrects malocclusion and improves jaw function and aesthetics following condylar resorption in orthognathic surgery patients.
da Silva et al., 2018 (40)	Retrospective study	Examining recurrence two years post-LF 1 osteotomy in oral cleft patients using digital cephalograms and 3D dental models.	Recurrence was examined post-LF 1 osteotomy in 17 oral cleft patients using digital cephalograms and dental casts at various stages.	Cephalometry revealed vertical recurrence after LF 1 maxillary advancement in oral cleft patients; other parameters remained unchanged.
Fahradyan et al., 2018 (41)	Prospective study	Examine the relationship between the degree of maxillary advancement and relapse.	Between 2008-2015, class III malocclusion patients underwent bimaxillary surgery: LF 1 or LF 1 with mandibular setback.	The recurrence rate was 28.6% with a mean maxillary advancement of 6.3 mm and a horizontal relapse of 1.8 mm.
Kim et al., 2018 (42)	Randomized clinical study	CBCT evaluates stability of skeletal and dental widths post-segmental LF 1 osteotomy for adult patients with class III malocclusion.	Segmental LF 1 osteotomies in 36 patients with class III malocclusion showed surgery number correlated with relapse degree.	Segmental LF 1 skeletal growth inversely related to postoperative skeletal relapse in experimental group.
Peleg et al., 2022 (43)	Retrospective cohort study	Reviewing mandibular Operations in orthognathic surgery (2010-2019) underscores the prevalence of IVRO and sagittal split osteotomy (SSO) as the	There were 144 patients present in all. The ratio of IVRO: SSO processes was 118:26.	Post-surgery, 53 issues occurred, including skeletal recurrence and temporomandibular joint impairment, among other complications.

		most common procedures.		
Politis et al., 2018 (44)	Retrospective cohort study	Assess the need for TMJ surgery following orthognathic surgery.	A total of 630 patients had LF 1 or sagittal split osteotomies between January 2013 and December 2016.	Patients with internal derangement had one- time occlusal deficits, unlike those with bilateral condylar resorption, where skeletal relapse was chronic.
Sahoo et al., 2020 (45)	Study *in vivo*	Instead of viewing relapse from a short-term standpoint, consider it over the long term.	46 mandibular orthognathic surgery patients categorized by purpose: mandibular Advancement or setback.	Significant correlations ($p < 0.05$) existed in all groups between surgical movement, intraoperative mandibular plane angle change, and relapse.

Inclusion and exclusion criteria

A list of the inclusion criteria is as follows; there exist three categories of research: human studies; full-text studies; and studies concerning recurrence after orthognathic surgery.

The categories of non-English language studies, book chapters, reviews, off-topic research, and *in vitro* or animal experiments were the exclusion criteria.

Quality assessment and risk of bias of included articles

Regarding the bias due to confounding (D1) most studies have some concerns. The bias arising from measurement (D2) is a parameter with mostly some concerns and low risk of bias. Many studies have high risk of bias due to bias in selection of participants (D3). Bias due to post exposure (D4) cannot be very precisely calculated due to high heterogeneity but has a majority of low risk and some concerns.

The bias due to missing data (D5) has mainly some concerns and low risk. Bias arising from measurement of the outcome (D6) is low. Bias in the selection of the reported results (D7) is low in more than half of the studies. The final results (Overall) show that 8 studies have low risk of bias, and only 1 has high risk of bias (Table II).

Table II. *Risk of bias.*

Authors	D1	D2	D3	D4	D5	D6	Overall
Al-Delayme et al, 2018 (37)	X	-	X	+	-	X	-
Antonarakis et al., 2019 (38)	X	+	X	X	-	-	X
Da Costa Senior et al., 2021 (39)	-	+	-	+	-	+	-
Da Silva et al., 2018 (40)	+	+	-	?	-	+	-
Fahradyan et al., 2018 (41)	+	+	-	?	-	+	-
Kim et al., 2018 (42)	-	+	-	?	+	+	-
Peleg et al., 2022 (43)	-	?	-	-	-	-	-
Politis et al., 2018 (44)	-	+	-	-	-	-	-
Sahoo et al., 2020 (45)	-	-	-	?	+	+	-

Domains:
D1: Bias due to confounding.
D2: Bias arising from measurement of the exposure.
D3: Bias in selection of participants into the study (or into the analysis).
D4: Bias due to post-exposure interventions.
D5: Bias due to missing data.
D6: Bias arising from measurement of the outcome.

! Very high
X High
\- Some concerns
\+ Low
? No information

RESULTS

Using the following databases, 482 articles were identified: Web of Science (2), Scopus (212) and PubMed (268). After removal of 158 duplicates, 324 articles remained. 198 papers were judged irrelevant based on title or abstract. We evaluated 30 reports to see if they qualified. Only 9 papers were included in this analysis, as 21 articles were discarded as irrelevant. In summary, this evaluation included 9 of the 482 original articles. (Fig.3, Table I).

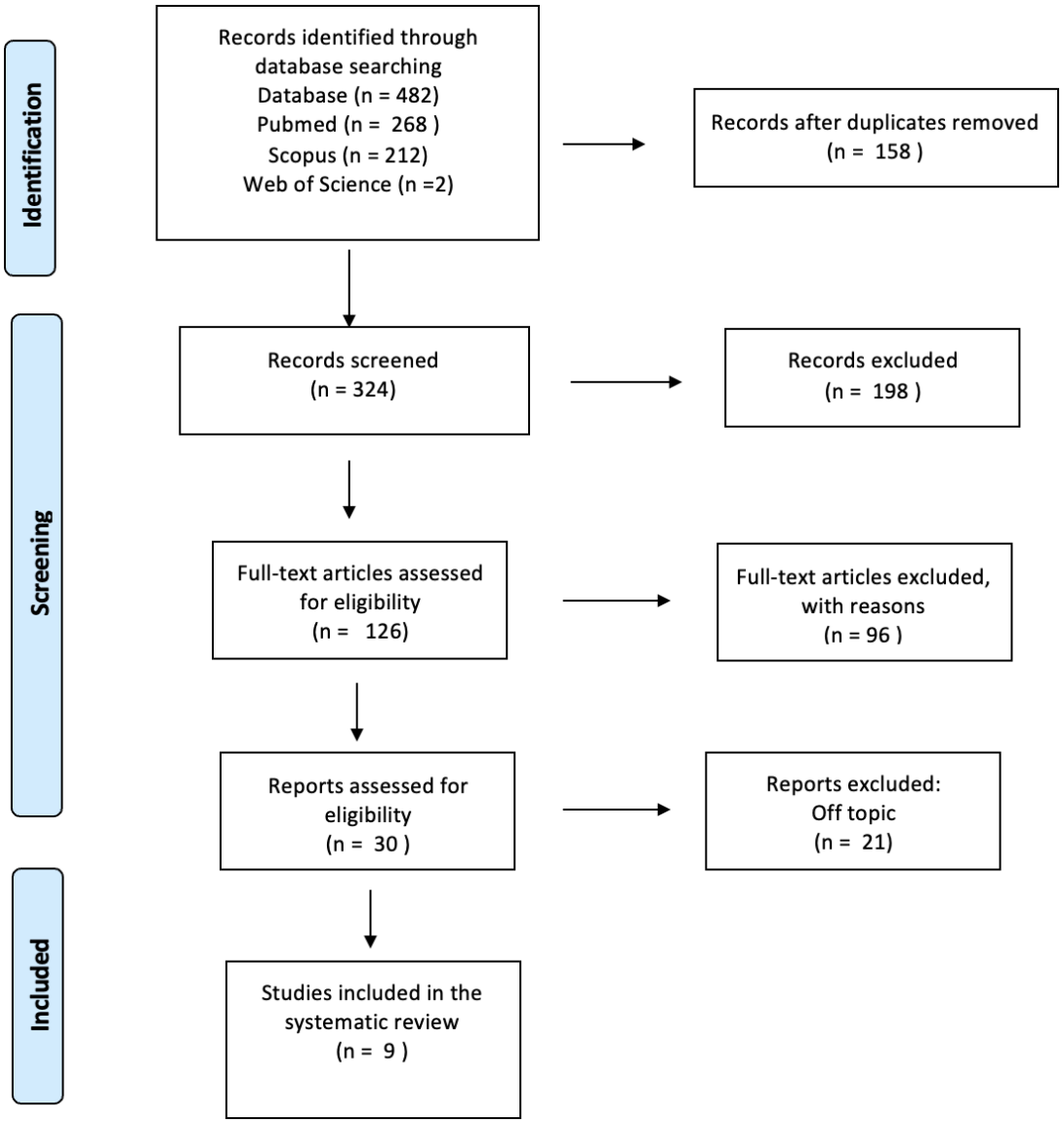

Fig. 3. *PRISMA flow chart.*

DISCUSSION

After orthognathic surgery, recurrence is a well-known problem that requires constant monitoring because of its persistent nature, as recent studies have shown. CL/P patients are more likely to recur because they have more risk factors. Studies reveal that recurrence rates are much higher in CL/P patients. For example, da Silva et al. found that despite the same preoperative overjet values and maxillary advancements, recurrence rates were higher on average in CL/P patients than in non-CL/P patients (40). Following surgery, the early healing phase might be difficult and extend for several weeks or months (37). To lessen the complicated effects of recurrence, it is essential to recognize and address its origins. The treatment results of 46 patients who had orthognathic mandibular surgery were evaluated in a study by Sahoo N. K. et al. (45). Twenty patients had mandibular retrusion (group 2) and twenty patients underwent mandibular advancement (group 1) in this study. Four time points were studied using cephalometric analyses: the week before surgery (T0), the week after surgery (T1), the year following surgery (T2), and the five years following surgery (T3) (45).

The findings showed a notable and swift regression starting at T1 and lasting until T3 ($p < 0.0001$). In comparison to group 1, group 2 showed a greater mean linear vertical and angular relapse in the majority of measurements ($p < 0.005$). Age, gender, surgical displacement, and modifications to the mandibular angle during surgery were all linked to relapse. But in both groups, there was no statistically significant positive connection ($p < 0.005$) between recurrence and age or gender at T1– T2 or T1–T3. This emphasizes how complex relapses are and how specialized postoperative care techniques are required (45).

Le Fort I Osteotomy

According to research, jaw recurrence can be reduced with a bone graft in the gap left by an LF osteotomy 1. According to one study, patients who received bone grafts had a lower recurrence rate than those who did not (45). For Class III skeletal malocclusion, patients who needed maxillary advancement underwent single (LF 1) or bilateral (LF 1 plus BSSO) maxillary surgery (40). Preoperative negative overjet values were higher in the bimaxillary surgery group despite similar maxillary advancements (42). Another study examined recurrence and maxillary hypoplasia in patients with CL/P following LF 1 osteotomy. The kind and degree of maxillary motions make this treatment intrinsically unstable, even though it is frequently used for maxillary retrusion. Using the Dolphin 3D program, researchers assessed bone and tooth repositioning three times: before surgery (T1), after surgery (T2), and six months to a year after surgery (T3) (41). Both dental and skeletal stability were essential for success. Up to two years after surgery, the study observed no horizontal relapse but 100% vertical maxillary relapse (43).

There was a tendency for both LF 1 osteotomy and its segmental variant to relapse, mostly because of the ligaments and soft tissues returning to their pre-surgery state. It is advised to use autologous bone grafting to stop relapses (45). At 12 months, the segmental LF 1 osteotomy had a 26% relapse rate, indicating good postoperative stability (45).

BSSO (Bilateral Sagittal Split Osteotomy)

When a patient needs adjustments larger than 6.7 millimeters due to severe jaw discrepancies, maxillary surgery is the recommended course of action (40). Bone grafts placed into the incision made by a LF 1 osteotomy have been shown to successfully prevent jaw relapses in a previous trial. One group receiving mandibular sagittal split ramus surgery with titanium miniplates, and the other with resorbable meshes (hydroxyapatite/poly-l-lactide) were compared for long-term skeletal stability in another study (41,47). When it came to long-term stability, the hydroxyapatite/poly-l- lactic acid group outperformed the titanium-fixation group (40,41). Furthermore, twenty-four patients were randomly assigned to groups receiving conventional osteotomy or sagittal curved osteotomy in order to explore the possibility of sagittal curved osteotomy as an alternative to conventional osteotomy for patients with retrognathism (49,50).

The study discovered that by lowering relapses in both soft and hard tissues, sagittal curved osteotomy may assist avoid recurrence following genioplasty (40).

Combined maxillomandibular approach

In order to improve facial symmetry and balance, this study investigates the efficacy of surgical and modified orthodontic methods in treating severe class III skeletal abnormalities and malocclusions (43,50). Mandibular prognathism must be treated with orthodontic surgery, which uses methods like BSSRO and IVRO to improve occlusion, masticatory function, and cosmetic results. A number of variables, including condylar location, intersegmental fixation, and surgical technique, affect postoperative mandibular stability (45). Significant variations in postoperative retrusion were observed in a comparison analysis among the groups, underscoring the significance of preserving mandibular stability in order to avert relapse (47,48).

A rise in the inter-incisive angle during a two-year period of treatment for bimaxillary protrusions showed minimal clinical recurrence, indicating stable effects (41). Retrospective cohort analysis revealed that, other from instances of bicondylar resorption, TMJ surgery is rarely required following orthognathic surgery. The study highlights the difficulties caused by skeletal and muscular problems by reporting the first instance of myotonic dystrophy with long-term follow-up following orthodontic and orthognathic treatment (45).

Further research indicated that there was no statistically significant correlation between relapse and maxillary progress, suggesting that overcorrection may actually be advantageous. Additionally, a modified intraoral osteotomy was developed to reduce the likelihood of condylar resorption recurrence (39). Patients with class III malocclusions had their skeletal and dental widths after LF 1 segmental osteotomy assessed by CBCT, which validated the incidence of skeletal malocclusions and their association with a concave face profile. These results underscore the importance of tailored surgical methods for achieving long-term stability and improved therapeutic outcomes (45).

CONCLUSIONS

Recurrence is a common issue in the post-surgical course following orthognathic surgery, as evidenced by numerous studies. Most relapses happen between six months and a year after the procedure. Relapse prevention strategies include replacing titanium plates with absorbable ones and transplanting bone into the LF 1 osteotomy's opening. However, significant mandibular advancements increase the chance of relapse regardless of whether the patient has a CL/P. Most studies are retrospective in character, and their limited sample sizes impose constraints on the research. Future research should focus mostly on large-scale, long-term clinical investigations to yield more trustworthy results.

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Consent Statement
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Data Availability Statement
Data are contained within the article.

Conflict of interest
The authors declare that they have no conflict of interest.

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Review

DIFFICULTIES AND PERSPECTIVES REGARDING BOTULINUM INJECTION AND BRUXISM

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ABSTRACT

The bacterial extract known as botulinum toxin (BTA) prevents muscular contraction by interfering with the absorption of acetylcholine. BTA is now being investigated for the treatment of bruxism. It is used in both general and aesthetic medicine. This scoping review searched PubMed, Web of Science, and Scopus for the terms "BRUXISM" and "BOTULINUM TOXIN" and looked at twelve papers published during the past ten years. Multiple muscle groups were injected with BTA: the masseters, the masseter and temporalis, or the masseter, temporalis, and medial pterygoid. BTA injections are a potential treatment option, particularly for patients who don't respond well to traditional therapies or who have poor compliance.

KEYWORDS: *Dental medicine, masticatory muscles, temporal muscles, subtype A, botulinum toxin, bruxism*

INTRODUCTION

Bruxism is the behavior of clenching or grinding teeth, which is distinct from chewing and swallowing as regular activities. It has been found that 10% of people have nighttime bruxism and 20% of people have daytime bruxism (1-3). During the day, bruxism entails clenching, but during the night, it combines clenching and grinding. Anxiety, stress, mood and sleep disorders, certain drugs, alcohol and drug misuse, and smoking are examples of etiological factors. Although

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there isn't a precise treatment, symptoms can be controlled. Botulinum toxin type A (12-18 U.I. in the masseter) can also help alleviate symptoms like morning headache and muscular hypertrophy. Muscle contraction is impeded by the bacterium Clostridium-derived botulinum toxin, which blocks acetylcholine uptake at synapses (4,5). In 1982, it was first used in oral and maxillofacial surgery to smooth the skin and reduce muscular bulk. For muscle spastic diseases, such as bruxism, BTA is helpful. Eight varieties are available: A, B, C1, C2, D, E, F, and G. Only types A and B are sold commercially (6,7). BTA causes SNAP-25 protein disruption, which stops the release of acetylcholine and results in transient muscle paralysis that can last for up to 3 months (8,9).

Applications of botulinum toxin in the head and neck can be classified as either medical-therapeutic or cosmetic (Fig.1).

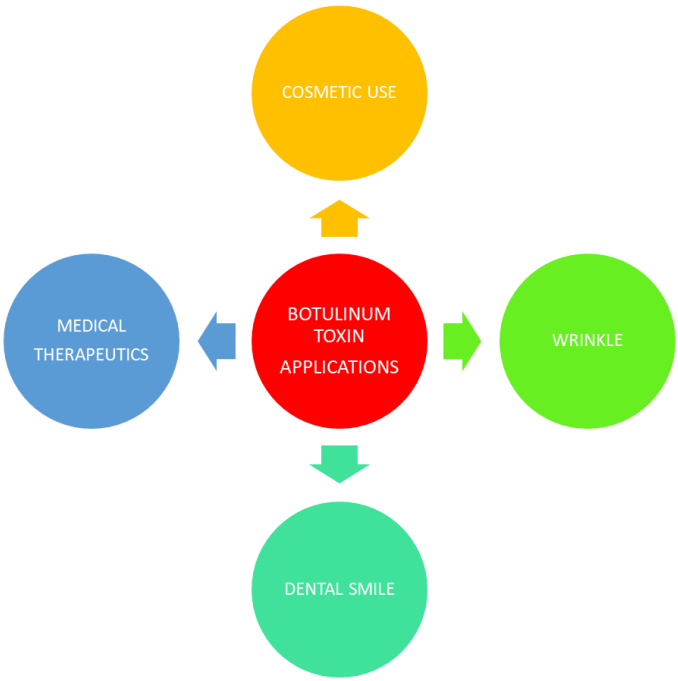

Fig. 1. *Botulinum toxin applications in medicine.*

Frontal-glabellar and frontal-periocular injections of type A botulinum toxin are common cosmetic procedures. Crow's feet, gummy smiles, frontal subtalar lines, leonine folds between the eyebrows, and expression lines are all smoothed by it (10,11).

Muscles are relaxed by botulinum toxin, which eventually reduces expression lines and solidifies them. Without requiring blepharoplasty, it can raise the tail of the eyebrow to expand the gaze (12-15).

Overexposure of the gingiva during smiling, which is frequently caused by hyperactive lip muscles, is treated with botulinum toxin. While traditional surgery can result in scarring and muscle relapse, botulinum injections provide a less invasive yet equally effective treatment option (18,33-35).

Types A and B of botulinum toxin are used to treat a variety of medical issues, beyond cosmetics. For hemifacial spasms and cervical dystonia, type B (Myobloc®) is approved (16-19).

Uses for Type A include:

• Chronic muscle spasms (such as blepharospasm, bladder hyperactivity, and post-stroke spasms) (20).

• Chronic headaches (when patients receiving treatment for appearance have seen improvement) (21,22).

• Hyperhidrosis, which affects the hands, feet, and armpits (23,24).

• Trigeminal neuralgia (which lessens tingling and numbness) (25-27).

Bruxism patients frequently experience masseter hypertrophy; minimally invasive botulinum injections are recommended over surgery in this case (28):

• Sialorrhea, which lowers discharges of saliva (29).

• Black triangles, which rebuild interdental soft tissue for approximately eight months, between prosthetic teeth (19).

Bruxism and temporomandibular disorders (TMDs) are disorders of the joints and muscles that result in pain, headaches, and joint clicks. Major reasons include periodontal problems and occlusal disharmonies. Injections of botulinum toxin have been shown to reduce joint discomfort and enhance oral opening (28,30).

Repetitive masticatory muscular action causes teeth clenching or wear and elevated mandibular muscle tone in sleep bruxism (SB). Daily parafunction, frequently associated with stress, is the reason for its rising prevalence (31).

It is suggested that BTA injections into the masseter and temporalis muscles temporarily partially paralyze the muscles in order to treat nocturnal bruxism. Because of its transient effects, recurrent therapy is necessary. BTA injections may be beneficial for treating long-term problems such as temporomandibular disorders (TMDs), according to a retrospective research published in the International Journal of Oral Maxillofacial Surgery (29). This is particularly true for patients who have co-occurring psychiatric conditions.

The purpose of this study is to evaluate the benefits and drawbacks of treating bruxism using botulinum toxin.

MATERIAL AND METHODS

Registration and Protocol

We followed PRISMA-ScR standards (32) for conducting this review (Fig.2).

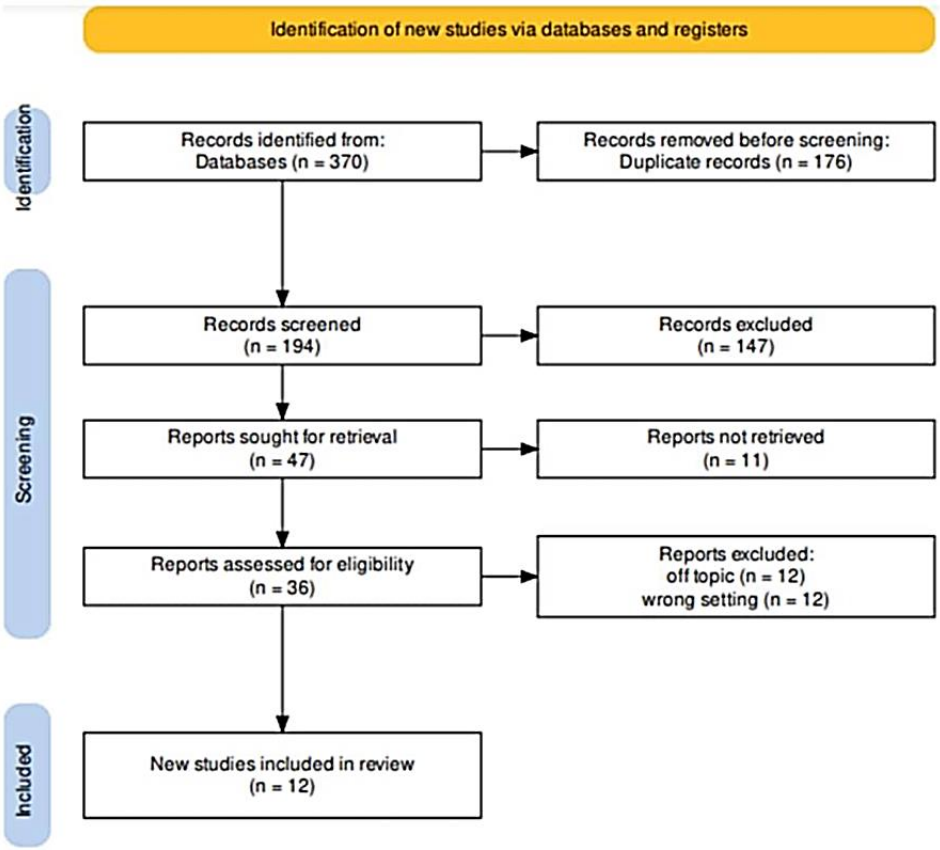

Fig. 2. *Literature search according to PRISMA Extension for Scoping Reviews (PRISMA-ScR) flow diagram.*

Analysis of Research Data

We looked through PubMed, Scopus, and Web of Science for pertinent studies on the use of botulinum toxin to treat bruxism. We amalgamated expressions associated with our review goal, emphasizing injection locations and procedures. Among the keywords were "BRUXISM" and "BOTULINUM TOXIN," joined by a "AND." Articles published in English between January 2013 and January 2023 were taken into account.

Criteria for Inclusion

The included studies had to fulfill the following requirements: (1) human subjects; (2) open access; (3) written in English (however there were English abstracts and texts in other languages); and (4) comparison with alternative treatments.

Disqualifying Standards

Studies that satisfied these criteria were excluded: Case reports, animal involvement, in vitro experiments, other reviews, off-topic articles, or studies on bruxism brought on by other illnesses (e.g., Alzheimer's, otalgia, brain injury, cerebral palsy) comprised the first six categories.

Information Processing

The relevancy of the abstract and title were used to filter the articles. The remaining articles' full texts were evaluated in light of the inclusion criteria. Disagreements over the choice of articles were settled through dialogue.

RESULTS

Using the keywords "BRUXISM" and "BOTULINUM TOXIN," 370 items were first found in PubMed (97), Scopus (164), and Web of Science (109). Duplicate articles were then removed (176), leaving 194 original papers. Additional screening of 147 papers (two animal-related, sixty-nine reviews, and seventy-six off-topic) was conducted based on the title and abstract. 37 papers were left for eligibility evaluation out of the 47 that were still available, 11 of which were not open access. Finally, only 12 papers were judged suitable for inclusion in this evaluation after entire texts were analyzed, irrelevant publications (12) and those that did not satisfy criteria were eliminated.

Quality Assessment and Risk of Bias of Included Articles

Regarding the bias due to confounding (D1), only some studies have some concerns. The bias arising from measurement (D2) is a parameter with mostly some concerns and low risk of bias. Many studies have high risk of bias due to bias in selection of participants (D3). Bias due to post exposure (D4) cannot be very precisely calculated due to high heterogeneity but has a majority of low risk and some concerns. The bias due to missing data (D5) has mainly some concerns and low risk. Bias arising from measurement of the outcome (D6) is low. Bias in the selection of the reported results (D7) is low in more than half of the studies. The final results (Overall) show that 5 studies have low risk of bias, 3 have some concerns and 3 have high risk of bias and only 1 has very high risk (Table I).

Table I. *Characteristics of the studies.*

Author	Type of study	Aim	Methods	Results
Shim et al. (33)	Randomized, placebo-controlled Trial	The study's objective is to examine how BTA affects SB management.	Two equal groups of thirty SB participants were randomly assigned. Each masseter muscle was injected with saline into the placebo group's and BoNT-A injections into the treatment group's masseter muscles. In the sleep lab, audio-video-polysomnographic recordings were taken prior to, four weeks following, and twelve weeks following the injection.	It is not possible to decrease SB episodes with a single BTA injection. However, by reducing the activity of the masseter muscle, it could be a helpful SB control technique.
Shehri et al. (34)	Randomized controlled trial	The purpose is to determine if injecting BTA into the masseters lowers SB.	A sham intervention was administered to the placebo group, while 22 participants who reported SB were randomly assigned to one of two groups. The control group was given 10 MU of BTA in the masseters. Electromyography (EMG) was used to evaluate muscle activity and pain perception in order to assess the efficacy of this therapy approach for SB.	The trial was completed by 20 patients. Before and after the injection, there were statistically significant differences in the visual analog scale (VAS) between the control and placebo groups ($p \leq 0.05$). The injection of BTA lessens the force of masseters contraction, hence relieving symptoms associated with allergies.
Mkhitaryan et al. (35)	Prospective longitudinal study	Evaluating how symptoms change following a BTA injection i s the objective.	In this study, 43 female patients were included. Before, two weeks, four months, and five months following the first BTA injection, as well as two weeks and five months following the second injection, assessment controls were performed. Photographs, orthopantomography, calliper measurements of the masseteres, and ultrasonography were used to support the study.	Following BTA injection, 74% of patients reported less pain and associated symptoms, and 26% of patients reported being symptom-free. The side effects were mild and quickly went away. When injected into the masseters, BTA was able to prevent lesions on the orofacial tissues and other symptoms.

Asutay et al. (36)	Retrospective study	The aim of the research is to assess the efficacy of BTA in the management of SB.	A comparison was made between the VAS values and the length of time and effectiveness of the treatment before and after 25 female patients who had BTA injections in both masseters.	Using BTA led to a considerable improvement in the pain scores. There were just two unfavorable effects found. For SB, the medicine BTA works efficiently.
Al-Wayli et al. (37)	Random mixed clinical trial	The study aims to assess the efficacy of BTA in treating symptoms associated with SB in comparison to other traditional treatments.	Following the injection of 20 U, patients were rechecked after three weeks, eight weeks, six months, and a year. The results were used to calculate the number of cases of bruxism. To evaluate the symptoms, a questionnaire was employed.	More than traditional therapies, botulinum toxin injections lessen muscular contraction intensity and hence lower pain scores.
Silva Ramalho et al.(38)	Randomized clinical trial	The purpose of the study is to assess clenching force, face's pain, and general relief of symptoms using two different protocols of BTA injection.	BTA was injected randomly in 2 groups of patients: group A received the injection into the masseters (3 points in each muscle, 10 U per point) and group B was injected still in the same 3 points in masseters and 2 points in each temporal muscle (10 U per point). The patients were monitored before the injection and after 15, 90, 120 and 180 days with VAS, general satisfaction, and a dynamometer for muscle strength.	In each group, ten patients finished the investigation. After 15, 90, 120, and 180 days, both groups indicated pain reduction in relation to the baseline. The posterior bite force only begins to decrease on day 120. Every follow-up appointment resulted in high levels of satisfaction for both groups. There were no variations amongst the groups during any of the research periods or assessments.
Shim et al. (39)	Randomized clinical trial	The purpose of the research is to examine the effects of BTA injection in individuals with orofacial discomfort who are not improving with oral splint therapy.	Twenty participants finished this trial. Ten volunteers (group A) received bilateral injections of BTA (25 U/muscle), while the other ten subjects (group B) received bilateral injections of the same dosage into the masseter and temporalis muscles. Recordings of video polysomnographic (VPSG) were made four weeks after the injection and before. Orofacial activity (OFA) and rhythmic masticatory muscular activity (RMMA) of the masticatory muscles were recorded and analyzed for a number of criteria (e.g., peak, number of episodes, etc.). The two muscles' electromyographic activity was also observed.	The frequency, number, or duration of RMMA episodes in response to BTA injection did not differ between the two groups. The injection decreased the peak amplitude of RMMA episode EMG bursts in the injected muscles in both groups. One month following injection, nine participants reported less teeth grinding, while eighteen respondents reported reduced morning jaw stiffness. For a minimum of one month, SB can be adequately controlled with a single BTA injection. The botulinum decreases the contraction's strength rather than its frequency of activation.
Hosgor et al. (40)	Randomized clinical trial	This study assesses the effectiveness of BTA injection in patients with SB and algicle symptoms into the masseter and temporal muscles.	A total of 44 individuals conducted clinical assessments (e.g., maximal mouth opening, range of voluntary non-painful movement) and VAS questionnaires before and after toxin injection in the masseters and temporalis muscles (after one, three, and six months).	BTA is a legitimate treatment for SB and pain because it considerably decreased patients' felt pain and increased their range of motion as compared to baseline.

Fontenele et al. (41)	Case study	Through the use of a device filled with optical fibers, the study aims to assess the degree of crunching following BTA injection.	The patient wore an interocclusal device equipped with fiber Bragg grating for monitoring while they slept. Sensor data sent to the program before and after the toxin injection are compared.	The value conflict shows a 25% decrease in muscular activation and an extension of the parafunctional activity-free interval. The values obtained for data processing are more dependable when compared to other devices, therefore a device with optical fibers is a useful tool for the physician to assess this kind of improvement.
Ondo et al. (42)	A double-blind, placebo-controlled study	The purpose of the study is to evaluate BTA treatment for SB patients.	Patients who were bruxers were given injections with BTA (control group) or saline solution (placebo group) in the masseters (60 U for each) and temporalis (40 U for each). In order to measure differences between pre-inoculation and 4–8 weeks post-inoculation, patients completed tests and questionnaires; polysomnography (PSG) and electrocardiogram data were also recorded.	BTA is a legitimate therapeutic option since, although two patients reported transient alterations in their smiles, there were no significant differences in the measures examined. Additionally, the patients reported longer sleeping duration and less bruxism episodes.
Sancak et al.(43)	Pilot study	The results of using both BTA and an occlusal splint on bruxism patients are compared in this study.	Three groups including seventy-three patients were randomly assigned. Group C received treatment with both options at the same time while Group A received treatment with an occlusal device and Group B received treatment with a BTA injection. Every person received the VAS, Jaw Function Limitation Scale, Oral Behavior Checklist (OBC) , Graded Chronic Pain Scale, and Temporomandibular Disorder Pain Screener before and six months after starting therapy.	In all three groups, the questionnaire and VAS ratings dropped. Compared to splinting treatment, patients treated with botulinum toxin (either alone or in conjunction with an occlusal splint) showed a better response. Therefore, adjuvant therapy is not necessary for patients receiving BTA.
Cruse et al. (7)	Double-blind, randomised, placebo controlled crossover study	The study's objective is to assess SB therapy in conjunction with BTA.	Group A obtained injections of BTA 60 U in bilateral masseters, group B 90 U in masseters and temporalis, and group C 1200 U in masseters, temporalis, and medial pterygoid. The trial involved 41 patients in total. After the injection, the authors measured changes in headache, bruxism, and pain one month and three months later.	BTA is a safe and efficient treatment for SB. A higher effect might be obtained by injecting BTA into more muscles, at higher doses overall, and in individuals with higher baselines.

DISCUSSION

Frequent chewing without a bolus is a characteristic of bruxism, which is caused by a muscle contraction. This might happen while they are asleep (sleep bruxism, SB) or while they are awake (awake bruxism, AB). According to recent research, bruxism may not so much be a movement condition as it is a "behavior" that predisposes people to joint, dental, and prosthetic disorders (33,44,45). Patients may exhibit the following clinical symptoms: mobility, masseter hypertrophy, wear on teeth, tongue indentations, linea alba along the genial mucosa, and vulnerability to TMD (44,46–48). Although the specific cause of bruxism is unknown, it is likely complex, neurologically linked, and highly psychosomatic (49,36,50). The first people to successfully treat bruxism in a patient who had suffered brain injury with botulinum toxin were Van Zandijcke and Marchau (51). Others then used the toxin to treat secondary bruxism linked to disorders such autism, amphetamine addiction, orofacial dystonia, and Huntington's chorea (36). For patients with bruxism, injections of toxins into the masseter, temporalis, and medial pterygoid muscles—muscles involved in raising the jaw—are a suitable alternative (52) (Table II).

Table II. *Bias characteristics of the studies.*

Authors (year)	D1	D2	D3	D4	D5	D6	D7	Overall
Shim et al. (33)	X	+	X	-	+	X	+	+
Shehri et al. (34)	X	+	X	+	+	X	+	+
Mkhitaryan et al. (35)	-	-	+	+	-	-	+	-
Asutay et al. (36)	?	-	+	!	+	+	X	!
Al-Wayli et al. (37)	-	-	-	+	-	-	+	-
Silva Ramalho et al. (38)	-	+	+	-	+	-	-	-
Shim et al. (39)	-	+	X	+	-	X	+	+
Hosgor et al. (40)	-	X	+	-	-	-	-	X
Fontenele et al. (41)	X	+	X	-	+	X	+	+
Ondo et al. (42) 28/01/2025 12:08:00	X	+	X	+	+	X	+	+
Sancak et al. (43)	-	+	X	X	+	-	+	X
Cruse et al. (7)	X	+	+	X	-	+	X	X

Domains:
D1: Bias due to confounding.
D2: Bias arising from measurement of the exposure.
D3: Bias in selection of participants into the study (or into the analysis).
D4: Bias due to post-exposure interventions.
D5: Bias due to missing data.
D6: Bias arising from measurement of the outcome.

! Very high
X High
- Some concerns
+ Low
? No information

Masseters

After a year of observation, significant and durable differences in the way Saudi female patients perceived pain were observed between those who received conventional treatment (group B) and those who had 20 U of BTA injected into three masseter sites (group A). Group A's mean pain score (MPS) was 0.2 ± 0.51 after a year, while group B's was 2.1 ± 0.74 (37). Shim's study (33), which focused on patients wearing occlusal splints, found that botulinum toxin reduces the intensity of masseter muscle contractions for at least 12 weeks without altering the frequency of repetitive motor action episodes. However, Shim contended that since RMMA is physiological, it need not be numerically diminished; instead, the objective of injection should be to reduce the muscle contraction's intensity (33). Ultrasound can be used to determine the best timing for botulinum toxin reinjection (35). Following injection at three masseter regions, 26% of female patients reported no symptoms of bruxism, and 74% reported less muscular tension or pain (35). After injection, muscle thickness must be closely monitored. If thickness returns to baseline, reinjection should occur within 4 weeks to maintain efficacy. Additionally, the face looks better with smaller muscles (35). After five months, it was discovered that the effects of injecting 20 U of BTA into four masseter regions were diminished. Nevertheless, the VAS scores of all patients exhibited improvement in their symptoms, with two exhibiting no change (34). There was no statistically significant difference in the voluntary mouth openings (36,53–55). An earlier decrease of effectiveness, about 3.51 ± 0.36 months after injection,

was observed with lower BTA dosages (10 MU each side at two masseter sites). In spite of this, VAS values consistently showed declines, peaking at two weeks and gradually returning to baseline by four months (37). Twelve weeks of lower electromyographic activity in the EMG data indicated a decrease in muscular force (34).

Temporalis and masseters

Bilateral BTA injections into the temporalis muscles are suggested when single muscle injections are the main treatment for SB (39). The study looked at a patient who had half the usual BTA dosage, which is 10 U in the temporalis and 15 U in the masseters, for a total of 50 U. Using specifically created occlusal devices equipped with FBG (fiber Bragg gratings), changes in clenching force and sleep hyperactivity were investigated. The decrease in masticatory strength peaked one month following the injection and then gradually returned to baseline after two months (56). In a second study, bilateral injections into the masseters or both the masseters and the temporalis did not alter the frequency of RMMA; however, they did alter the strength of the muscular contractions that occurred during sleep. Following treatment, patients who received combination injections exhibited less morning stiffness (39). Reduced maximal masticatory force and RMMA episode duration were found in the EMG data, which suggested a decrease in the force of muscle contraction. But there were no appreciable variations across the groups (39). BTA injections into the masseters (group A) and both the masseters and temporalis (group B) were compared in a clinical experiment. Patients in both groups reported subjective pain relief at 15 days after injection, however this improvement was not statistically significant. Bite force decrease was seen, and there was no statistically significant variation in patient satisfaction across groups (38). Patients who did not respond well to occlusal splint therapy were able to benefit from botulinum toxin (43). Patients in this trial were given occlusal splints as a conservative measure, BTA injections into the masseters and temporalis, or a combination of the two. There was no discernible difference in pain reduction between the combined and BTA-only therapies, while BTA injection was superior than occlusal splints alone (43). During follow-up visits up to six months after treatment, patients in another trial assessing BTA injection into the masseters and temporalis displayed reduced discomfort and increased range of motion. Reduced parafunction may be caused by psychological reasons (40).

Medial Pterygoids, Temporalis, and Masseters

Injections of the masseter and temporalis muscles were combined with injections into the medial pterygoid muscle. Though no significant differences were seen after 12 weeks, a larger fall in the Bruxism Index (BI) was observed after 4 weeks, probably as a result of motor function improvement (7,57).

Side Effects

All of the analyzed studies reported side effects, such as muscle weakness and discomfort at injection sites. Most of the problems resolved in a matter of weeks, and they were usually mild and transient. The off-label usage of BTA, varying dosages and injection sites, various evaluation methodologies, and heterogeneous patient samples are among the limitations (7,38,42,58).

CONCLUSIONS

For individuals who are not responding to traditional treatments, botulinum toxin injection is a feasible therapeutic option. It is crucial to standardize dosages and processes in order to maximize therapy effectiveness and reduce side effects. Addiction phenomena and the best times for reinjection should be the main topics of future study.

Author Contributions

A.D.I., A.M.I., A.L..,S.C. A.M., I.R.B. and V.C.; investigation, G.D., A.P., M.C.., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I. and G.D.; data curation, G.D., S.C.,V.C., A.P. and F.C.T.; writing—original draft preparation, A.D.I., A.M.I., G.D., S.C. and V.C.; writing—review and editing, F.I., A.P., A.L.., A.D.N. and A.L..; visualization, S.C., V.C.., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T..; project administration, M.C.., G.D., S.C, A.M.I., I.R.B. and V.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Not applicable.

Consent Statement

The patient gave written informed consent for the publication of this case study and the photos that go with it. The chief editor of this journal can evaluate a copy of the written consent.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

ANALYSIS OF THE LITERATURE ABOUT MOUTH CANCER

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ABSTRACT

Oral squamous cell carcinoma represents the sixth most common cancer causing 7000 patients die from this type of cancer each year. Incidence is higher in the male sex because men typically consume more alcohol and smoke than women do in most countries, predominant location in tongue and gingiva. This historical study explores the ways in which our knowledge of oral cancer has changed throughout time. It aims to determine if the apparent reduced frequency of oral cancer in antiquity stems from misreadings of antiquated medical literature or from the lack of contemporary environmental and lifestyle factors. In summary, the review highlights the significance of comprehending the past course of oral cancer diagnosis and treatment to improve existing procedures and direct future research endeavors.

KEYWORDS: *Oral cancer; oral surgery; oral infections; history of oral surgery; history of medicine*

INTRODUCTION

Oral squamous cell carcinoma represents the sixth most common cancer causing 7,000 patient deaths from this type of cancer each year.

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Incidence is higher in the male sex because men typically consume more alcohol and smoke than women do in most countries (1), predominant location in tongue and gingiva with subsequent bone invasion. Cancer cells often invade bone, which leads to the osteolytic destruction by proteolytic enzymes and osteoclasts that involved acid phosphatase (2,3). The cell-cell interaction, which influences carcinogenesis, progression, and therapy response, is necessary for this process.

The prelude, which gives a historical overview of oral cancer and highlights geographical differences influenced by lifestyle, access to healthcare, and environmental conditions, is also covered in the review (4). It discusses the substantial global impact of oral cancer, its incidence rates, and related risk factors such as environment, heredity, and infectious diseases like HPV. Research indicates that little progress was achieved in treating oral cancer during the Middle Ages, with the majority of ancient treatments relying on surgical techniques such tumor excision and cauterization (5). However, knowledge of the etiology, histology, and management of squamous cell carcinoma has advanced worldwide since the Renaissance (6).

MATERIAL AND METHODS

A thorough search was conducted using a variety of databases and historical documents that date back to antiquity as part of the study approach.

The paper also describes the technique, which included studying historical documents in different languages to learn more about the medical and historical backgrounds of oral cancer. There were 145 papers in all, covering diagnosis and therapy in various medical cultures, and they ranged in date from 1665 to 2024 (7).

RESULTS

The late 4th millennium BC saw the rise of ancient Egypt, which is credited with many notable medical discoveries, including advances in pharmacology and surgical methods. Egyptian knowledge of anatomy, surgery, and dentistry dates back to the third millennium BC, and medical literature such as the Ebers and Edwin Smith Papyri shed light on therapies for possibly dangerous tumors (8).

A thorough description of oral disorders, including cancer, may be found in the ancient Sanskrit medical literature Sushruta Samhita, which dates back to the middle of the first millennium BC in India (9). Surgical techniques for treating different types of tumors were described, taking into account the frequency of oral cancers and the usage of betel quid as an acknowledged risk factor at the time (10).

Considerable advancements in the knowledge and management of cancer occurred throughout the eras of ancient Greece and Rome. Prominent individuals such as Hippocrates and Galen advocated for surgical procedures including cauterization and removal of neoplastic tumors (11). Cornelius Celsius and other Roman writers classified malignant tumors and recommended surgical removal, especially for lip cancer. Galen, on the other hand, supplied precise classifications and suggested exacting surgical techniques (12,13).

Building on the groundwork set by Greek medicine, Byzantine physicians provided comprehensive descriptions of oral operations along with innovative methods of diagnosis and treatment for diseases of the mouth, such as cancers of the tongue and lips (14). Prominent scholars who addressed a variety of oral diseases and surgical methods included Oribasius of Pergamon, Aëtius of Amida, Paul of Aegina, and Alexander Trallianus. Nikolaus Mirepsus the Actuarius's pharmaceutical prescriptions, which included a variety of chemical concoctions, were also used (15).

Monastic centers functioned as the first hospitals, offering therapeutic and diagnostic services, and Byzantine physicians were specialists in a variety of medical specialties (16). Together with the Emperor, the Imperial Church strengthened public health infrastructure and supported social initiatives; notable hospitals such as the "Pantocrator Xenon" were established in Constantinople in 1136 (17).

Otolaryngology went into hibernation in Western Europe throughout the Middle Ages as a result of Catholic Church prohibitions against surgical operations and anatomical dissections (18,19). Consequently, until the Renaissance, information regarding treatments for oral cancer was limited and unclear (20,21).

Developments in science and culture during this time allowed for a better comprehension of human anatomy and more thorough observations on the surgical management of mouth cancer. Notably, the anatomy research carried out by Renaissance luminaries like Andreas Vesalius was crucial in expanding our understanding of medicine in this area (22).

Over the 19th century, knowledge about oral oncology and related treatment approaches have seen significant advancements (23,24). Originally, surgical methods were outdated and relied on direct repair of superficial injuries (25).

However, with the introduction of general anesthesia in 1846, new surgical approaches, such as lip ligation and mandibular excision, became possible. Notwithstanding the advances in the microscopic understanding of tumors, histopathological biopsies were not widely accepted (26).

Prominent figures such as Rudolph Virchow and Karl Thiersch have made significant contributions to our understanding of the origins of cancer (27).

A pivotal figure in the establishment of contemporary oncology, Simon-Emmanuel Duplay helped build the groundwork for a "Anti-Cancer League" (28,29). Due to mouth cancer, Grover Cleveland and Ulysses Grant, two US presidents, lost their lives toward the end of the century. Additionally, Sigmund Freud battled mouth cancer, which was caused by excessive smoking (30).

Henry Trentham Butlin has played a significant role in oral cancer surgery, helping to popularize novel surgical and palliative techniques. His work has been acknowledged by esteemed assignments within the medical community (31) (Table I-III).

Table I. *Overview of the main steps of the knowledge about oral cancer and its therapy.*

Historical Timeline on Oral Cancer	
Chronology	Main Events
3000–1600 BC	Edwin Smith and Ebers' Egyptian papyri descriptions of cancers
1000 BC	The encyclopedic Sanskrit medical text, Sushruta Samhita, describes different head and neck cancers.
6th century BC	Pythagorean Alcmaeon's of Croton studies on the oral sensory system in "Περι Φυσεως" (About Nature).
5th–4th century BC	Hippocrates' work "Ιπποκρατικό Σώμα" (Corpus Hippocraticum) first uses the terms cancer/carcinoma (καρκίνος/καρκίνωμα)
1st–2nd century AD	Galen's use of the term oncos (όγκος) to describe the tumor in the treatise "Παρὰ φύσιν ὄγκοι" (On Tumours against Nature), describing also pharmacological and surgical treatment. The Roman author Celsus' medical encyclopaedia "De Medicina" describes malignant growths.
5th–14th century AD	Greek Byzantine and later Arab's medical texts with detailed descriptions of head/neck and oral cancers (Byzantine diagnostic and therapeutic procedures took place in Ξενώνες (Xenones=Hostels), precursors of modern hospitals).
15th–17th century AD	Andreas Vesalius writes one of the most influential books on anatomical studies, "De humani corporis fabrica" (On the Human Body's Factory). Introduction of tobacco in the Western World The surgeon P. Marchetti performs the first glossectomy for tongue cancer.
17th–19th century	Infectious theories about origin of cancer. First hospital for cancer patients in Rheims, France
19th century	Introduction of general anaesthesia in 1846 allowed increasing cancer excisions with the development of many surgical access routes for oral cancer. Beginning of the microscopic era and of the surgical biopsies for diagnostic purposes.
1885	Henry T. Butlin, head and neck surgeon, describes in his book "Diseases of the Tongue" an even more radical dissection of the primary tumor "*en bloc*" with surroundings cervical nodes.
1905–1906	G.W. Crile (1864-1943) publishes two papers describing a systematic and radical approach to "*en bloc*" dissections.
1938–1958	Hayes Martin's team carries out 1,450 radical neck dissections on patients with oral cancers and cervical metastases.
1968	Osvaldo Suarez proposes a "functional or modified neck dissection" preserving the accessory nerves and their functions.
1990	Shah et al. demonstrate that the risk of metastasis in nodes of 1801 patients in levels IV and V was only 9% and 2%, so they concluded that their radical removal in not indispensable in N0 neck cancers.
2002	The American Head and Neck Society standardizes neck dissection terminology and techniques, dividing neck nodes in a 6-level classification system.
21th century	Even more super-selective nodes dissections in early tumours with multi-integrated pharmacological therapies and reconstructive surgery.

Table II. *Summary of established and presumed risk factors for oral cancer.*

Precursor Conditions	Environmental Factors	Genetic Factors
Infections: HPV, EBV, HIV, *Treponema pallidum* and others (chronic Candidiasis ?)	Lifestyle (e.g., alcohol abuse, distilling cider, tobacco smoking/chewing, Betel quid or guṭkha chewing, marijuana (?), poor dental and oral hygiene)	Fanconi's anemia
Chronic mouth's irritation (aggressive mouthwashes, faulty dental prostheses, periodontal disease, gastro-esophageal reflux)	Low socio-economic status (poor or no access to oral health care facilities)	Hereditary genodermatoses (dyskeratosis congenita, xeroderma pigmentosum, scleroderma)
Immune suppression and immune disorders (i.e., trans-planted patients, due to the chronic inflammatory state associated with graft-versus host disease (GVHD)	Industrial pollution or occupational exposures (sulfuric acid, asbestos, formaldehyde, pyrene, methyl pyrene, leather and textile industries workers)	Plummer-Vinson (aka Patterson-Brown-Kelly) syndrome
	Dietary factors (deficiencies of vitamins A, E, B complex, zinc, low intake of fruit and vegetables, especially carrots, fresh tomatoes, and green peppers, manipulated aliments as fried foods)	Genetic polymorphisms of genes coding for enzymes (i.e., P450 and XMEs)
	Radiation exposure (UV-A, Ionizing radiation/radiation therapy)	Diabetes

Table III. *The most important viruses associated with oral cancers and their molecular effects in the host.*

Most Important Viruses Associated to Oral Cancers	
Virus	**Host Events**
EBV (Epstein Barr Virus)	It stimulates B lymphocytes proliferation and LMP1 production → essential for lymphocytes B transformation It doesn't have a direct role in carcinogenesis, but it is associated with immunodeficiency A synergy with HPV is assumed (however it has not been demonstrated)
CMV (Cytomegalovirus)	It has been implicated with other Herpesviruses in the etiology of several human carcinomas
HPV (Human Papilloma Virus)	It is associated with various types of oral lesions: vulgar wart (HPV-4), papillomas (HPV-11), vulgar warts in HIV+ pts (HPV-7), acuminate condylomata and leukoplakia (HPV-6) and squamous cell carcinoma (HPV-16 >98% is associated and HPV-18)
HSV-1 (Herpes Simplex Virus type 1)	It causes oral carcinoma only if associated with TAR (tobacco associated residues): TAR molecules block the synthesis of DNA polymerase, thymidine kinases, γ proteins → interference with viral shedding → increase of infected cell α-proteins (ICP4 and ICP27) It can directly cause oral cancer or it can be HPV cofactor

In the 20th century, more advancements in the medical and surgical management of breast cancers were noted, including the use of laser therapy and reconstructive surgery in addition to appropriate non-surgical options for the full treatment of mouth cancer (32). Beginning in 1790, the use of lymph nodes in cancer has been used as a predictor of incurability (33). William Stuart Halsted showed at the end of the 19th century that drastic resection combined with "en bloc" dissection of lymph nodes could reduce the risk of recidivation (34,35).

George Washington Crile has detailed the procedures of over 250 surgeries and developed a systematic approach to "en bloc" dissections, paving the way for more effective surgical procedures

(36). Hayes Martin and his team performed radical neck dissections on over 1,450 patients with oral tumors, gradually improving surgical outcomes (37). Osvaldo Suarez has subsequently introduced a more conservative method, preserving the nerve accessories and their functions (38).

Radiotherapy has been used to prevent the catastrophic effects of significant surgical interventions (39,40). But the survival rate would remain low; nowadays surgery remains the primary treatment for oral cancer, with the use of radiation

and/or chemotherapy as adjuvant or palliative measures (41). The prognosis for squamous cell carcinoma is still uncertain due to often delayed diagnosis (42).

Further advancements are being made in patient genetic profiling and stem cell technologies to enable more individualized and targeted management of oral cancer. Furthermore, prevention is essential, with a greater focus on environmental and physical risk factors (43) (Fig.1,2).

Fig. 1. *Squamous cell carcinoma of the lip.*

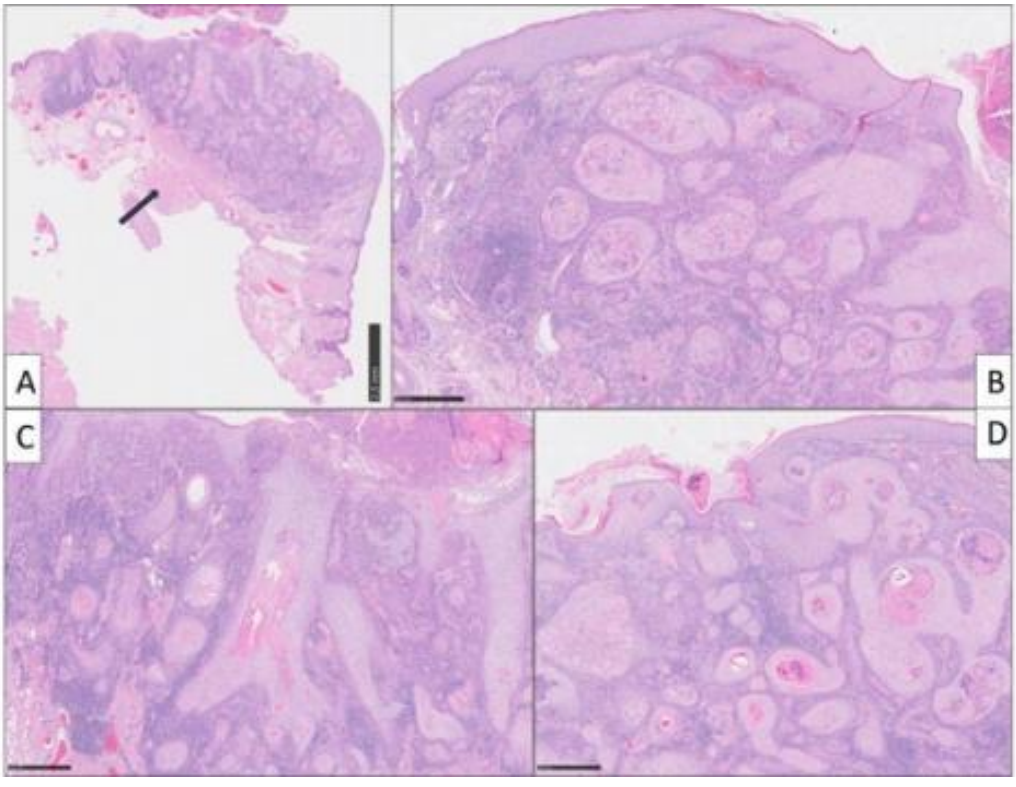

Fig. 2. *Squamous cell carcinoma of the lip infiltrating the striated muscle, indicated by the arrow (**figure A** - hematoxylin and eosin; very low magnification). Note the well-differentiated grade of the tumor including large nests, cords and islands of cells with pink cytoplasm and prominent squamous pearls (**figures B, C and D** - hematoxylin and eosin; medium and high magnification).*

DISCUSSION

Studies on oral cancer have demonstrated important considerations for both identification and prevalence over the years. Early medical books from Greece, India, Egypt, and Rome provide a general overview of a variety of tumor kinds

without going into detail about the traits and behaviors particular to each subtype of neoplasia. The initial outcomes of oral reimplantation are attempts to restore lost oral tissue, carried out using non-selective surgical procedures (44–46).

The rise in oral cancer cases worldwide has primarily been linked to modern lifestyle choices and environmental factors that raise cancer risk, such as smoking, eating, and living in close quarters. However, we have not investigated whether the prevalence of the disease was lower in earlier human societies compared to modern societies, or whether the relatively low incidence and prevalence of the disease in earlier human populations may have been caused by inaccurate identification and translation of those documents (47).

In fact, there is another theory that could explain the lack of literature on this issue: the older texts are clearly written in an archaic language that is frequently very different from modern language, and this leads to subjective interpretations and inaccurate translations by individual translators, particularly in light of the medical language's specificity (48).

Furthermore, it is extremely difficult to determine whether a term, which is frequently ambiguous, is related to a particular illness that is accurately described by a precise modern scientific nomenclature, distinguishing between etiologies that are not carcinogenic and those that are in relation to such conditions in ancient literature.

For example, it is challenging to determine whether a genetically modified organism that mimics a cystic tumor inside the oral cavity is an indication of a neoplastic or inflammatory mass. In this sense, we should always remember that historical cancer diagnoses should always be based on anatomical, medical, and scientific understanding of the relevant historical culture (49,50).

However, the possibility that that the lack of specific references to oral cancer in medical literature prior to the 19th century was caused by a number of zoological factors cannot be highlighted, such as the use of alcohol and tobacco as well as syphilis, which did not become widespread in Europe until the late 19th and early 20th centuries (51).

Actually, the clinical aspect of oral tumors is so obvious and disruptive, especially in advanced stages, that it is impossible for doctors to ignore them; it is believed that if they occur today, they would occur with the same frequency (52,53).

Despite this, it has been believed for centuries that genetic predisposition was a significant risk factor (54). More accurately, however, the slight incidence of mouth cancer may be associated with a lower life expectancy in the past, when it was around 30 years old (55). Furthermore, cancer was seen as a less serious illness than incurable diseases, particularly tuberculosis and syphilis. As a result, many cases of mouth cancer were not reported to current researchers (56–58).

CONCLUSIONS

The difficulty in solving these issues should act as a warning to always evaluate story conclusions cautiously and critically. Several correlations between oral cancer and antiquity lead one to believe that the illness may be linked to mechanisms other than those resulting from environmental risk factors. This could potentially direct future research on oral cavity treatments toward cellular and molecular approaches.

Author Contributions

Conceptualization, A.D.I., F.I., L.M., F.B., A.M.I., G.P. and A.P. ; methodology, A.D.N., D.C., P.M., F.C.T., G.I. and A.P. software, F.I., G.D., A.D.I., D.C. and L.M.; validation, F.I., A.M.I., G.D.,M.C., F.S. and P.M. formal analysis, A.D.I., E.X., A.M.I., F.B., G.D., ,D.C. and A.R.; investigation, F.S., G.D., A.P., M.C., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I. and G.D.; data curation, G.D., D.C.,P.M., A.P. and F.C.T.; writing—original draft preparation, A.D.I., A.M.I., G.D., D.C. and A.R.; writing—review and editing, F.I., E.X., A.P., A.L.., A.D.N. and A.L.; visualization, D.C., A.R., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T.; project administration, M.C., G.D., L.B, A.M.I. and A.R. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Article

SEVEN-YEAR FOLLOW-UP OF CLINICAL OSTEONECROSIS OF THE JAW CASES MANAGED WITH CGF AND PIEZOSURGERY

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ABSTRACT

The disorder known as medication-related osteonecrosis of the jaw (MRONJ) is characterized by bone loss and necrosis in the jaw as a result of unfavourable drug interactions. The treatment strategies and results for MRONJ patients are assessed in this case series. Over a 60-month period, MRONJ patients were treated and observed as part of the retrospective study. Concentrated growth factor (CGF) and piezosurgery were used in the treatment. There are six clinical case reports in detail. According to the study, during the follow-up period, there was no recurrence of necrotic MRONJ lesions in any of the patients. Bone resections and the application of CGF were two surgical procedures that effectively promoted mucosal healing and stopped the disease's progression. The results highlight how difficult it is to manage MRONJ and how interdisciplinary thinking is essential. Patients' quality of life was enhanced and symptoms were effectively controlled with conservative measures and minimally invasive operations. Finding the best course of action is still difficult, which highlights the need for more study into complementary therapies and reconstructive surgery. For individualized and interdisciplinary care, a thorough preoperative evaluation and cooperation between dental, endocrinology, and cancer professionals are essential. In order to better understand MRONJ management and investigate novel therapeutic approaches, ongoing research is crucial. This will ultimately help patients who are coping with this challenging illness.

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KEYWORDS: *Medication-Related Osteonecrosis of the Jaw (MRONJ), Piezosurgery, concentrated Growth Factor (CGF), Bisphosphonates (BPs), multidisciplinary Approach*

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a drug-related adverse reaction causing jawbone destruction without radiation treatment (1,2). Osteoblasts, vital for bone remodeling, produce osteoprotegerin, halting osteoporosis growth and preserving bone homeostasis (3,4).

The jaw is mainly affected by MRONJ (5–7) due to: Quicker bone turnover in the maxilla, particularly in the maxillary sinus and post-extraction alveoli; Mandibular terminal vascularization; Exposure to trauma while chewing; Elevated concentration of bacteria within the salivary biofilm; and the periodontal ligament is present.

The kind, dosage, frequency, length, and timing of medicine administration are risk factors (8–10). MRONJ-related drugs include:

- Long-term usage of bisphosphonates (BPs), which are used to treat osteoporosis and bone metastases, raises the risk of MRONJ (11–13);
- Tyrosine kinase inhibitors: Associated with MRONJ; used in the therapy of cancer, such as sunitinib (14–16);
- Monoclonal antibodies: Associated with MRONJ, used to treat osteoporosis and bone metastases (e.g., denosumab) (17);
- Angiogenesis inhibitors (bevacizumab, for example): Prevent blood vessel creation and impede the repair of the jawbone (18–20);
- Fusion proteins, such as aflibercept, are linked to MRONJ and are used in the therapy of cancer (21–23);
- mTOR inhibitors: These medications, which cure cancer, include Everolimus (24,25);
- Radiopharmaceuticals (such as radium-223): Associated with MRONJ; used in the treatment of prostate cancer (26–28);
- Estrogen inhibitors: Associated with MRONJ, used in osteoporosis and breast cancer (e.g., raloxifene) (29–31);
- Immunomodulators: affect the immunological response and are associated with MRONJ (e.g., methotrexate, corticosteroids) (32–34).

Local triggers such as tooth extraction (61%), chronic inflammation from periodontitis, bone biopsies, crown elongation, bone surgery, or dental implants are frequently the cause of MRONJ (35–38).

The 2014 introduction of MRONJ staging by Favia et al. directs treatment (39,40):

- Stage 0: Nonspecific radiological findings and symptoms without exposure of the bone;
- Stage 1: Bone exposed less than 2 cm, either painfully or not;
- Stage 2: 2–4 cm of exposed bone; NSAIDs are useful for managing pain;
- Stage 3: >4 cm of exposed bone, excruciating agony, and potential consequences such as fistulae.

A multidisciplinary approach, symptom monitoring, and individualized treatment plans are necessary for the effective therapy of MRONJ (41–44) Surgical therapy was given priority at first, but according to AAOMS guidelines, non-surgical treatments are now promoted early on, and surgery is advised for severe stages (45–47).

MATERIALS AND METHODS

Protocol for choosing patients and treatments

The University of Bari Dental Unit treated patients with MRONJ using a multidisciplinary approach, including conservative and surgical treatments. Patients were prescribed NSAIDs, antibiotics, and mouth rinses, with surgical procedures like piezosurgery for late stages or those not responding. Autologous preparations like concentrated growth factor (CGF) were applied to promote bone regeneration and repair, ensuring long-term, stable healing.

Follow-up and Clinical Evaluation

The study utilized CBCT, OPT, and radiographic examinations to assess MRONJ lesions, using Favia's staging technique. Patients were monitored for six months to track healing and detect recurrence, including clinical tests and pain symptoms assessments.

Results

A study involving six individuals with MRONJ at the University of Bari Dental Unit in Italy outlines their treatment strategies, including CGF use, surgical intervention, and medication therapy. The investigation was carried out in compliance with ethical norms and was declared exempt from ethical review by the University of Bari due to small risks and non-identifiable human information

DESCRIPTIONS OF CASES

Our study group evaluated the patients' 60-month follow-up. who underwent CGF and piezosurgery for MRONJ lesions. Necrotic MRONJ lesions did not return in any of the individuals. The following uses six of this group's clinical cases as examples.

Clinical Case 1

A female patient, age 78 with MRONJ fractured her mandibular corpus. After receiving intravenous BPs, she underwent surgery to remove a significant section of the jaw and rebuild it. Within 21 days, she experienced good mucosal healing, and six months later, no recurrence was found (Fig.1-4).

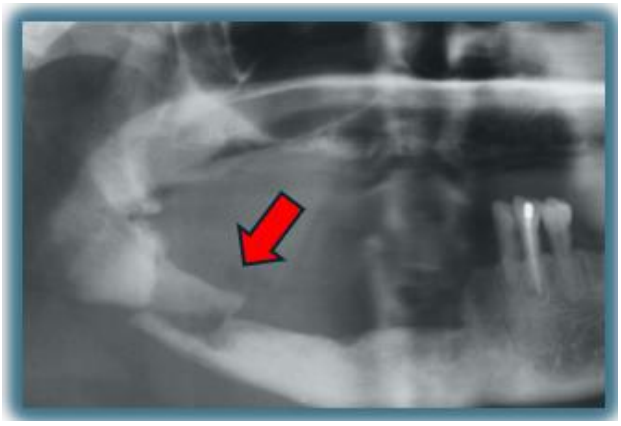

Fig. 1. *Pre-operative radiograph of the lesion.*

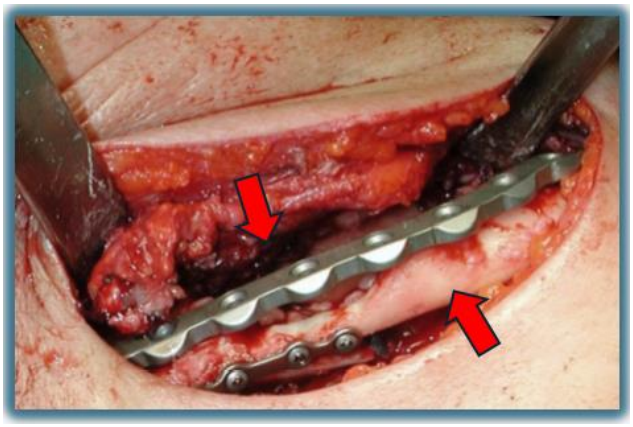

Fig. 2. *Application of mandibular plate.*

Fig. 3. *Follow up at 3rd week.*

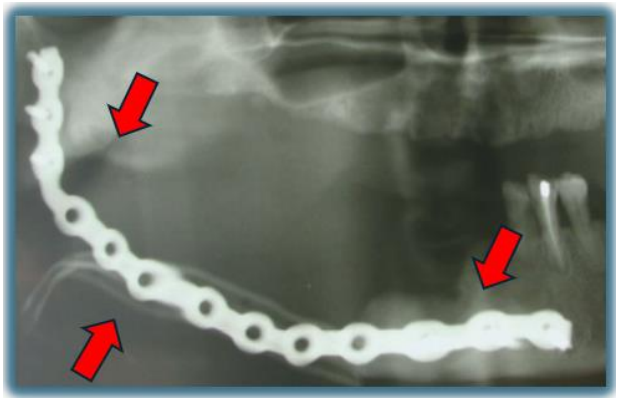

Fig. 4. *Post-operative radiographic checkup.*

Clinical Case 2

An osteoporosis-affected female patient, age 74, was administered intravenous BPs that resulted in MRONJ in regions 33–35. Clinically, the lesion, which was classified as stage II by Favia, was characterized by a substantial region of intraoral bone exposure. The lesion's boundaries and size were evaluated by radiographic examination and CBCT. Piezosurgery was used to remove necrotic bone tissue as part of the treatment, and full-thickness flap surgical access was used. After seven days, the mucosa healed and the sutures were taken out. CBCT was used for the six-month radiographic follow-up (Fig.5-8).

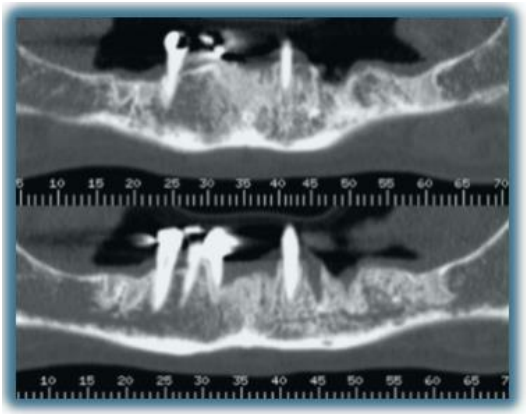

Fig. 5. *Pre-operative radiographic examination.*

Fig. 6. *Intra-oral clinical evaluation of the lesion.*

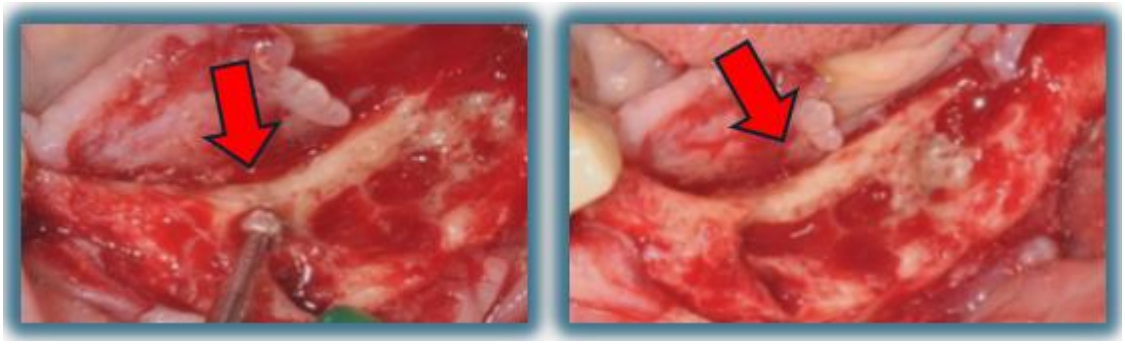

Fig. 7. *Removal of necrotic tissue with piezosurgery.*

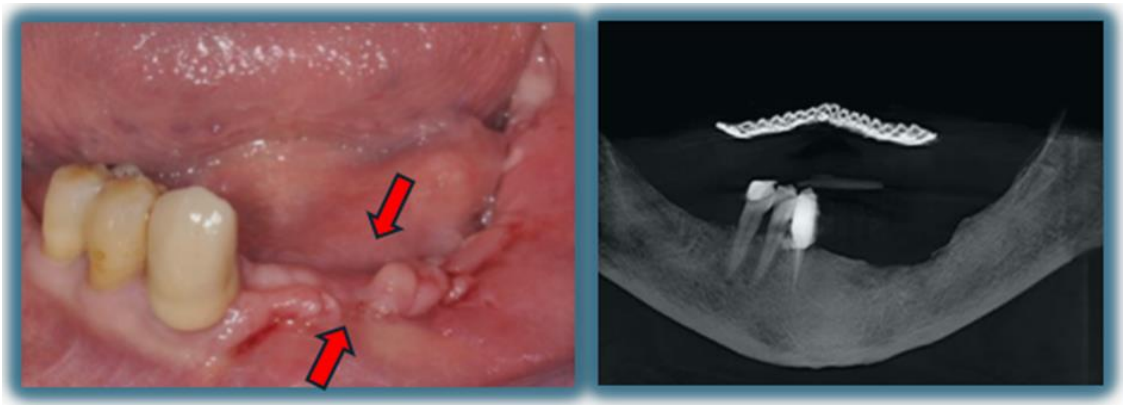

Fig. 8. *Follow up at 1 week and post-surgical radiographic evaluation.*

Clinical Case 3

Using Favia's classification, a degree I lesion appeared in the second quadrant in a 77-year-old male patient undergoing BPs treatment. The three rounds of medication—metronidazole, ceftriaxone, and antinflammatory medications—produced a cessation of the discomfort but had little effect on the lesion's size. The bone tissue in necrosis was subsequently intended to be exposed and removed by piezosurgery using a full-thickness flap. After 21 days, full mucosal healing was facilitated by curettage and appropriate flap suturing (Fig.9-13).

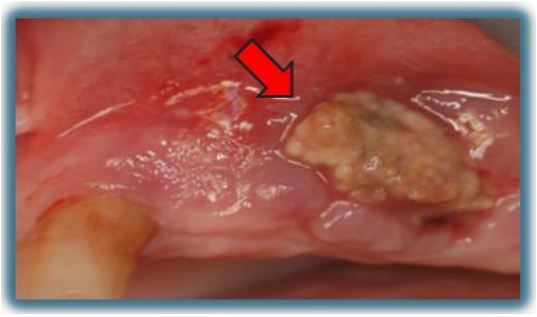

Fig. 9. *Intra-oral clinical evaluation of the lesion.*

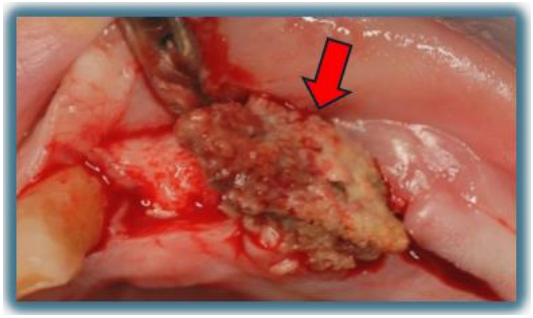

Fig. 10. *Surgical access and exposure of necrotic tissue.*

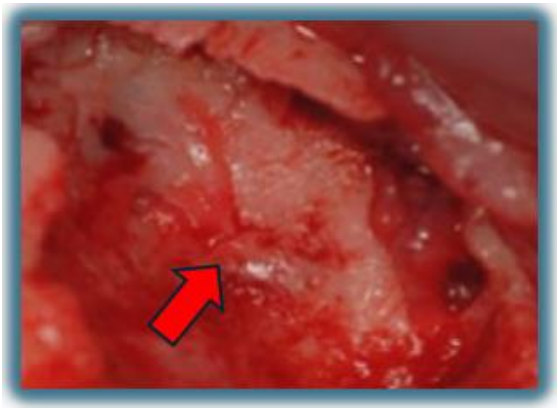

Fig. 11. *Post curettage with piezosurgery of bone tissue.*

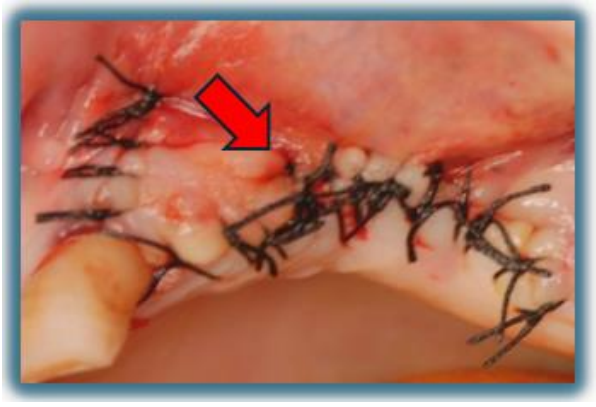

Fig. 12. *Suture of surgical access flap.*

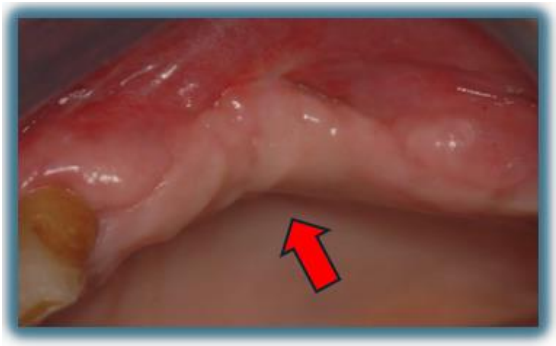

Fig. 13. *Follow up at 3 weeks.*

Clinical Case 4

A female patient aged 75 experienced MRONJ in the vicinity of teeth 35–36 after using oral BPs. Orthopantomography was used radiologically to find the lesion (OPT).

The surgical technique was piezosurgery. To improve intraoperative visibility and reveal the lesion, the creation of a full-thickness flap was realized. The bone plug was taken out again after the lesion was marked out with the PL3 Mectron® tip (Fig.14-17).

Fig. 14. *Pre-operative OPT.*

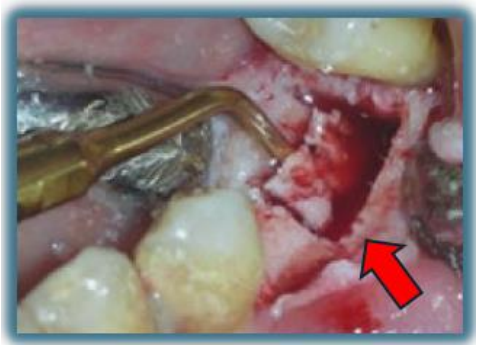

Fig. 15. *Removal of bone plug.*

Fig. 16. *Closure of cavity with concentrated growth factor membrane.*

Fig. 17. *Follow up at 3 weeks.*

Clinical Case 5

A 72-year-old female patient with breast cancer was treated with BPs. According to CBCT, she had a large grade III lesion in the first quadrant that also affected the maxillary sinus. In order to facilitate appropriate mucosal healing, a membrane and suture were applied after the necrotic bone fragment was debrided using piezosurgery (Fig.18-21).

Fig. 18. *Pre-operative CT scan.*

Fig. 19. *Initial lesion.*

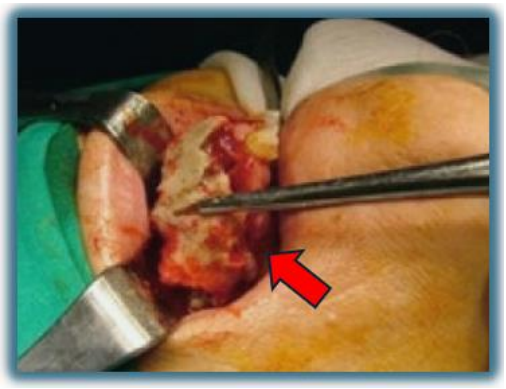

Fig. 20. *Intra-operative stage.*

Fig. 21. *Suture post remotion.*

Clinical Case 6

A 74-year-old male patient who had been receiving intravenous therapy with BPs for six years was observed to have MRONJ in area 3.7. This patient's condition was identified by both clinical and radiographic tests using orthopantomography. He reported a grade I lesion that underwent three rounds of medicinal therapy (metronidazole, ceftriaxone, and anti-inflammatory medications), followed by piezosurgery-assisted excision (Fig.22-25).

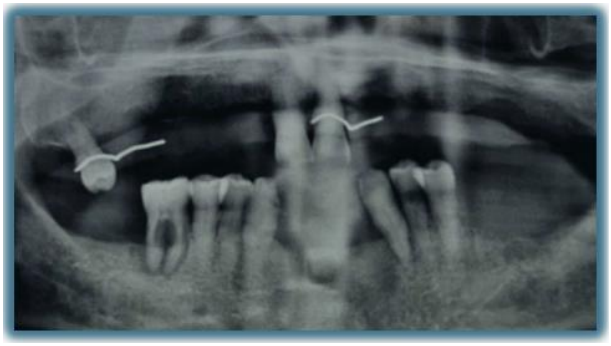

Fig. 22. *Pre-operative OPT evaluation.*

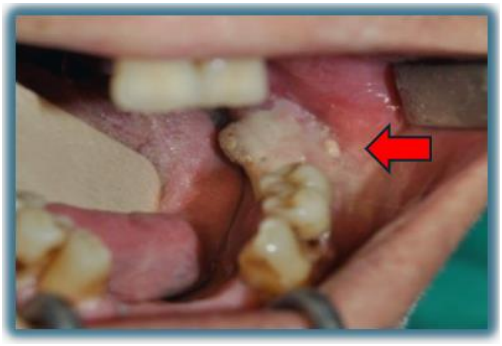

Fig. 23. *Pre-operative clinical evaluation.*

Fig. 24. *Exposure of necrotic bone tissue.*

Fig. 25. *Resected fragment of necrotic tissue.*

DISCUSSION

MRONJ can be treated with either non-surgical (conservative) or surgical methods. First, a conservative strategy is advised, utilizing medicine to stabilize the situation by reducing discomfort and controlling infection. Antibiotics like penicillin with metronidazole and antibacterial mouth rinses such as 0.2% chlorhexidine are examples of non-surgical treatment. For penicillin allergy, substitutes such as clindamycin or erythromycin are utilized (48).

When conservative therapy is ineffective or MRONJ is advanced, surgery is the next step. Minimally invasive methods such as sequestrectomy and debridement are used in the early stages. More intricate procedures, such as marginal or segmental reconstructive surgery, which includes mandibulectomy and maxillectomy, are necessary for advanced phases. Reconstruction is accomplished using either vascularized bone flaps or titanium reconstruction plates (49).

Autologous platelet concentrates (APCs) such as PRF, CGF, and PRP, along with intraoperative imaging, can improve bone healing. APCs are made from the patient's blood and release growth factors that promote the regeneration of soft tissues and bones. Studies reveal that PRP, despite its risk of infection, aids in a quicker recovery and better results for MRONJ patients. Immunological biocompatibility is provided by PRF and CGF, which are also useful in treating MRONJ (50).

Problems and treatment modalities

The administration of MRONJ includes conservative measures, such as mouthwashes with antibacterial agents, antibiotics, and NSAIDs to manage discomfort and infections; in cases where the condition has progressed, surgery may be necessary. The degree of illness severity and the specific demands of each patient determine the course of treatment.

Success and Efficacy Rates

Clinical cases have shown that non-surgical and surgical interventions for MRONJ are equally successful. It has been demonstrated that autologous preparations like CGF encourage bone regeneration and repair.

Adverse Events and Side Effects

MRONJ treatment risks recurrence, postoperative infections, and subsequent operations. Careful evaluation of resection margins is crucial for removing bone tissue that is diseased while leaving healthy tissue intact.

Effect on Life Quality

MRONJ has a substantial negative influence on patients' quality of life, requiring interdisciplinary care, careful symptom monitoring, and individualized treatment plans.

LIMITS

There are many restrictions on the investigation of medication-related osteonecrosis of the jaw (MRONJ). Because it is a case series from a single dental facility, its representativeness and generalizability are constrained. Due to the retrospective design's potential for bias introduction and the lack of a control group, evaluating the efficacy of various treatments is challenging. The 60-month follow-up period might not be long enough to assess recurrence rates and long-term results. Additionally, confounding variables that may influence treatment outcomes, such as concurrent drugs or comorbidities, are not taken into account in this study. To provide solid data and recommendations for the care of MRONJ, more study is required, particularly randomized controlled studies with longer follow-up times and larger sample numbers (17,36,46).

CONCLUSIONS

The intricacy of treating MRONJ is highlighted by this set of clinical cases including bisphosphonates and monoclonal medications. Conservative measures that reduce symptoms and enhance patients' quality of life include topical medications, antibiotics, and surgery with less intrusive methods. Still, selecting the optimal course of action is difficult and necessitates more research on options such as resective surgery or teriparatide therapy. Thorough preoperative assessments are essential for long-term recovery. To develop individualized treatment programs, clinicians from different specialties, such as oncology, endocrinology, and dentistry, must work together. To improve MRONJ management and investigate novel medicines, ongoing research is necessary.

Author contributions

Conceptualization, A.D.I., F.I., L.M., F.B., F.S., G.D., E.X., A.M.I., G.P. and A.P.; methodology, A.D.N., C.C., P.L., F.C.T.. and A.P. software, F.I., G.D., A.D.I., P.L. and L.M.; validation, F.I., A.M.I., G.D., M.C. and P.L., formal analysis, A.D.I., A.M.I., L.M., C.C.. and A.R.; investigation G.D., A.P., M.C., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I., E.X., F.B. and G.D.; data curation, G.P., P.L., F.S., C.C, A.P. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., C.C. and A.R.; writing-review and editing, F.I., A.P., L.M., A.D.N.; visualization, C.C. A.R., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T..; project administration, M.C., G.P., C.C, A.M.I. and A.R. All authors have read and agreed to the published version of the manuscript.

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Informed consent statement

Not applicable.

Data Availability Statement

Data are contained within the article.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

ORTHODONTIC BRACKET PLACEMENT: DIRECT AND INDIRECT BONDING TECHNIQUES. A SYSTEMATIC REVIEW.

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ABSTRACT

Since the introduction of the straight wire technique in orthodontics, precise bracket (BRK) placement has become essential to avoid unwanted tooth movements. Two main techniques are used: direct bracket bonding (DBB) and indirect bracket bonding (IBB). DBB involves placing braces individually on teeth, while IBB uses a plaster cast to position braces in removable trays for single-session application. IBB improves accuracy, reduces chairside time, and addresses issues like poor hygiene and high bond failure rates. Advances in adhesion technology have significantly changed orthodontic practices since the 1960s. Early adhesives had limitations, but innovations in the 1970s and 1980s, including chemically cured composites and heat-cured resins, improved bonding efficiency. Digital technologies like CAD/CAM and 3D scanners further refined BRK placement, enabling virtual bracket positioning and custom transfer trays. Studies show that DBB and IBB achieve similar results in terms of bond strength and effectiveness. Recent research highlights that while IBB offers advantages such as reduced clinical time and lower enamel demineralization, it requires more total time due to laboratory phases. Both techniques demonstrate comparable bond failure rates and placement accuracy, though digital advancements promise to enhance these methods, improving orthodontic treatment precision and efficiency.

KEYWORDS: *Orthodontics, Bonding technique, brackets, Direct technique, Indirect technique, Tooth bonding*

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INTRODUCTION

Since the introduction of the straight wire technique in orthodontics, there has been an increased need for precise bracket (BRK) placement on the buccal surface of teeth following the facial axis of the clinical crown (FACC). Accurate placement is crucial to avoid unwanted movements such as rotation, tipping, in/out movements, extrusion/intrusion, and torque (1) (Fig.1,2).

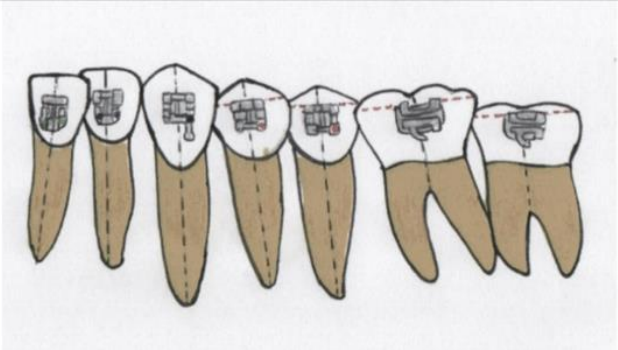

Fig. 1. *Upper arch; direct bracket bonding (DBB); facial axis of the clinical crown (FACC).*

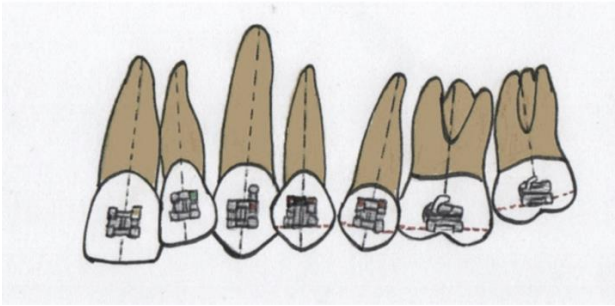

Fig. 2. *Lower arch; facial axis of the clinical crown (FACC), direct bracket bonding (DBB).*

Currently, there are two main techniques for BRK placement: direct bracket bonding (DBB) and indirect bracket bonding (IBB). DBB, the traditional method, involves placing braces individually on the tooth surface (2). IBB, a more developed technique, involves creating a plaster cast of the patient's dental arch, identifying the ideal position of the braces on this model, placing them in removable trays, and then positioning them in the oral cavity in a single session (3). The development of IBB was driven by advancements in adhesive systems and a need to improve the accuracy of orthodontic BRK positioning, reduce chairside time, and counteract issues such as poor oral hygiene and high bond failure rates (4).

Adhesion in dentistry has enabled significant changes, including the transition from using bands on teeth for fixed therapy to braces bonded directly to tooth enamel (5). Adhesion was first introduced in orthodontics in the 1960s, but early adhesives, like epoxy-based ones pioneered by George Newman, had limitations such as prolonged curing times. Innovations in the 1970s, such as Silverman et al.'s method of positioning brackets with cement on a cast model, facilitated transferring brackets to the mouth using a concave tray (3). Subsequent developments by Thomas in 1979 and improvements in chemically cured composite techniques aimed to enhance bonding efficiency, though issues with shear bond strength persisted (6).

Throughout the 1980s, heat-cured resins (HCR) were tested, but they were not ideal for BRK bonding (3,7). However, by the late 1980s, studies reported that IBB could achieve similar bond strength to DBB and easier debonding with less residual resin on teeth. By the 1990s, advancements in bonding systems and the introduction of Adhesive Precoated Brackets (APC) aimed to reduce chairside time. Despite new protocols, such as the addition of silica filler in the late 1990s, traditional DBB remained widely used (8–10) (Fig.3).

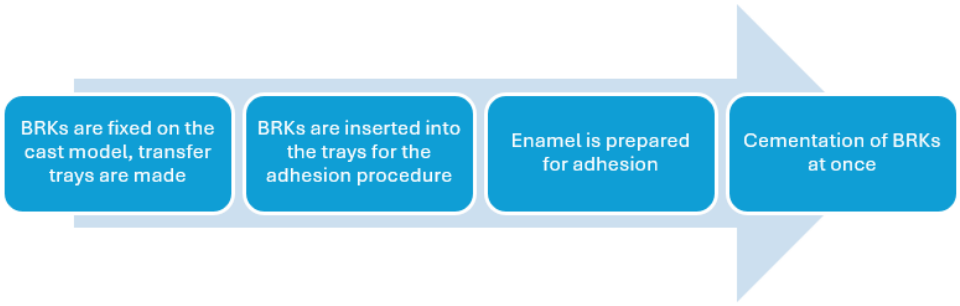

Fig. 3. *IBB phases.*

The integration of digital technologies, like Computer-Aided Design (CAD) and Computer-Aided Manufacturing (CAM), into orthodontics has further refined BRK placement (11–13). Digital workflows involve using 3D scanners to digitize dental impressions, allowing for virtual BRK placement with high accuracy and the creation of 3D-printed transfer trays (14–16). In 2010, stereolithography techniques producing transfer trays called "jigs" were introduced, demonstrating effectiveness in cases of mild crowding (17–19).

Despite the advancements, early virtual BRK placement (VBP) systems faced challenges in accurately mapping dental cusps, a critical reference point for orthodontists (20,21). However, software improvements and techniques like the one introduced by El-Timamy et al., which consider root axes for BRK positioning using 3D images and CBCT scanning, have shown promise in improving accuracy (12,22,23) (Fig.4).

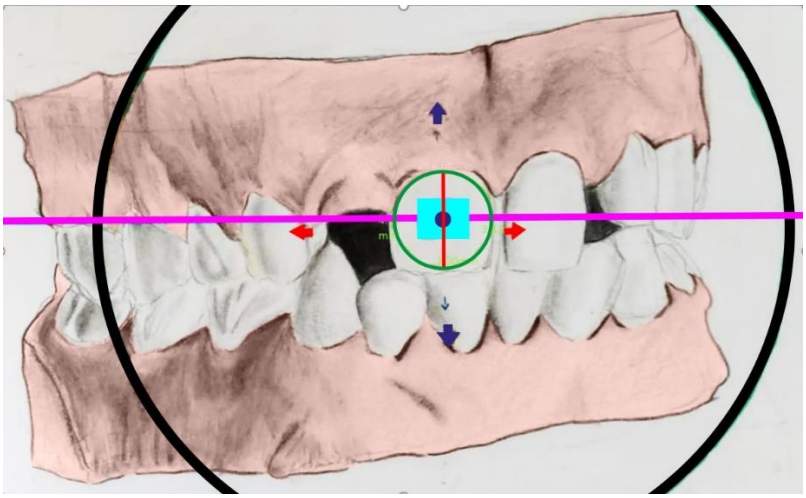

Fig. 4. *Virtual bracket placement (VBP).*

Recent studies indicate that DBB and IBB techniques achieve similar results in terms of effectiveness (24–26). For example, a 2006 comparative study by Linn et al. found no significant difference in mean bond strength between DBB and IBB using different adhesive protocols (27). A 2004 study by Polat et al. also found no significant differences in shear bond strengths and bond survival between indirect and direct bond procedures, both *in vitro* and *in vivo* (28). However, a 2022 systematic review by Dos Santos et al. noted that while initial bonding failures were similar, DBB had a lower failure rate over 12-15 months compared to IBB (29).

In summary, while both DBB and IBB techniques are effective for BRK placement, continuous advancements in digital technologies and adhesive systems are refining these methods, making orthodontic treatments more precise and efficient.

MATERIALS AND METHODS

Protocol of Review

The review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and is registered at PROSPERO with the code 555829.

Search Processing

A comprehensive literature search was conducted on PubMed, Scopus, and Web of Science databases, covering publications from May 1st, 2024, to June 1st, 2024. The search was restricted to English language articles and used the Boolean keywords: "orthodontic bracket* AND (bonding OR placement)".

Inclusion Criteria

The selected articles had to meet the following criteria:

(1) *In vivo* studies;

(2) *In vitro* studies;

(3) Studies comparing direct and indirect orthodontic bracket bonding;

(4) Clinical trials, including prospective, retrospective, and observational studies;

(5) Full text available.

Exclusion Criteria

Studies were excluded if they:

(1) Were not written in English;

(2) Did not compare direct and indirect orthodontic bonding;

(3) Were reviews, comments, book chapters, letters, or case reports;

(4) Lacked an abstract;

(5) Did not have the full text available.

Review Criteria (PICOS)

- Participants: Adults and children requiring multi-brackets.
- Interventions: Indirect bonding.
- Comparisons: Direct bonding.
- Outcomes: Accuracy of bracket positioning, chairside time, and bonding failure.
- Study Types: Randomized clinical trials, retrospective, and observational studies.

Data Processing

Two reviewers (L.C. and P.N.) independently searched the databases and evaluated the quality of the studies according to the selection criteria. Selected articles were downloaded into Zotero. Any disagreements were resolved by a senior reviewer (F.I.).

RESULTS

The database search identified 3,820 studies (PubMed: 1,332; Scopus: 1,267; Web of Science: 1,221). After removing duplicates, 1,976 studies remained for the title and abstract screening. Out of these, 1,960 were excluded (1,949 were off-topic and 11 were reviews), resulting in 16 records selected for full-text evaluation. Five papers were excluded after full-text evaluation for not meeting the inclusion criteria, leaving 11 studies selected for qualitative analysis (Fig. 5). The selection process and the characteristics of the studies are detailed in Table I.

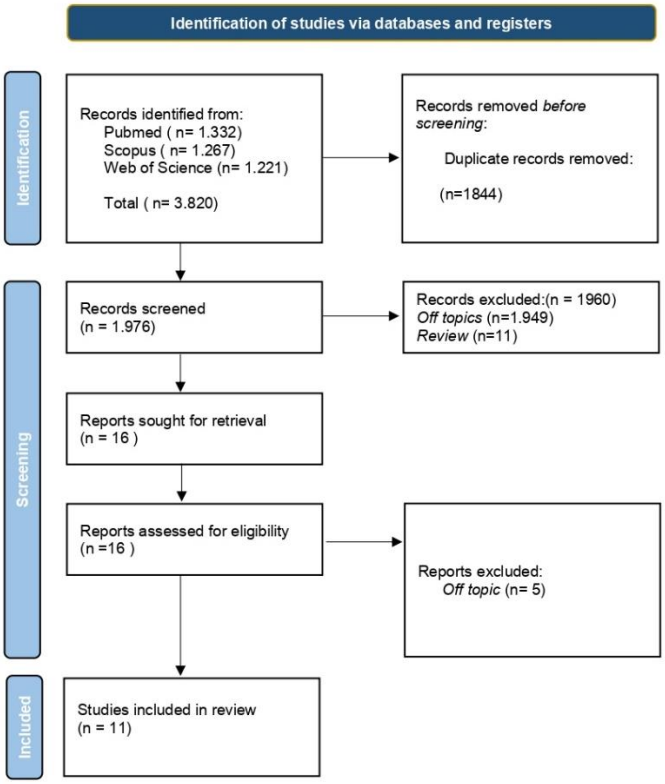

Fig. 5. *PRISMA diagram of the inclusion process.*

Table I. *Descriptive summary of item selection.*

Authors (Year)	Type of study	Aim of study	Materials and Methods	Results
Menini et al. (2014) (30)	Clinical longitudinal study	Efficacy of IBB technique considering BRK detachment during treatment	1,248 BRKs: 792 with DBB and 456 with IBB.	No significant difference in bond failure rate between IBB and DBB.
Atila et al. (2020) (31)	Two- arm parallel trial	Enamel demineralization and WSLs in IBB vs. DBB technique	Photos, dental models, radiographs pre- and post-treatment.	Group 1 (IBB) had reduced WSL formation.
Murakami et al.(2016) (2)	Prospective randomized	Total treatment time, occlusal index, oral hygiene, chair time, BRK detachment in IBB vs. DBB	BRKs directly on enamel (DBB), on plaster model then transferred (IBB).	Prospective evaluation of IBB vs. DBB.
Bozelli et al.(2013) (32)	Prospective study	Evaluate time of DBB and IBB techniques	17 patients, 304 BRKs: 151 DBB, 153 IBB.	IBB technique required more time than DBB.
Aboujaoude et al.(2022) (33)	Clinical trial	Differences between digital indirect and direct placement techniques of BRKs	Differences between digital indirect and direct placement techniques of BRKs.	Negligible height differences between direct and indirect approaches, self-ligating BRKs significantly differed from ordinary BRKs.
Flores et al. (2015) (34)	*In Vitro* study	Using the IBB and DBB techniques, compare the shear strength (SBS) and adhesive remanence index (ARI) of Transbond (XT) with Beauty Ortho Bond (BO).	Groups I-IV received different bonding treatments. Groups V-VIII were the same but also underwent thermal cycling. Group I and II teeth were etched with phosphoric acid, while Group III and IV used self-etching primer. All groups were light-cured for 30 seconds. Shear Bond Strength (SBS) and Adhesive Remnant Index (ARI) were tested and examined.	SBS values were substantially lower in IBB groups than in DBB groups. All groups' SBS values dropped with thermal cycling.
De Oliveira et al. (2019)(35)	Vitro study	Examine the accuracy of DBB and virtual orthodontic procedures.	Ten orthodontists treat 280 teeth in each group. Ten sets of solid and digital models were produced after a dental mannequin was digitalized. Orthodontists used	Accurate BRK placement was made possible by virtual bonding, with notable variations in both

			software to achieve virtual bonding and DBB on solid models. Models were compared to optimal bonding sites after being scanned.	horizontal and vertical dimensions.
Panayi et al. (2020) (36)	Prospective cross-sectional comparative study	Using loupes or eye vision, compare the precision of virtual indirect bonding with the three-dimensional world of direct bonding on orthodontic patients.	Direct bracket application was done by one dentist on 18 patients (298 teeth). Loupes were employed to improve the localization of BRK. Dental arches were scanned, overlaid, and measured in three dimensions.	In BRK location, virtual indirect bonding was more accurate for all teeth and most tested tooth groups.
Czolgolsz et al. (2021) (37)	Randomized controlled trial	Using direct or computer-aided indirect bonding, assess the cost, bonding time, and BRK debonding.	Split-mouth design; two groups: indirect and direct bonding methods.	Indirect bonding took longer (28 min 14 sec) and was more expensive but had fewer bracket losses.
Yildirim et al. (2018) (1)	Randomized clinical trial	Compare the orthodontic treatment methods of DBB and IBB.	Each group had 420 bonded BRKs, and each one's clinical time, plaque accumulation, WSLs, and bond failure were assessed.	Group A's clinical and lab sessions lasted longer. There were no variations in the length of treatment, plaque, WSLs, or bond failure across groups.
Demirovic et al. (2018) (38)	*In Vitro* and *in vivo* study	In terms of IBB and DBB approaches, compare SBS and ARI.	Teeth prepped, bonded with Transbond XT, and evaluated SBS and ARI.	Similar SBS and ARI results for both techniques.

Quality Assessment and Risk of Bias Measurement

The risk of bias assessment was conducted for a total of eleven studies (Table II).

Table II. *The risk of bias for a total of eleven studies.*

Authors (year)	D1	D2	D3	D4	D5	D6	Overall
Menini et al. (2014) (30)	X	+	-	+	-	+	+
Atilla et al. (2020) (31)	-	+	X	-	X	+	-
Murakami et al. 2016 (2)	-	+	+	-	?	-	-
Bozzelli et al. 2013 (32)	X	+	-	?	+	-	+
Aboujaoude et al. (2022) (33)	-	+	-	?	+	-	+
Flores et al. (2015) (34)	+	X	+	+	+	-	+
De Oliveira et al. (2019) (35)	-	+	+	?	+	-	+
Panayi et al. (2020) (36)	-	+	+	?	+	-	+
Czolgosz et al. (2021) (37)	+	+	-	?	+	+	+
Yildirim et al (2018) (1)	-	-	+	+	+	+	+
Demirovic et al. (2018) (38)	X	-	X	+	?	-	X

Domains:
D1: Bias due to confounding.
D2: Bias arising from measurement of the exposure.
D3: Bias in selection of participants into the study (or into the analysis).
D4: Bias due to post-exposure interventions.
D5: Bias due to missing data.
D6: Bias arising from measurement of the outcome.

! Very High
X High
\- Some Concerns
\+ Low
? No information

Confounding bias is a major source of bias in most studies. One parameter that has a low chance of bias is measurement bias. Due to participant selection bias, many studies have a low risk of bias. The significant heterogeneity makes it impossible to calculate bias resulting from post-exposure. In most studies, there is a significant bias in the selection of the published results.

Nine studies have a low risk of bias, two have some concerns of bias, and one has a high risk of bias, according to the results.

DISCUSSION

This article reviews and compares the direct bonding bracket (DBB) technique and the indirect bonding bracket (IBB) technique used in fixed orthodontic appliances. Key parameters evaluated include bracket placement accuracy, chairside time, oral hygiene, and bond detachments (39,40).

Atilla et al. studied the presence of enamel demineralization and white spot lesions (WSLs) using quantitative light-induced fluorescence (QLF) in patients treated with IBB and DBB techniques (31). The IBB group showed a lower degree of enamel demineralization and fewer WSLs compared to the DBB group. However, the IBB technique used a fluid composite instead of the traditional one used in DBB (2,36).

Bozelli et al. compared the clinical and laboratory times, as well as the frequency of loose brackets, between DBB and IBB techniques over 24 weeks (32). They found that while the total time required for IBB was longer due to the laboratory phase, the clinical phase was shorter for IBB compared to DBB (41,42). Yıldırım and Saglam-Aydinatay also found that IBB required a longer total time due to the added laboratory time but had a shorter clinical phase, leading to better marginal ridge and overall scores (1).

Aboujaoude et al. assessed the accuracy of bracket placement using conventional twin brackets and self-ligating brackets in both DBB and IBB techniques (33,35). They found no significant differences in height changes between the two techniques but noted that self-ligating brackets exhibited greater placement deviations than conventional brackets. De Oliveira et al. demonstrated that virtual bonding software can enhance the precision of bracket placement compared to traditional methods (33).

Czolgosz et al. compared bonding times and immediate debonding rates between direct bonding and computer-aided indirect bonding. The study found that computer-assisted indirect bonding required significantly less clinical chair time but more total time due to the digital setup phase. Additionally, there were more instances of immediate debonding with the computer-assisted method (37).

A study by Menini et al. evaluated the bond failure rates of brackets placed using DBB and IBB techniques. They found no significant difference in bond failure between the two techniques. Another study by Demirovic et al. compared the shear bond strength (SBS) and adhesive remnant index (ARI) between DBB and IBB techniques, finding no significant differences (30).

Flores et al. conducted an *in vitro* study on the SBS and ARI of two adhesive systems (Transbond XY and Beauty Ortho Bond) in both DBB and IBB techniques. The study found that the SBS was higher with the Transbond XY system, which requires phosphoric acid etching, due to increased enamel porosity. However, the IBB technique resulted in lower SBS values for both adhesive systems. Thermal cycling decreased SBS values, with the self-etching adhesive system showing lower SBS but still clinically acceptable values (34,38).

The study acknowledges limitations, including the heterogeneity of the included studies and the inability to assess the quality of these studies comprehensively. The research comprised eight *in vivo* studies, one combined *in vivo* and *in vitro* study, and two *in vitro* studies.

The review highlights various aspects of the DBB and IBB techniques in orthodontic treatment (43–45). While IBB offers advantages such as reduced chairside time and lower enamel demineralization, it requires more total time due to the laboratory phase. Both techniques show comparable bond failure rates and placement accuracy, though the type of bracket and adhesive system used can influence outcomes (46,47). Further research, particularly involving computer-assisted techniques, is necessary to refine these methods and improve clinical efficiency and patient outcomes (48–50).

CONCLUSIONS

The analysis of studies reviewed indicates that accurate bonding of pre-adjusted orthodontic brackets (BRKs) is crucial for effectively treating malocclusions and reducing chairside time. While the indirect bracket bonding (IBB) technique offers superior positioning accuracy, both IBB and direct bracket bonding (DBB) techniques produce similar results in terms of chairside time reduction and bonding failure rates, with no statistically significant differences observed between the two methods.

The use of digital workflows and intraoral scanners equipped with specialized software enables virtual bracket positioning and the creation of custom transfer trays tailored for individual patients. However, current digital software

faces limitations, particularly in accurately identifying dental cusps, which are essential reference points for precise bracket placement. This limitation results in less precise virtual bracket positioning, especially in cases involving severe crowding.

Orthodontic practitioners are optimistic that future advancements in digital software will enhance the precision and effectiveness of the IBB technique, ultimately improving treatment outcomes and efficiency in orthodontic practice.

Author Contributions

Conceptualization, F.I., L.C., G.D., E.X., A.M., P.N. A.P., M.G. and A.D.I.; methodology, F.I., G.D., A.P., L.C., A.L, and A.M.I.; software, A.D.I., A.P., and G.D.; F.T.; validation, A.M.I., F.I., G.P., F.S., A.D.I., and F.I.; formal analysis, A.D.I., F.I., A.M., P.M., P.N., A.M.I., A.P., F.S. and G.D.; resources, A.D.I., A.M.I., M.C., F.I, L.C., A.L and G.P.; data curation, G.D., F.I., A.M.I., A.D.I., L.C., E.X., A.M., P.N.,and G.D.; writing—original draft preparation, F.I., A.D.I., A.M.I., M.P., L.C., P.N.; F.T., and G.D.; writing—review and editing, A.P., A.M., I.P., M.G., L.C., P.N., F.I., G.D., A.M.I., and A.D.I.; visualization, A.M.I., F.I., A.D.I., P.M., G.P., G.D., and A.P.; supervision, G.D., F.T. L.C., P.N., A.D.I., A.M.I., A.P., and F.I.; project administration, G.D., A.M.I., A.D.I., M.C.and F.I. All authors have read and agreed to the published version of the manuscript.

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Review

IMPACT OF ENDODONTIC TREATMENT ON SYSTEMIC OXIDATIVE STRESS IN CHRONIC APICAL PERIODONTITIS: A PROSPECTIVE STUDY.

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ABSTRACT

Introduction: Increased cardiovascular morbidity is one potential systemic effect of increased oxidizing species generation linked to reactive oral illnesses like chronic apical periodontitis (CAP). In order to determine if endodontic therapy may correct the imbalance in oxidative stress levels between participants with chronic periodontitis and healthy controls, we conducted a study. *Materials and Methods*: Patients were chosen at random from two groups of dental clinics and private research. The biological antioxidant potential (BAP) test on plasma samples and the reactive oxygen metabolites (d-ROMs) test were used to assess the levels of oxidative stress in both CAP patients and healthy controls. Prior to endodontic therapy, as well as 30, and 90 days following treatment, measurements were obtained. *Results*: At baseline, oxidative stress levels were considerably greater in CAP patients than in controls. Following treatment, CAP patients' d-ROMs values dropped and their BAP values rose before reaching normal levels ninety days later. *Conclusions*: This research shows that oxidative stress and CAP are positively correlated. Risky oxidative stress is experienced by CAP patients; nevertheless, this stress can be lessened with appropriate endodontic therapy, reestablishing oxidative equilibrium and lowering the likelihood of associated systemic illnesses.

KEYWORDS: *Oxidative stress, chronic apical periodontitis, endodontic treatment*

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INTRODUCTION

Reactive chemical species (RCS) are extremely reactive molecules, atoms, or ions that are involved in physiological reactions that control essential functions (1). They include reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive carbon species, and reactive chlorine species. Oxidative damage can be caused by processes triggered by radicals such as hydrogen peroxide, hydroxyl radical, superoxide anion, and singlet oxygen (2,3). The body has evolved antioxidant defense mechanisms, which include thiols, uric acid, flavonoids, ubiquinone, lipoic acid, ubiquinone, proteins (lactoferrin, ferritin, superoxide dismutase, albumin, and ceruloplasmin), and enzymatic and non-enzymatic systems like peroxidase to guard against such damage (4,5).

These systems lessen oxidative stress in conjunction with removal, repair, and inactivation mechanisms (6).

Infections and pathological situations can also cause an increase in ROS, in addition to physiological circumstances (Fig.1). Carbohydrates, fats, and amino acids can all be impacted by oxidative damage, but it's not obvious if ROS cause or exacerbate disease (7). It is challenging to diagnose the connection between pathogenic diseases and oxidative stress because the latter does not exhibit distinct clinical symptoms (8).

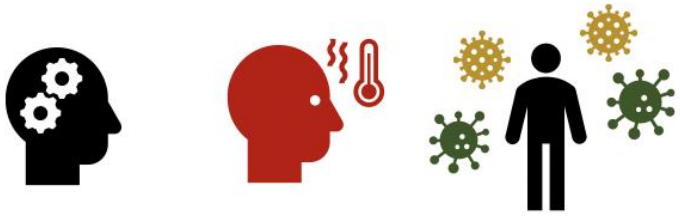

Fig. 1. *Causes of increased ROS.*

Since then, numerous clinical disorders, including type 2 diabetes, aging, cancer, heart disease, lung diseases, and liver diseases, have been associated with oxidative stress. Nevertheless, no research has looked into the connection between endodontic illness and oxidative stress (9,10).

In the oral cavity, the generation and removal of ROS must be precisely balanced and oral illnesses may become more likely if there is a rise in ROS production and/or a decrease in their removal (11) (Fig.2). Increased cardiovascular morbidity and other systemic effects could result from either a decrease in ROS clearance or an increase in the risk of oral illnesses (12,13). Numerous bacteria, including Prevotella intermedia, Phorphyromonas gingivalis, Fusobacterium nucleatum, Bacteroides forsythus, Peptostreptococcus micros, and Streptococcus intermedius, are involved in the pathophysiology of endodontic disorders (14,15).

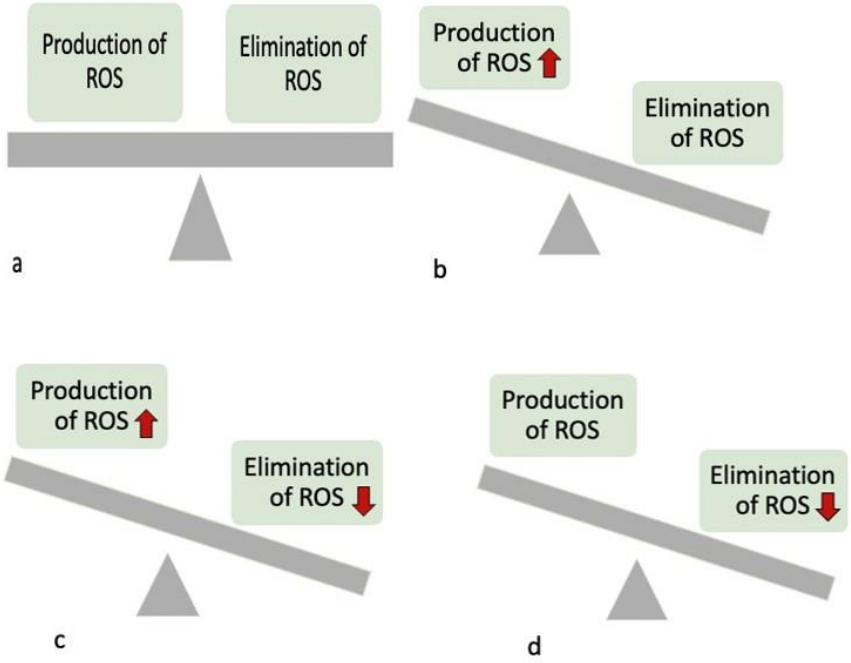

Fig. 2. ***a)*** *Normal balance of ROS values;* ***b, c, d)*** *alterations in the normal balance between ROS production/elimination*.

Depending on the extent of the infection, these pathogens increased inflammatory processes and leukocyte recruitment result in an oxidative attack (16,17). In bacterial infections that cause bone resorption, ROS are one of the most potent pathogenic processes (18,19). This is seen in acute apical periodontitis (AAP), where the affected subjects' neutrophils produce larger levels of superoxide anion and hydrogen peroxide, which normalize after surgical therapy (20,21).

We conducted a prospective study based on these considerations to see whether endodontic therapy could restore the oxidative balance to normal and whether participants with chronic periodontitis had greater oxidative stress values compared to reference values prior to treatment (22,23).

This is the first study to assess the possible systemic effects of the oxidative stress condition brought on by untreated endodontic disease using plasma samples (24,25).

Studies have previously looked at the relationship between changes in biomarkers in crevicular fluid and inflammatory diseases, either acute or chronic, that may impact the periodontium or tooth pulp (26)-(27). Nonetheless, it is clear that the cellular, protein, and enzymatic components of circulating plasma are not present in crevicular fluid (28). This study examines the potential relationship between systemic oxidative stress imbalance and persistent apical periodontitis, which prompts a renewed focus on endodontic diseases (29,30).

MATERIALS AND METHODS

The study included two patient groups: Group 1 comprised 33 patients (21 men and 12 women) with a diagnosis of chronic apical periodontitis (CAP) of a single tooth, ranging in age from 30 to 68 years; Group 2 included 103 patients (58 men and 45 women), ranging in age from 30 to 68 years, but without any indications of chronic apical periodontitis. Individuals who were receiving medical interventions or conditions that would affect the outcome, like using antibiotics or anti-inflammatory medications within the last three months, smoking, being obese, having systemic inflammatory or metabolic illnesses, or having poor dental hygiene, were not included. All of the CAP-affected teeth were bi- or multi-rooted, and the radiographic lesions did not include anatomical structures like the maxillary sinus or inferior alveolar bone; they were no larger than 2 cm. An integrated analytical instrument made up of a mini-centrifuge and a photometer (FRAS4, H&D s.r.l., Parma, Italy) was used to assess oxidative stress. Following collection, blood samples were centrifuged right away, and 10 μL of plasma was examined for antioxidant activity (Biological antioxidant potential (BAP) test) and total oxidant capacity (Reactive oxygen metabolites (d-ROMs) test). The d-ROMs test measures, photometrically at 37°C at 505 nm, a plasma sample's capacity to oxidize N,N-diethylparaphenylendiamine to a cationic radical. The results are represented in Carratelli Units (CARR U, ΔAbs5050 nm/min). Based on the ability of a plasma sample to reduce iron from a complex containing ferric ions to a colorless ferrous derivative, the BAP test measures reduced iron in μmol/L using ascorbic acid as the standard. The test is conducted photometrically at 37°C at 505 nm. The BAP test has a normal value of greater than 2200 μM.

At time T0, the patients in Group 1 had their diagnoses and treatment plans determined. Blood was also drawn at that time. Thirty days after treatment completion (T2), patients were summoned back for a clinical and radiological evaluation, and endodontic therapy was carried out seven days later (T1). At T2 and again sixty days later (T3), the BAP and d-ROMs tests were redone. Measurements were done by all individuals at 30 and 90 days. SPSS software was used to analyze data, and the results were presented as mean ± SD. ANOVA and the Student’s T-test were used to determine statistical significance, with values less than 0.05 regarded as significant.

RESULTS

Systemic oxidative stress levels were higher in CAP patients than in the general population. Group 1's average d-ROMs test results at recruitment were 458 ± 36, while Group 2's BAP test results were 1790 ± 64. Group 2 values, on the other hand, showed normalcy, with d-ROMs test results of 261 ± 10 and BAP test results of 2227 ± 55.

Group 1's oxidative stress levels gradually reverted to normal following endodontic therapy. A mean 25% decrease in the d-ROMs test value and an 11% mean increase in the BAP test value were noted during the first follow-up, which occurred 30 days following therapy (T2). Ninety days later, at the second follow-up (T3), Group 2 values stayed same, but there was a further 20% mean increase in the BAP test value and a 26% mean decrease in the d-ROMs test value.

DISCUSSION

Numerous diseases are linked to systemic oxidative stress. According to our research, systemic oxidative stress is significantly higher in CAP participants, which may have consequences for their general health (31,32). Normal levels of

oxidative stress were restored by endodontic therapy, indicating that prompt diagnosis and treatment are essential to avert systemic harm (33,34).

Chronic inflammation and the presence of microorganisms that promote ROS production are the likely causes of the increase in oxidative stress observed in CAP patients (35,36). The goal of endodontic therapy is to lessen inflammation and infection in order to lower the oxidative load. The findings imply that treating endodontic infections may benefit the body both locally and overall (37,38).

These findings are consistent with earlier research that shown the impact of inflammation and persistent infections on systemic oxidative state (33,39). To validate these theories and learn more about the underlying molecular processes, more research is necessary (40,41).

Our research emphasizes how crucial it is to assess oxidative stress in endodontic pathology patients in order to minimize tissue damage to the periodontal ligaments and avoid systemic effects (42). Thus, prompt diagnosis and treatment of endodontic infections may be a useful tactic to enhance oral and overall health (43,44).

Lastly, it's critical to recognize the limitations of our research (45). We did not take into account additional potential causes of oxidative stress that might have an impact on the outcomes, and the patient sample was somewhat small (46,47). Furthermore, since the follow-up period was just 90 days, it is possible that future improvements will take place (48). Our findings, however, lay the groundwork for further investigations into the function of oxidative stress in endodontic disorders and the possible systemic effects of endodontic therapy (49,50).

CONCLUSIONS

Endodontic therapy can greatly lower the systemic oxidative burden, and oxidative stress plays a substantial role in chronic endodontic diseases. These results highlight the value of treating endodontic infections holistically, taking into account both the local and systemic consequences to enhance patients' general health.

Author contributions

Conceptualization, F.S., A.D.I., F.I., L.M., F.B., A.M.I., E.X., G.D. and A.P.; methodology, A.D.N., B.F.P.P., R.V.G., F.C.T., A.D.I. and A.P. software, B.F.P.P., G.P., A.D.I., R.V.G. and L.M.; validation, F.I., A.M.I., G.D., M.C. and B.F.P.P.; formal analysis, A.D.I., A.M.I., A.L., B.F.P.P. and R.V.G.; investigation, G.D., A.P., F.S., F.I. and F.C.T.; resources, A.M.I., A.P., F.S., A.D.I., F.I. and G.D.; data curation, G.P., B.F.P.P., R.V.G., A.P., F.S. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., B.F.P.P. and R.V.G.; writing-review and editing, F.I., A.M., E.X., A.P., L.M., A.D.N. and G.P.; visualization, B.F.P.P., R.V.G., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T.; project administration, F.B., F.S. L.M., G.P., B.F.P.P., A.M.I. and R.V.G.. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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Review

NATURAL ANTIOXIDANTS' ADVANTAGES FOR DENTAL HEALTH

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ABSTRACT

More research is being done on the relationship between oxidation-reduction processes and human health. Oxidation and damage are facilitated by free radicals, especially reactive oxygen species. Endogenous antioxidants are produced by the body to counteract these effects. The antioxidant capability of nutraceuticals includes vitamins and flavonoids, which are present in diet. The goal of research is to understand how reactive oxygen species, exogenous antioxidants, and bacteria interact to support defense and preserve a dynamic equilibrium. Researchers studying nutraucetics have discovered that certain foods contain flavonoids, lipoic acid, carotenoids, lycopene, selenium, coenzyme Q-10, and vitamins A, B, C, and E that have antioxidant properties. In order to promote increased protection via the peroxidation of macromolecules (proteins and lipids) by maintaining a dynamic balance among the species that make up the microbiota, a number of research areas aim to investigate the interaction between reactive oxygen species, exogenous antioxidants, and the microbiota. The purpose of this scoping review is to map the body of research on oxidative stress in relation to the oral microbiota and the use of natural antioxidants to mitigate it. It also aims to evaluate the quantity, kind, and nature of studies that are currently available and to identify any potential gaps that may arise from the analysis.

KEYWORDS: *Natural antioxidant; oral health; oral disease; vitamins; ROS; reactive oxygen species; antioxidants; dental health; dentistry; oxidative stress*

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INTRODUCTION

Although reactive oxygen species (ROS) are produced during oxidation-reduction events, these reactions are essential for cell metabolism (1,2). These radicals are resisted by vitamins and glutathione, which are endogenous antioxidants; nonetheless, excessive ROS can overcome these defenses. Vitamins, polyphenols (PFs), coenzyme Q-10, and other nutraceutical antioxidants all aid in controlling ROS levels (Fig.1).

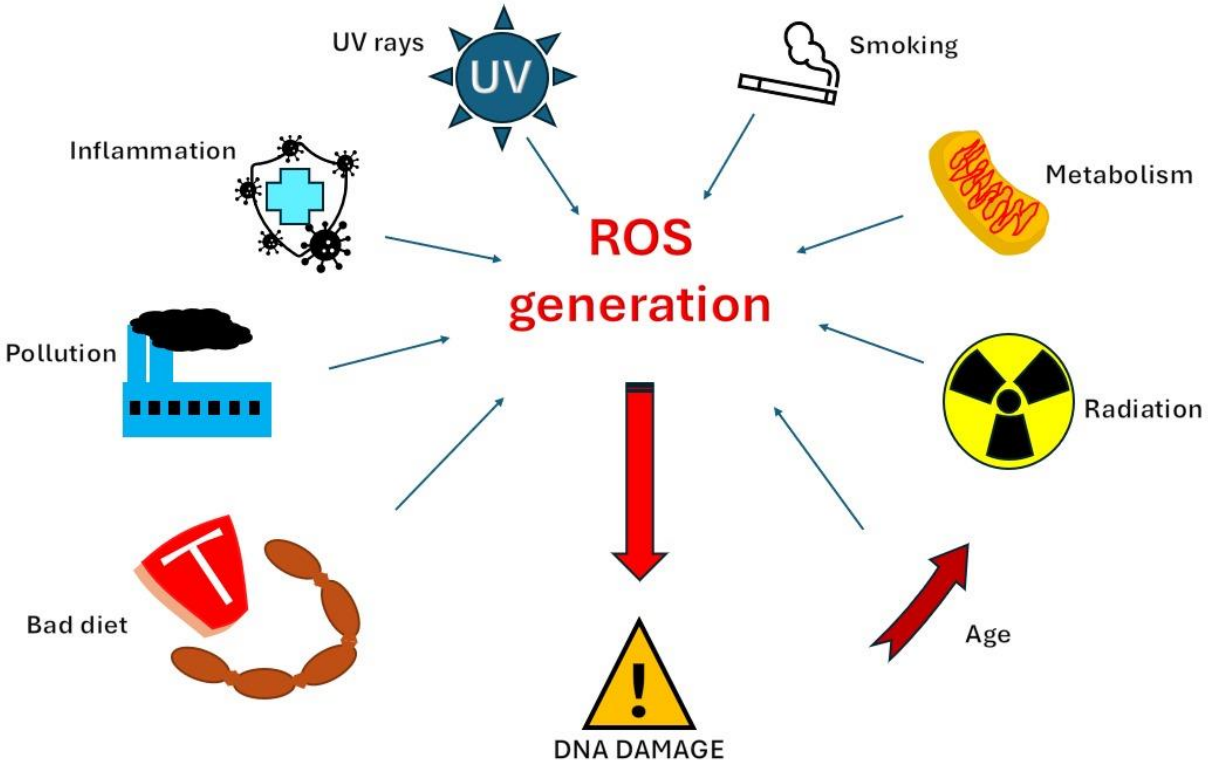

Fig. 1. *Factors inducing ROS formation.*

Antioxidant-rich diets, like the Mediterranean diet, help prevent disease. Resveratrol (RSV), curcumin (CUM), and green tea (GT) are examples of polyphenols that have anti-inflammatory and anti-cancer qualities. They can also affect gene expression to control cancer therapy and degenerative diseases. There is evidence that GT and CUM lower inflammation and prevent cancer (3–5).

Green Tea

By decreasing inflammation and pro-inflammatory cytokines in periodontal tissue, green tea (GT) extract, which is high in catechins like EGCG and EGC, protects teeth against cavities and prevents periodontal disease (6,7). The antibacterial qualities of EGCG aid in the prevention of gingivitis and cavities. GT mouthwash lessens halitosis and promotes healing following dental procedures. By modifying gene expression, it exerts chemopreventive effects on oral cancers. Furthermore, GT promotes the integration of dental implants by reducing the risk of osteoporosis, hyperlipidemia, and cholesterol. On the other hand, hepatotoxicity, thyroid issues, and caffeine-related side effects might result from overindulging (8,9).

Curcumin

The main ingredient of Curcuma longa, curcumin, has several advantages, including anti-inflammatory and antioxidant qualities. It efficiently fights oral germs such as S. mutans and P. gingivalis, lowering the formation of biofilm and averting dental problems (10). Furthermore, it prevents Candida colonization, particularly in conjunction with quitting smoking. But in order to improve bioavailability, nanomedicine techniques are required due to its quick metabolism. Even though it has advantages, taking too much of it might cause problems including reduced iron absorption and uterine contractions during pregnancy, therefore it must be stopped before surgery (11–14).

Resveratrol

Resveratrol (RSV), a polyphenol and phytoalexin, has numerous medicinal benefits, including anti-inflammatory, anti-tumor, antiviral, anti-aging, antifungal, and antithrombotic effects. It is found in red wine, fruits, and plant barks. So RSV, that is also a potent antibacterial, can prevent osteonecrosis, prevent periodontal disease, and inhibit Porphyromonas gingivalis biofilm formation, but faces challenges like low bioavailability and chemical instability. Nanopharmaceutical techniques, drug delivery systems, and particular carriers have been created to solve these problems by preserving and releasing PFs at action locations (15–17). This method improves the effectiveness of treatment for illnesses of the oral cavity by allowing the co-administration of hydrophilic antibiotics and lipophilic PFs (18–20).

Vitamins

Vitamins are essential for healthy teeth and metabolism.

Colorful veggies provide vitamin A, which promotes the growth of teeth and bones and the integrity of the epithelium. beneficial for treating periodontal disease, however high dosages may be dangerous if taken while pregnant.

B vitamins are necessary for tissue repair and cell metabolism. Gingival hemorrhage and disturbances of the oral epithelium are caused by deficiencies. essential for reducing craniofacial abnormalities during pregnancy and for wound healing during periodontital surgery.

Iron absorption, collagen formation, and cell metabolism are all enhanced by vitamin C. It serves as an immunostimulant and antioxidant. Scurvy, gum bleeding, and tooth loss are all caused by deficiencies. Suggested for lesions on the oral mucosa and for healing after surgery.

Vitamin D is essential for strong bones and a healthy immune system. prevents dental calcification abnormalities, osteoporosis, and rickets. stimulates bone repair and inhibits Porphyromonas gingivalis. Deficiency is associated with some malignancies and jaw osteonecrosis.

Antioxidant vitamin E promotes cellular function and guards against cancer. shields against damage from cigarette smoke and pollutants (21–23).

Each vitamin is necessary to keep the mouth and body healthy, and vitamin shortages can cause serious health problems.

Aloe Vera

Aloe vera's calming and anti-inflammatory qualities are beneficial to dental health. It aids in the prevention of gum infections, lowers inflammation, soothes mouth ulcers and irritation, and quickens healing. Aloe vera also promotes periodontal health and inhibits the growth of bacterial plaque (24,25).

Propolis

Propolis has antibacterial, anti-inflammatory, and antioxidant qualities that help maintain dental health. It heals mouth ulcers and gingivitis, lessens inflammation, promotes healing, and keeps plaque and tartar away from teeth and gums. To confirm its medicinal potential, more research is required (26–28).

MATERIALS AND METHODS

Protocol and Registration

This review was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and it was registered under the number 550633 on PROSPERO (The International Prospective Register of Systematic Reviews).

Search Processing

The current review was carried out in accordance with the PRISMA-ScR methodology. To find publications pertinent to the study topic, a search was conducted on the PubMed, Web of Science, Scopus, and Cochrane Library databases. The search was restricted to articles published in English between January 2018 and December 30, 2022. The following Boolean keywords were included in the search strategy, along with other pertinent terms to the study's goal: "natural" AND "antioxidant"; "oral" AND "health"; and "oral" AND "disease" (Table I).

Table I. *Database search indicator.*

Articles screening strategy	
KEYWORDS:	A: “natural”; B: “antioxidant”; C: “oral”; D: “health”; E: “disease”
Boolean Indicators:	(“A” AND “B”) AND ((“C” AND “D”) OR (“C” AND “E”))
Timespan:	from January 2018 up to 30 December 2022
Electronic Databases:	PubMed,Web of Science, Scopus, and Cochrane Library

Inclusion Criteria

Based on inclusion criteria that included human participant participation, open-access publications, randomized controlled clinical trials, English language, and beneficial effects of natural antioxidant substances on oral health, the reviewers evaluated the studies.

RESULTS

Quality Assessment and Risk of Bias

In 75% of the investigations, the risk of bias was minimal, and was estimated utilizing RoB 2. On the other hand, 75% submitted all outcome data, and 25% eliminated performance bias. Bias in results reported by the self was also removed in much research (Fig.2).

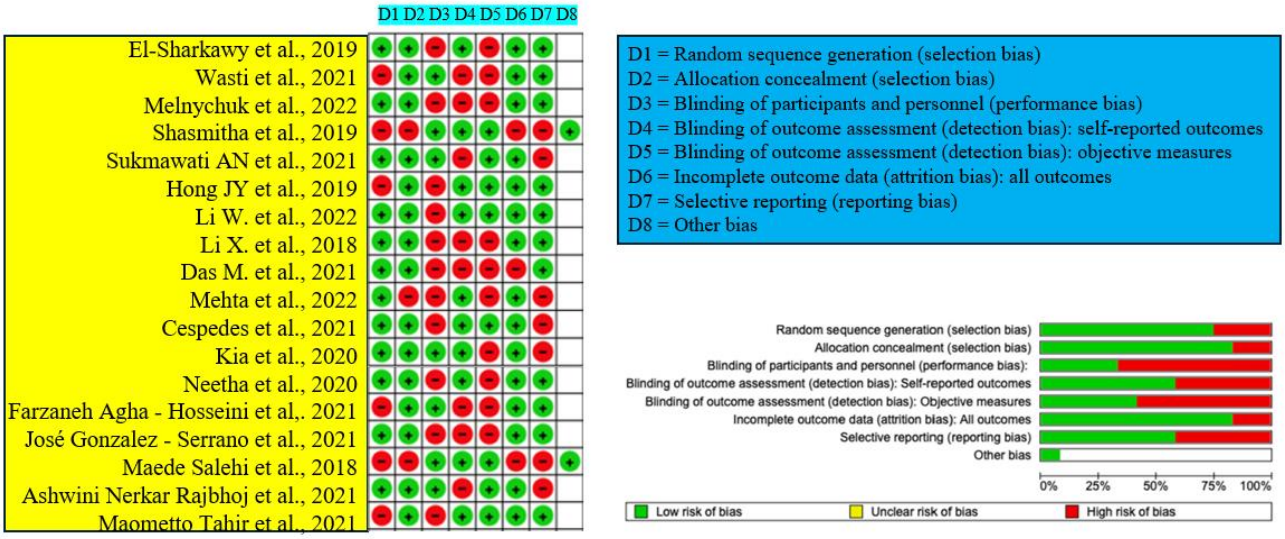

Fig. 2. *Risk of Bias domains of the included studies.*

Prism

The PRISMA-ScR technique (73) was used in the execution of the current review. An investigation was carried out using the PubMed, Web of Science, Scopus, and Cochrane Library databases to locate papers relevant to the subject of the study. Only English-language articles released between January 2018 and December 30, 2022 were included in the search parameters. Together with other relevant terms to the study's objective, the following Boolean keywords were included in the search strategy: "natural" AND "antioxidant"; "oral" AND "health"; and "oral" AND "disease" (Table I).

In the end, eighteen articles were considered suitable for quality examination (Table II). Figure 3 provides an overview of the selection procedure (Fig.3).

Table II. *Descriptive summary of item selection.*

Author (Year)	**Study Design**	**Number of Patients**	**Average Age (Years)**	**Materials and Methods**	**Pathology**	**Outcomes**
El-Sharkawy et al., 2019 (29)	RCT	A study involving 74 patients with chronic periodontitis and primary	The mean age of the test group was 45.6, while the control group had a	The study involved patients taking SRP and melatonin capsules daily for 2 months, while a control group received a placebo, and the	Periodontitis	Melatonin improved probing depth and CAL at 3 and 6 months, with no significant differences in plaque

		insomnia was conducted, with a control group consisting of 20 patients and a control group.	mean age of 46.7.	researchers measured CAL gain after 3 and 6 months.		index, gingival index, or bleeding upon probing between the two groups.
Wasti et al., 2021 (30)	RCT	48 healthy patients, into 24 test and 24 control groups.	Unspecified	The test group received a prescription for CLIK®, containing GT extract and natural lycopene, and saliva samples were collected at baseline and 45 days post-operatively.	Gingivitis	The test group showed improved gingival health, with improved antioxidant profile, compared to the control group, indicating a significant improvement in overall health.
Melnychuk et al., 2022 (31)	Observational study	161patients;125 had periodontitis; 36 had intact periodontium	19–45	The study utilized a supplement containing blue-green microalgae Spirulina platensis, a paste made from spirulina powder and silica enterosorbent, and Spirulina tablets twice daily for four weeks.	Periodontitis	The treatment effectively regulated the patients' elevated levels of malonic dialdehyde, diene conjugates, catalase activity, transferrin iron saturation, and ceruloplasmin activity, resulting in a stabilised periodontitis.
Shasmitha et al., 2019 (32)	Clincial trial	42 orthodontic patients with widespread, persistent gingivitis	14–30	Patients were evaluated for gingivitis using various tests, and a modified Brass brushing technique using total care herbal toothpaste was demonstrated, subsequently assessing their gingival condition.	Gingivitis	The pre-treatment and post-treatment GI and OHI index scores showed marginally higher results than pre-treatment scores, but neither was statistically significant.
Sukmawati et al., 2021 (33)	Comparative Study	6 patients	Unspecified	Group A received 10% propolis post-curettage, while Group B received 1% tetracycline. PPD, BOP, and IL-1 concentrations were measured at baseline and 21 days post-curettage.	Periodontal disease	10% propolis, used as a subgingival irrigation agent, significantly improved periodontal tissue and IL-1 concentration in patients with CP compared to 1% tetracycline.
Hong et al., 2019 (34)	RCT	112 patients	19–80	Patients were randomly assigned to receive vitamin C and E, lysozyme, and carbazochrome (CELC) or a placebo for four weeks, followed by measures of GI, PI, PD, and CAL at four and eight weeks.	Periodontal disease	Following 4 and 8 weeks, the test group's GI significantly improved. CELC dramatically reduced gingival inflammation when compared to a placebo.
Li W et al., 2022 (35)	cross-sectional study	8959 patients	Mean age: 52.4	The US National Health and Nutrition Examination Survey (NHANES, 2009–2014) was utilized to identify participants who underwent a periodontal examination and reported their micronutrient intake levels.	Periodontal disease	Consuming adequate micronutrients like vitamin A, B1, B2, and E reduces periodontitis risk, while high intake of B1, C, and copper increases the incidence of periodontitis.

Li X et al., 2018 (36)	RCT	128 patients	Mean age: 44.9	Group A received guided bone regeneration dental implants, group B received Bio-Oss Collagen implants, group C had CP implants, and group D had implants without bone grafting or periodontal disease.	Periodontal disease	Vitamin C supplementation aids patients with CP and those receiving GBR or Bio-Oss Collagen grafts in faster healing after dental implants.
Das M et al., 2021 (37)	RCT	72 patients	Mean age: 39.2 ± 8.6	Two groups of patients with periodontal pockets were randomly divided into a test group and a control group, and clinical measurements were taken at baseline and three months.	Periodontal disease	At the end of 3 months, the test group showed PD↓ and RAL↓; there was no discernible difference between PI and GI. It might be advantageous to control periodontal pockets via the intra-pocket application of GSE and SRP.
Mehta et al., (2022) (38)	Prospective study	120 (60 cases: 36 M 24 F-60 controls:31 M 29 F)	18–40	The CUM gel was applied daily for two months, and cytomorphometric analysis was conducted using CHROMagar.	tobacco users' candidiasis	CUM effectively decreases the number of micronuclei and Candida colonies.
Cespedes et al., (2021) (39)	Double-blinded RCT	40 (20 cases-20 controls)	Unspecified	Comparing Chlorhexidine mouthwash with Carica papaya	Caries	Carica papaya contains anti-S. mutans properties similar to those of chlorhexidine.
Kia et al., (2020) (40)	Double-blinded RCT	57 (29 case-28 controls)	51,86 (CUM-cases) 53.67 (prednisolone- controls)	The study compares the administration of 80 mg CUM in Nano-Micellar Soft gel capsule and 10 mg Prednisolone in capsules.	Oral lichen planus (OLP)	CUM is a potential alternative therapy for patients who are not prescribed corticosteroids, effectively preventing the recurrence of OLP lesions.
Neetha (2020) (41)	Double-blinded Randomised preliminary study	60 (20 GT; 20 CUM; 20 combination)	45.5 (16–82)	The study evaluated biomarkers Ki67, cyclin D1, and p53 at time 0 and 12 weeks after 3 months of topical and systemic administration of GT extract or CUM.	Potentially malignant oral conditions (OPMDs)	After 12 weeks, there are therapeutic improvements and a downregulation of molecular indicators due to the synergistic activity of CUM and GT extract.
Farzaneh Agha-Hosseini et al,. 2021 (42)	RCT	60 patients	at least 18 years old (no maximum age limit)	A mouthwash mixture containing 0.1% triamcinolone, 0.2% vitamin E, and 0.2% hyaluronic acid was created.	oral mucositis brought on by radioactivity	The intervention group showed a significantly higher reduction in inflammation and pain.
José Gonzalez-Serrano et al., 2021 (43)	double-blind RCT	46 patients	around 60 years old	Gel containing nanovitamins C and E, as well as propolis extract	Peri-implant mucositis (PM)	The intervention group showed full PM resolve.
Maede Salehi et al., 2018 (44)	double-blind clinical trial	50 patients	26–70	Two 50 mg propolis pills every day	Chemotherapy-induced oral mucositis	The healing of oral mucositis was significantly different for the intervention group.
Ashwini Nerkar Rajbhoj et al., 2021 (45)	RCT	60 patients	15–55	Oral physiotherapy combined with CUM gel and aloe vera gel	Oral submucous fibrosis (OSF)	Both gel types improved symptoms, but aloe vera gel showed a statistically significant

						improvement in remedying burning.
Maometto Tahir et al., 2021 (46)	Prospective comparative study	28 patients	Mean age: 26.14 ± 5.33	The study compares alpha lipoic acid with aloe vera gel and hydrocortisone.	OSF	The study compared alpha lipoic acid with aloe vera gel group and hydrocortisone group, revealing nearly identical results.

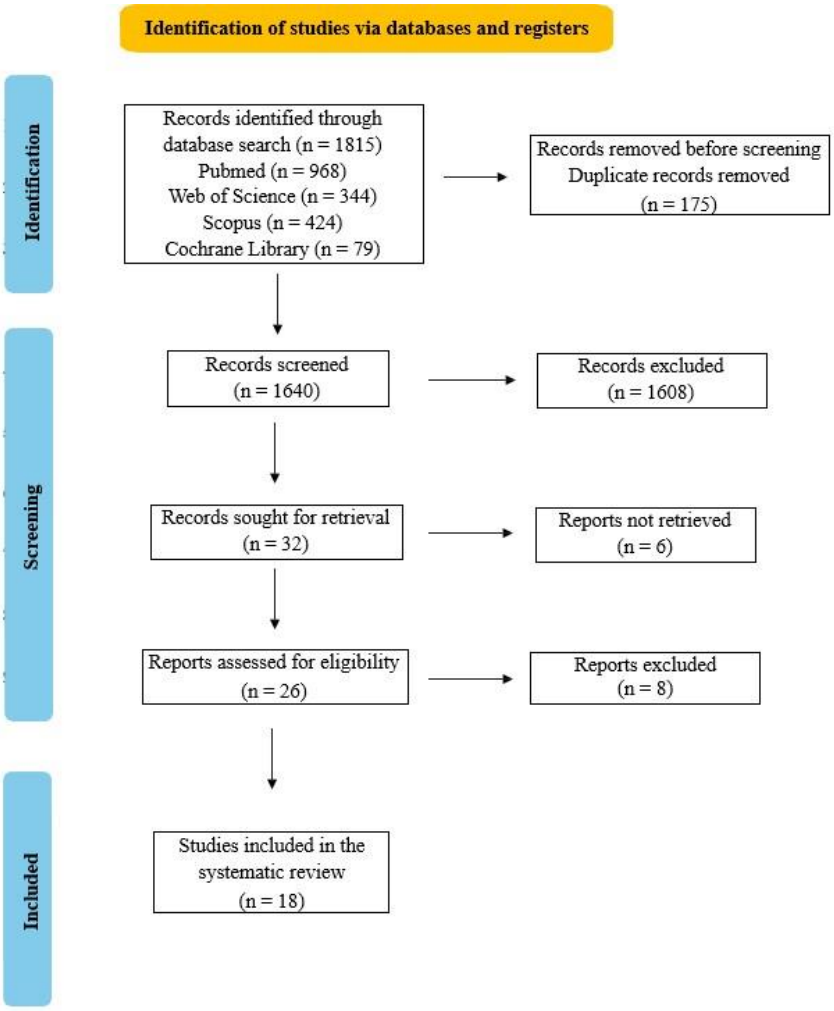

Fig. 3. *PRISMA flowchart of the systematic review.*

DISCUSSION

In order to assess the possible advantages of natural antioxidants, the review looks at oral diseases such as periodontal disease, mucositis, fibrosis, candidiasis, caries, OLP, and possibly malignant conditions (Fig.4, Table III).

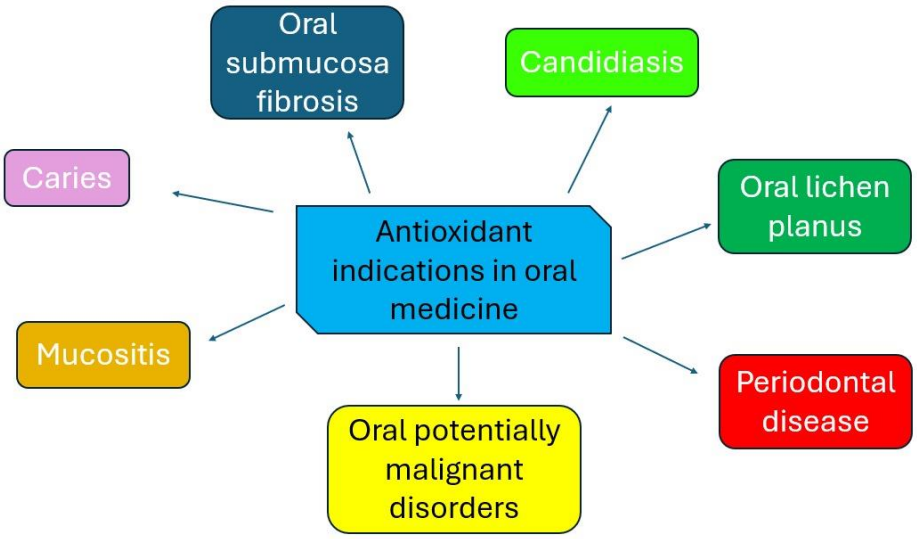

Fig. 4. *Oral diseases affected by antioxidant intake.*

Table III. *Schematic summary of the examined factors.*

Oral Disease	Nutraceutical/Food Substance
Periodontal disease	Propolis, vitamin C, vitamin E, vitamin A, vitamin B2, copper, sage essential oil, grape seed, green tea, uric acid, menthol and thymol essential oils, ferulic acid and phloretin, and melatonin
Mucositis	Vitamin E, triamcinolone and hyaluronic acid, propolis, and Vitamin C
Oral submucosal fibrosis	Curcumin and aloe vera
Oral candidiasis	Curcumin
Caries	Papaya
Lichen planus	Curcumin
Malignant oral cavity disorders	Green tea and curcumin

Periodontal Health

A bacterial infection called periodontitis breaks down connective tissue and bone. Since ROS and pro-inflammatory mediators contribute to pathophysiology, pharmaceutical inhibition is advised as a backup plan. These effects are lessened by micronutrients such vitamins and carotenoids. Vitamin C, a water-soluble reducing chemical, effectively transfers electrons, scavenges reactive oxygen species (ROS) from oxidative stress and inflammatory reactions, while maintaining cell redox potential equilibrium (47,48) (Fig.5).

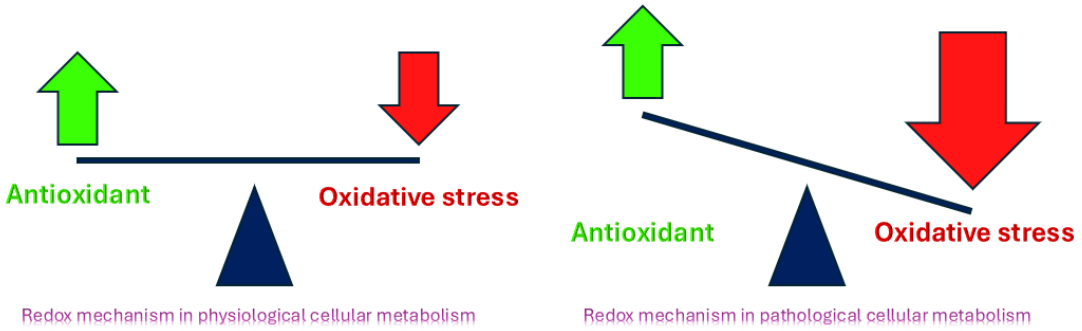

Fig. 5. *Redox mechanism in physiological and pathological cellular metabolism.*

Lipidone oxidative damage is prevented by vitamin E, which is present in cell membranes. When taken together, vitamins E and C may have synergistic benefits that help people with gingivitis and periodontitis. For example, vitamin C promotes wound healing following dental implants, and a combination of C, E, lysozyme, and carbazochrome (CELC) dramatically reduces gingival inflammation (34–37).

Propolis decreases inflammation and speeds up healing when used to treat gingivitis and mouth ulcers because of its antibacterial and anti-inflammatory qualities. When used in conjunction with scaling and root planing (SRP), grape seed extract (GSE) improves clinical metrics such as gingival inflammation and plaque index, further supporting periodontal health. (30,31)

It has been demonstrated that periodontal health can be improved by antioxidant-rich diets and supplements including lycopene, green tea extract (GT), and melatonin. For example, supplementation with lycopene and GT extract greatly improves clinical parameters in the management of periodontal disease. Because of its antioxidant qualities, melatonin helps individuals with chronic periodontitis who also suffer from insomnia by lowering inflammation and improving clinical outcomes (29,32)

Although further clinical research is required to completely confirm the therapeutic efficacy of vitamins and natural compounds, these findings demonstrate the potential of these substances to improve oral health (33,49).

Mucositis

Agha-Hosseini et al. investigated the use of a mouthwash containing vitamin E, triamcinolone, and hyaluronic acid in 2021 to treat head and neck cancer patients who had radiation-induced mucositis in order to reduce pain and inflammation (42). Propolis pills were proven to be beneficial in the recovery of mucositis caused by chemotherapy by Salehi et al. (2018) (44). Gonzalez-Serrano et al. (2021) suggested a gel that achieved a 26% resolution for post-radiotherapy mucositis by combining propolis extract, nanovitamin C, and E (43). These trials demonstrate the advantages of antioxidant treatments for mucositis following chemotherapy or radiation therapy.

Oral Submucosa Fibrosis

In a trial on the care of oral submucosal fibrosis, Ashwini Nerkar Rajbhoj et al. (2021) divided 60 patients into two groups and gave them oral physiotherapy and either curcumin or aloe vera gel. Both gels alleviated symptoms, however aloe vera demonstrated a noticeably better resolution of burning feeling. In their comparison of aloe vera gel and alpha lipoic acid with intralesional steroids for the treatment of oral submucosal fibrosis, Muhammad Tahir et al. (2021) found that both treatments were useful, especially for patients who are steroid intolerant (45,46).

Candidiasis

The oral microbiome can be upset by tobacco use, which can result in pathological Candida overgrowth and exacerbate oral diseases. Mehta et al. investigated how curcumin (CUM) gel affected smokers' Candida. For two months, CUM—which has antibacterial and anticarcinogenic qualities—was administered three times a day. Significant changes in cell properties and Candida colonization were detected after stopping smoking and receiving CUM treatment, in a trial including 120 smokers. These findings suggest that CUM may be used in conjunction with smoking cessation to prevent the growth of Candida (38).

Caries

The Moluccas Island native papaya is well known for its therapeutic qualities in folk medicine. Fruits, leaves, seeds, and latex have all been used to treat a variety of health conditions because they contain high levels of antioxidant

vitamins and proteolytic enzymes that have antiviral, antibacterial, and antifungal properties. The fruit's seeds and leaves include triterpenes, alkaloids, polyphenolic compounds, proteolytic enzymes, and antioxidants such as carotene, vitamins A, C, B, and E, flavonoids, and minerals. Cespedes et al. studied the antibacterial activity of papaya mouthwash against Streptococcus mutans. The findings suggested papaya mouthwash as a potential substitute by inhibiting S. mutans, although more investigation is required to validate this (39).

Oral Lichen Planus

The symptoms of Oral Lichen Planus (OLP), a chronic inflammatory condition that affects the oral mucosa, can range from excruciating pain to a burning sensation. Corticosteroids are usually used as a kind of treatment, but due to its negative effects, many are looking for other options. Turmeric's phytochemical curcumin (CUM) has demonstrated potential because of its many uses. In order to compare the effectiveness of oral nano-CUM for OLP with prednisolone, Kia et al. There was no discernible difference in the reduction of lesions and pain between the two treatments. With a reduced dosage of 80 mg, Nano-CUM demonstrated efficacy and improved solubility, indicating its promise as a therapeutic agent for OLP. Additional research is required before it may be applied clinically (40).

Potentially Malignant Oral Conditions

OSMF and other PMDs increase the risk of oral cancer. Chemotherapy tries to stop them, however medications such as retinoids can be dangerous. Green tea (GT) and curcumin (CUM) both have low toxicity levels and prevent cancer. GT and CUM combined were shown by Neetha et al. to be more efficacious in PMDs, blocking carcinogenesis stages. Three months later, they work together to lessen the growth of cancer cells and biomarkers. They don't improve the survival rate from oral cancer (41,50).

LIMITS

According to the literature, human models are rarely used in the current studies on oral cavity antioxidant principles, which calls for the establishment of research that takes into account both large human subject populations and animal models.

CONCLUSIONS

Comprehending the advantages of nature is essential while tackling medical issues. Research centers on natural substances known as "Nutraceutics," which improve health by interacting with biochemical processes. Organic or synthetic antioxidants protect against illness, but further research is needed to be certain. Novel insights into molecular pathways are made possible by the connections between basic research and clinical viability.

Author contributions

Conceptualization, A.D.I., F.I., F.B., L.M., A.M.I., G.P., F.S. and A.P.; methodology, A.D.N.,E.X, F.S., L.M., C.C., P.L., F.C.T.. and A.P. software, F.I., G.D., A.D.I., P.L., F.B. and L.M.; validation, F.I., F.S., A.M.I., G.D., M.C. and P.L., formal analysis, A.D.I., A.M.I., L.M., C.C.. and A.R.; investigation G.D., A.P., F.S., M.C., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I. and G.D.; data curation, G.P., P.L., C.C, A.P. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., C.C. and A.R.; writing-review and editing, F.I., A.P., L.M., A.D.N.; visualization, C.C. A.R., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T..; project administration, M.C., G.P., C.C, A.M.I. and A.R. All authors have read and agreed to the published version of the manuscript.

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Data are contained within the article.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

EXPLORING THE POSITIVE IMPACT OF PROBIOTICS ON ORAL HEALTH: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Aim: Studies have shown that probiotic microorganisms, which are frequently used to support gut health, may also provide advantages for tooth health. Probiotics (PBs) have been linked to a decrease in cariogenic bacteria and a defense against periodontal diseases, while it's unclear exactly how they work in the mouth. Our research focused on conditions like cavities, gum disease, poor breath, mucositis, and periimplantitis in an effort to investigate how PBs might be used to enhance oral health. *Materials and methods:* We searched the PubMed, Scopus, and Web of Science databases using the Boolean keywords "Oral health" AND "Probiotics." Only articles published in English between January 1, 2019, and April 13, 2023 were included in the search. *Results:* our automated search turned up a total of 3460 articles. Twelve papers were chosen for inclusion after duplicates were eliminated, the papers were examined, and their applicability was assessed. *Conclusion:* It is difficult to determine how bacteria in food or dietary supplements could affect the stable oral microbiota. Probiotic microorganisms have been shown to have demonstrable therapeutic effects, however there is currently insufficient data to support their use in oral health. To fully comprehend the long-term impacts of probiotic bacteria on the oral environment, including their capacity to colonize and build biofilms, more research is required.

KEYWORDS: *Probiotics, oral health*

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INTRODUCTION

All bodily surfaces are home to microorganisms, with mouth mucosa housing the second-highest concentration of these organisms after the colon (1). The physiological microbiota and the health of the organism it lives in are mutually reliant (2). Within certain bounds, bacteria and yeasts can reproduce and feed on their host by releasing helpful molecules, and they can self-regulate to prevent the growth of more aggressive strains and species (3,4).

The buccal bacterial flora, a varied and healthy microbiota found in the oral cavity, aids in preventing infections. It has been determined which bacterial species are linked to oral problems and which are associated with excellent health (5,6). Less than 1% of the culturable microbiota in the mouth is typically made up of lactobacilli, yet some species can be found in both oral and fecal specimens (7).

The microbiome of patients with periodontitis and those with healthy periodontal tissues differs in terms of the species composition of Lactobacillus and Bifidobacterium bacteria (8). Bifidobacteria and lactobacilli are connected to dental decay, and exogenous and opportunistic invaders—possibly brought in by food—have been found as lactobacilli and bifidobacteria linked to caries (9) (Fig.1).

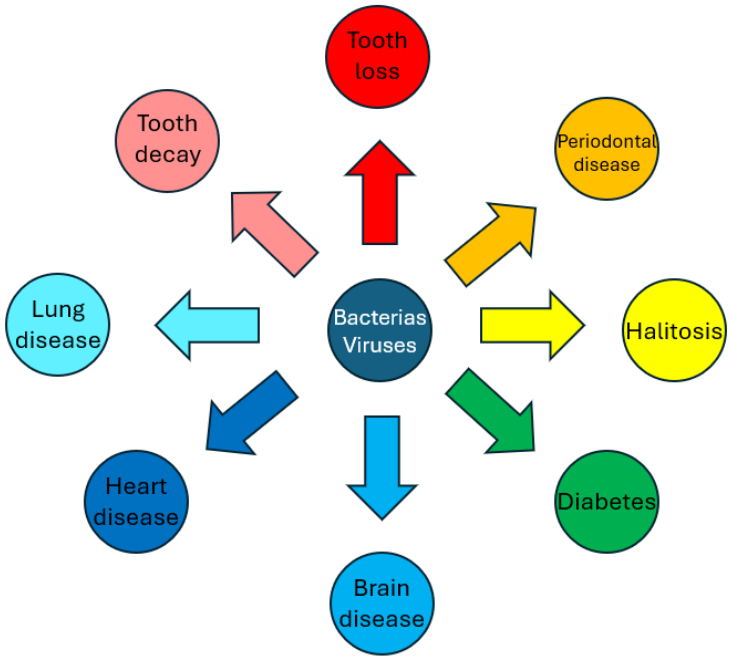

Fig. 1. *Effects of the imbalance of the oral microbiota on systemic health.*

When given in adequate amounts, probiotics (PBs) can improve the host's health by offering advantages including dissoluble and not dissoluble fibers (10,11). In addition to producing chemicals like lactic acid, hydrogen peroxide, and bacteriocins and regulating the inflammatory response, they are linked to the reduction of colony-forming units (CFU) of cariogenic pathogens and the avoidance of periodontal diseases (12,6). The oral microbiome requires more investigation, taking into account aspects that regard the clinical and biochemical factors (13,14) (Fig.2).

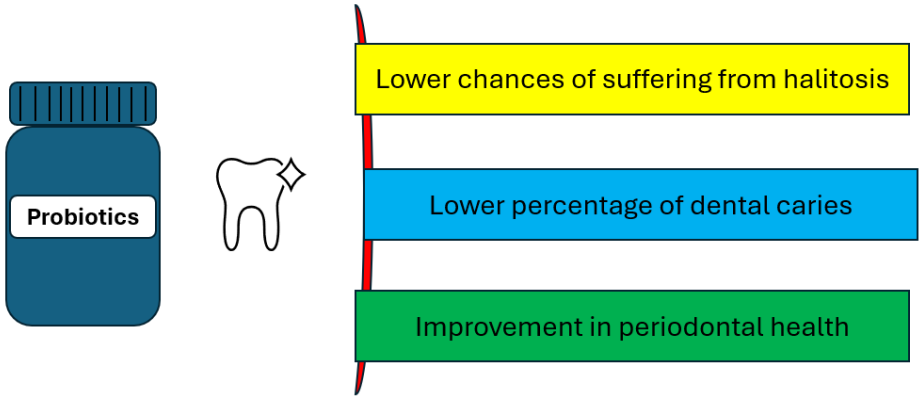

Fig. 2. *Effects of PBs on oral health.*

MATERIALS AND METHODS

Protocol and Registration

The evaluation employed PRISMA protocols, which are recorded at PROSPERO with ID 549480.

Search Processing

With a focus on comprehending the influence of probiotics (PBs) on oral health, notably caries, periodontal disease, and halitosis, the study used the Boolean keywords "Probiotics" and "Oral health" to search for English-language papers from 2019 to 2023.

Eligibility Criteria and Study Selection

To investigate the impact of PBs on the disorders of the mouth, the study employed two phases: full-text examination and evaluation of the title and abstract. Articles that satisfied requirements including complete text in English, treatment comparisons, and human intervention trials were accepted. Two reviewers gathered pertinent studies and evaluated them for inclusion.

Data Processing

After doing separate database searches to find pertinent studies, two reviewers assessed the papers' quality and saved the chosen ones in Zotero. When there were differences, a senior reviewer was consulted (Fig.3).

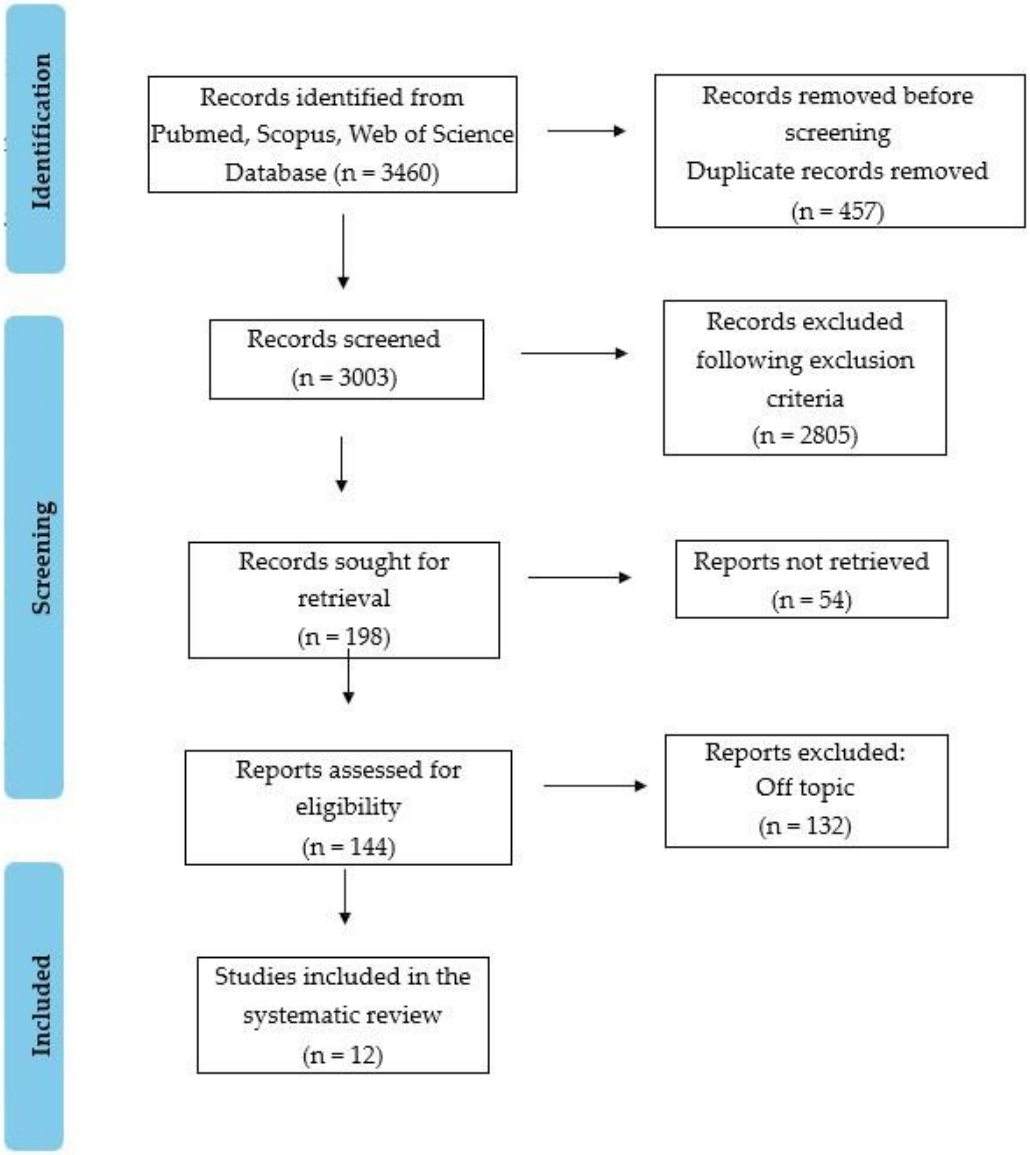

Fig. 3. *PRISMA flowchart of the systematic review.*

Quality Assessment

The bias risk of publications was evaluated by two reviewers applying the tool of Cochrane of the risk of bias for randomized trials; any disagreements were then debated with another reviewer and then a consensus was reached.

PICOS Criteria

Table I displays the PICOS criteria components used in this evaluation and incorporate population, intervention, comparison, outcomes, and design of the study (Table I).

Table I. *PICOS criteria.*

Criteria	Application in the Present Study
Population	Both children and growups
Intervention	Utilizing PBs to enhance dental health
Comparisons	Comparing how using PBs affects various oral diseases
Outcomes	Effectiveness in averting caries, gingivitis, halitosis, mucositis, and periimplantitis
Study design	Clinical Trials

Results

These studies demonstrate the benefits of probiotics for enhancing dental health. Probiotic-fortified cheese has been discovered to affect oral microbiota, and daily probiotic ingestion has been demonstrated to lower salivary S. mutans levels. It has been discovered that probiotic capsules lessen halitosis and enhance dental health and quality of life. It has been demonstrated that giving kids regular short-term probiotics can delay the onset of dental caries. It has also been discovered that probiotic lozenges help people with periodontitis have shallower pockets. Additional investigation is required to comprehend their enduring consequences (Table II).

Table II. *Descriptive summary of item selection.*

Authors	Type of Study	Object	Study Design and Timeline	Results	Number of Participants
Sarmento et al., 2019	Clinical study	Examine the effects of adding PBs to petit-suisse cheese on children's salivary microbiome.	Giving cheese enriched with Lactobacillus casei for 28 days and then measuring salivary flow	The development of probiotic bacteria that the petit-suisse cheese can carry presents a viable alternative for lowering potentially hazardous oral flora.	
Laleman et al., 2019	Randomized pilot study	Examine the microbiological and clinical benefits of a dual-strain L. reuteri probiotic for the non-surgical management of first peri-implantitis.	Individuals suffering from peri-implantitis received cleanings and full-mouth prophylaxis. Probiotics and placebos were administered together with study lozenges and drops applied to peri-implantitis regions. Microbes were examined in implant-level factors, bleeding, PPD, full-mouth bleeding, plaque scores, and subgingival, tongue, and saliva samples.	After 12 and 24 weeks, the study observed significant decreases in the amount of plaque at the implant level and full-mouth BOP sites in the probiotic group, but no discernible changes in microbiology.	10
Kang et al., 2020	Randomized, double-blind, placebo-controlled trial	This study sought to assess the impact of W. cibaria CMU (oraCMU) on oral microbiota and periodontal health.	A probiotic tablet called oraCMU was found to significantly enhance periodontal clinical measures, including BOP, PD, GI, plaque index, and microbiota in gingival sulcus, in a trial involving 92 persons without periodontitis.	Probiotic medication increased BOP in patients with periodontitis throughout an 8-week period; PD, GI, or PI did not significantly change. The oral environment and BOP were greatly improved by CMU.	92
Schlagenhauf et al., 2020	Randomized controlled trial	The aim of this study was to determine whether periodontal and dental health in navy sailors could be improved by regular ingestion of L. reuteri PBs.	The main outcome of 42-day research with 72 healthy sailors compared probiotic strains of Lactobacillus reuteri to placebo was opacity of the bone marrow.	Probiotic L. reuteri strain consumption resulted in a substantial improvement in test group scores at 14 and 42 days, suggesting a useful and simple way to maintain periodontal health and oral hygiene.	72
Laleman et al., 2020	Randomized controlled clinical trial	To look into the additional effects of re-instrumenting residual pockets with a probiotic strain of Lactobacillus reuteri.	For a duration of 12 weeks, 39 patients with periodontitis received probiotic or placebo drops, lozenges, and re-instrumentation. investigated the amounts of plaque, recession, bleeding on probing, and probing pocket depth.	After 24 weeks, probiotic lozenges dramatically decreased PPD overall, especially in deep and intermediate pockets, decreasing the number of sites and pockets that required surgery and decreasing thickness from 4 mm to 3 mm.	39
Invernici et al., 2020	Randomized clinical trial	Assess the impact of Bifidobacterium animalis subsp. lactis HN019 on immunological characteristics of saliva, immunocompetence, and clinical periodontal markers.	Thirty patients underwent scaling and root planing (SRP) and were observed at start, 30, and 90 days post-procedure. Both groups received probiotic lozenges for 30 days.	Probiotic B. lactis HN019 may improve the outcomes of periodontal therapy without surgery.	30

Lee et al., 2021	Randomized, Double-Blind, Placebo-Controlled Study	The study aimed to examine the impact of oral probiotic Weissella cibaria tablets on halitosis and psychological indicators.	Participants were randomly divided into experimental or control groups, and either W. cibaria CMU or a placebo was consumed daily before sleep for eight weeks.	The eight-week oral probiotic regimen may be a helpful nursing intervention for improving oral health quality of life and halitosis reduction.	100
Duraisamy et al., 2021	Randomized controlled trial	This study aims to ascertain how well probiotics and synbiotics reduce the level of S. mutans in children's saliva after 15 days of regular ingestion of probiotic and synbiotic curd.	For 15 days, 40 kids between the ages of 6 and 12 were given probiotic and synbiotic curd. Saliva samples were taken, and the amount of S. mutans was assessed.	Salivary S. mutans numbers significantly decreased in both groups, with the probiotic group exhibiting greater growth suppression.	
Hasslof et al., 2022	Randomized controlled trial	To evaluate the effect of probiotic-containing drops on preschoolers' recurrence of dental caries	38 preschoolers received restorative therapy, were observed at 6 and 12 months, and were advised to put L. reuteri in their mouths on a daily basis by their parents.	Notable differences existed between the groups.	38
Santana et al., 2022	Randomized controlled trial	This study looks at how changes in BOP in edentulous individuals with peri-implant mucositis are affected by a multispecies probiotic coupled with mechanical debridement.	Clinical and immunological data were obtained at baseline and after 24 weeks, and patients were randomized to either the probiotic test or the placebo control group. Topical gel and MD treatments were administered twice a day for 12 weeks.		36
Janiani et al., 2022	Randomized controlled trial	To find out how quick probiotic milk consumption affects kids' plaque scores and the amount of S. mutans in their saliva	34 youngsters between the ages of 3 and 6 received PBs for a week; the results were compared to the control group.	After taking probiotics, there was a significant decrease in S. mutans in saliva with a karyostatic impact, but there were no long-term effects identified.	34
Staszczyk et al., 2022	Open Label Randomized Controlled Trial	The purpose of the study is to find out if, after two weeks of daily consumption, chewing thermally inactivated L. salivarius tablets lowers the 12-month caries growth in comparison to the control group.	A study involving 140 healthy children aged 3-6 with or without ECC measured the 1-year increase in dental caries incidence and prevalence, cavitated and apparent dentinal caries, and dental plaque buildup.	The mean OHI-S scores at the beginning and end of the probiotic group did not change substantially from one another. In summary, regular short-term PB ingestion may delay the development of caries.	140

Quality Assessment and Risk of Bias

In 75% of the investigations, the risk of bias was minimal, and was estimated utilizing RoB 2. On the other hand, 75% submitted all outcome data, and 25% eliminated performance bias. Bias in results reported by the self was also removed in much research (Fig.4,5).

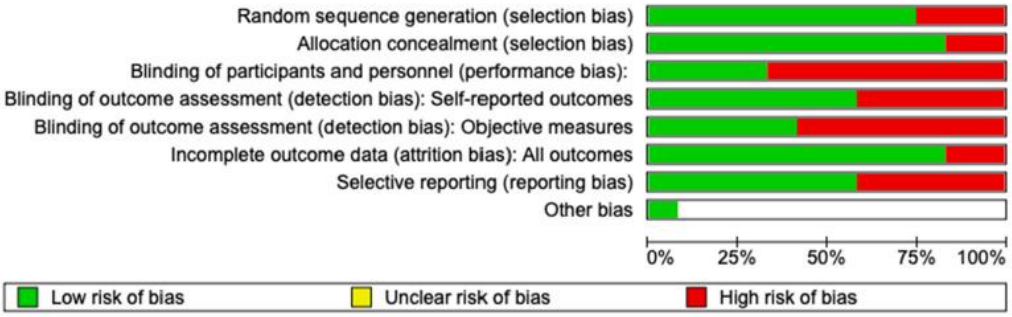

Fig. 4. *Risk of Bias domains of the included studies.*

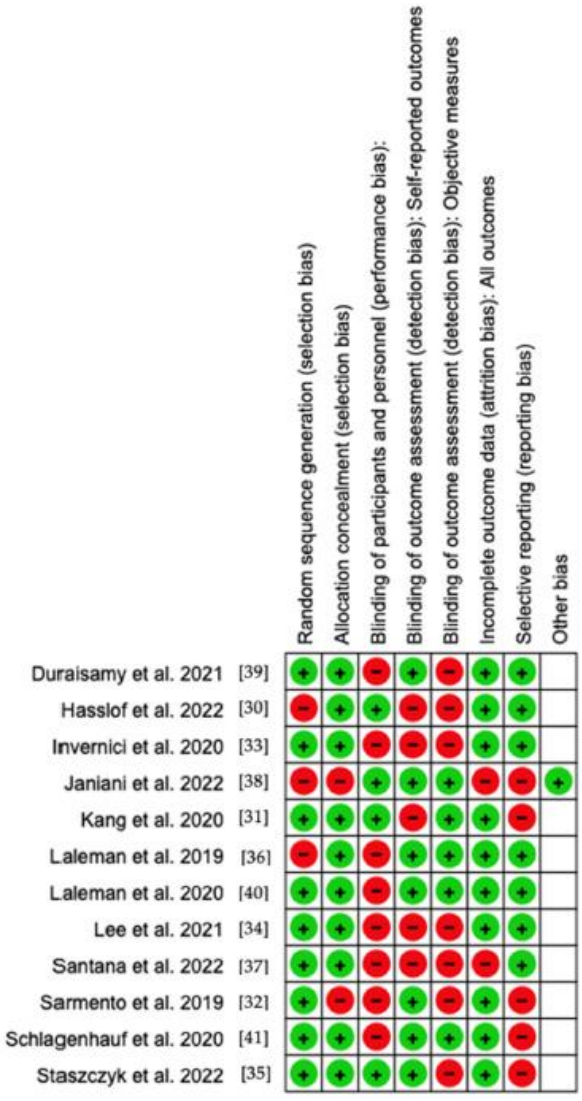

Fig. 5. *Risk of Bias domains of the included studies.*

DISCUSSION

This part of the study looks at the effects of probiotics that have been observed regarding the health of the mouth (15).

Dental decay and microbes linked to it

Probiotic bacteria (PBs) alter the host's microflora and maintain or restore a natural microbiota, both of which have beneficial effects on the host (16). Early microbial colonization and development of the mouth are especially significant

since pre- and probiotic therapies can affect the microbiota during the first 1000 days of life (17). Research indicates that ingesting lactobacilli or probiotic bifidobacteria may reduce the amount of S. mutans in saliva (18). Not every study, though, detects this effect. An RCT was carried out by Hasslof et al. to assess the effect of probiotic bacteria-containing drops on preschoolers' dental caries recurrence. The efficacy of probiotics and symbiotics in lowering S. mutans in children's saliva was assessed by Duraisamy et al (19,20).

Sarmento et al. investigated the impact of cheese on the overall number of microorganisms in the saliva of participants, and also the reduction of S. mutans using Lactobacillus casei. Janiani et al. investigated how children's plaque scores and salivary S. mutans levels were affected by ingesting probiotic milk and powder (21,22).

Chewing gum that incorporates Lactobacillus salivarius HM-6 Paradens reduced dental caries in children in preschool who had a lot of cavities, according to a clinical trial by Staszczyk et al (23,24). After a year of follow-up, the study saw a significant drop in the incidence and prevalence of early childhood caries, denoting that Lactobacillus salivarius HM-6 Paradens may be more functional for secondary prevention than primary prevention. Nevertheless, additional investigation is required to validate these results (25).

Periodontal Disease

Probiotics containing Lactobacillus reuteri have been shown to help with periodontal disease and gingivitis (26). Numerous indicators, including BOP, GI, PI, attachment level, and pocket depth, have improved, according to studies (27). It has been demonstrated that the Gram-positive bacteria W. cibaria CMU inhibits carious disease and treats periodontal disease. Because of its antibacterial and immunological qualities, Bifidobacterium animalis subsp. lactis HN019 (HN019) has been discovered to be beneficial in nonsurgical periodontal therapy (28,29). Re-instrumentation using ultrasonic tips in conjunction with L. reuteri probiotics dramatically boosted periodontal pain reduction (PPD), lowering the need for surgery and reducing the rate of advancement of the illness, according to research by Laleman et al. Further research is needed to fully understand the immunomodulatory processes of PBs in re-instrumentation (30).

Halitosis

Dong-Suk Lee et al. assessed how W. cibaria affected the subjects' halitosis (31,32). Participants were randomly designated to one of the groups (experimental or control), and after eight weeks, there were notable differences in the participants' subjective halitosis and life satisfaction in relation to dental health (33,34).

Mucositis and Peri-Implantitis

Santana et al. looked at the use of multispecies probiotics (PBs) as an adjuvant therapy for peri-implantitis (PiM) in a double-blind, randomized, controlled experiment (35,36). According to the study, probiotic treatment enhanced the clinical and immunological effects of traditional mechanical debridement (MD). The study did, however, admit its brief evaluation time and suggested more investigation to establish the probiotic therapy's long-term effectiveness for treating PiM (37,38).

In their investigation into the impact of PBs on non-surgical peri-implantitis therapy, Laleman et al. discovered that curettage and oral hygiene guidelines enhanced clinical characteristics (36). It was challenging to obtain completely healthy peri-implant tissue, suggesting that non-surgical treatment would not be sufficient to completely eradicate peri-implant inflammation (39,40).

Future studies ought to concentrate on more effective instruments, frequent probiotic drop application, and PB use for peri-implant stability maintenance (41). Given the variety of patient groups and the potential benefits of any given bacterial strain for oral health, it is very important to critically assess research findings (42).

CONCLUSIONS

Taking into account variables such as age, comorbidities, socio-cultural characteristics, and patient demographics while analyzing investigational data, even though each type of bacteria has the capacity to enhance dental health, it is important to assess each one independently (43,44). Probiotic bacteria have health benefits that include halitosis prevention, oral bacterial balance maintenance, and prevention of gum disease and tooth decay (45,46). Additionally, they fortify the immune system against oral infections (47,48). To understand their persistence in the mouth and their capacity to reproduce themselves and form biofilms, additional research is necessary in order to pinpoint any potential barriers or restrictions on their efficacy (49,50).

Author contributions

Conceptualization, A.D.I., F.I., A.M.I., G.P., E.X., F.B., F.S., L.M. and A.P.; methodology, A.D.N., C.C., P.L., F.C.T.. and A.P. software, F.I., F.S., G.D., A.D.I., P.L., F.S. and L.M.; validation, F.I., A.M.I., G.D., M.C., F.B, F.S. and P.L., formal analysis, A.D.I.,G.D., F.S., A.M.I., A.L., C.C.. and A.R.; investigation G.D., A.P., M.C., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I. and G.D.; data curation, G.P., P.L., C.C., A.P., E.X., A.M. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., C.C. and A.R.; writing-review and editing, F.I., A.P., L.M., A.D.N.; visualization, C.C. A.R., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T..; project administration, M.C., G.P., C.C, A.M.I. and A.R. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement
Not applicable.

Informed consent statement
Not applicable.

Data availability statement
Data are contained within the article.

Conflict of interest
The authors declare that they have no conflict of interest.

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Review

THE KEY ROLE OF THE PALATAL EXPANDER IN ORTHODONTICS

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ABSTRACT

Aim: This narrative review explores the anatomy of the palate and teeth, focusing on the role of Rapid Palate Expanders (RPE) in correcting maxillary transverse discrepancies. It emphasizes the importance of understanding anatomical features, treatment protocols, and the benefits and challenges associated with RPE applications, including advancements like miniscrew-assisted rapid palatal expansion (MARPE). *Materials and Methods:* A comprehensive literature review was conducted using PubMed, Web of Science, MEDLINE, Google Scholar, and Cochrane databases up to June 2022. Search terms included "Rapid Palate Expander," "RPE," "applications," and "therapeutic values." Two authors independently screened articles, removing duplicates and resolving disagreements through discussion. Backward citation tracking was performed to identify relevant studies. *Conclusions:* RPEs play a critical role in orthodontics, particularly for addressing transverse discrepancies in the maxilla. These devices are effective for treating conditions like cross-bites, which result from factors such as genetic predisposition, thumb-sucking, or delayed tooth loss. RPE treatment realigns the maxillary and mandibular arches, enhancing function and oral health. Timing is crucial; rapid and slow expansion protocols cater to patients at different stages of skeletal development, with MARPE offering effective solutions for older individuals. However, adverse effects such as discomfort, phonation issues, and recurrence necessitate meticulous diagnosis and individualized treatment planning. Advances in RPE design and techniques have improved patient comfort and outcomes, reinforcing their importance in achieving stable, long-term results in managing maxillary deficiencies.

KEYWORDS: *Rapid Palate Expander (RPE), Maxillary transverse discrepancies, Cross-bite correction, Miniscrew-assisted rapid palatal expansion (MARPE), Orthodontic treatment protocols.*

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INTRODUCTION

The anatomy of the palate and teeth is fundamental to functions like eating, speaking, and maintaining oral health. The palate, located in the roof of the mouth, is divided into the hard palate and the soft palate. The hard palate is the anterior, bony part formed by the palatine processes of the maxilla and the horizontal plates of the palatine bones. It provides a rigid barrier between the oral and nasal cavities and is covered by a mucous membrane with ridges called rugae that aid in manipulating food during chewing. The alveolar processes of the maxilla and mandible contain teeth, which are necessary for speech and chewing. The 32 permanent teeth that humans normally have are divided into four categories: incisors, canines, premolars, and molars. Each type of tooth has a unique structure and purpose. Canines shred, premolars smash, molars grind, and incisors slice food (1).

Rapid Palate Expander (RPE) is a tool used in orthodontics and orthopedics to help maintain good transverse concordance between the upper and lower jaws, particularly in early childhood. Rapid expansion of the upper jaw has gained prominence in modern orthodontics as a safe, predictable, and effective method of correcting maxillary deficits in the transverse plane across a wide range of clinical conditions. The application of RPE is especially important in treating conditions such as cross-bite, where the transverse relationship of the teeth is altered, causing the upper teeth to be positioned posteriorly to the lower teeth, either in the front or back of the mouth. Cross-bites can result from various factors, including genetic predisposition, prolonged thumb-sucking, delayed tooth loss, or abnormal jaw growth, and if left untreated, can lead to significant oral health problems (2).

Understanding the precise etiology and selecting the appropriate treatment protocol is crucial in managing transverse discrepancies. Various types of expanders and expansion protocols—rapid, slow, and semi-rapid—offer different advantages and challenges, necessitating careful diagnosis and individualized treatment planning. Recent advancements, such as mini-implant-assisted rapid palatal expansion (MARPE), have further refined the approach, minimizing adverse dentoalveolar effects and enhancing outcomes, particularly in patients beyond the peak of pubertal growth (3). Despite potential adverse effects like discomfort, speech difficulties, and risk of recurrence, RPE remains a cornerstone in orthodontic treatment, underscoring the importance of accurate diagnosis and tailored therapeutic strategies to achieve optimal results. In this narrative review we address these important aspects with a discussion of the different kinds of RPE and their application.

MATERIAL AND METHODS

Literature research was conducted on PubMed, Web of Science, MEDLINE, Google Scholar, and Cochrane, until June 2022, using keywords: “Rapid Palate Expander”, “RPE”, “applications”, and “therapeutic values”. Two authors conducted the research independently, duplicates were eliminated, and articles were collegially discussed. Backward literature research was conducted on selected articles.

RESULTS

Anatomical features

The anatomy of the palate and teeth is fundamental to functions like eating, speaking, and maintaining oral health. The palate, located in the roof of the mouth, is divided into the hard palate and the soft palate. The hard palate is the anterior, bony part formed by the palatine processes of the maxilla and the horizontal plates of the palatine bones. It provides a rigid barrier between the oral and nasal cavities and is covered by a mucous membrane with ridges called rugae that aid in manipulating food during chewing. The alveolar processes of the maxilla and mandible contain teeth, which are necessary for speech and chewing. The 32 permanent teeth that humans normally have are divided into four categories: incisors, canines, premolars, and molars. Each type of tooth has a unique structure and purpose. Canines shred, premolars smash, molars grind, and scissors slice food (1,4).

Definition of Rapid Palate Expander

Rapid Palate Expander (RPE) is a tool used in orthodontics and orthopedics to help maintain good transverse concordance between the upper and lower jaws, particularly in early childhood (2).

Rapid expansion of the upper jaw has gained prominence in modern Orthodontics as a safe, predictable and effective method of correcting maxillary deficits in the transverse plane in a wide range of clinical conditions.

Applications of RPE in different conditions

Indeed, there are situations where the palate causes a stretched or contracted palate (referred to as an occlusive palate), which reduces the arch space available for teeth to deteriorate permanently. In these cases, an interceptive treatment

involving dental sutures is required in order to correct the direction of tooth growth and allow superior teeth to accommodate inferior teeth in order to maintain good occlusion and function (5,6). The superior teeth are expected to adapt with their correct occlusal positions to "recognize" the inferior teeth, based on precise transversal and antero-posterior diameters (7). More in detail, a situation in which it is important to use the RPE as an interceptive treatment is represented by the cross-bite, in which there are changes in the transverse relationships of the teeth, determining that the upper teeth are in a posterior position compared to the lower teeth, with the 'exact inversion of the normal position (8). Cross-Bite can occur in the anterior (front) or posterior (back) of the mouth and may involve one or multiple teeth. An anterior cross-bite affects the front teeth, causing the upper front teeth to sit behind the lower front teeth. A posterior cross-bite, on the other hand, involves the back teeth, where the upper molars and premolars sit inside the lower molars and premolars (9). A number of issues, such as hereditary predisposition, prolonged thumb-sucking, delayed tooth loss in infancy, or aberrant jaw growth, can result in cross-bites. If left untreated, this illness can result in a number of oral health problems. These problems include temporomandibular joint (TMJ) disorders, which can lead to jaw pain and dysfunction, tooth wear and erosion from irregular biting habits, and gum disease from misaligned teeth that are more difficult to clean (10,11).

In particular, the causes that determine a transversal underdevelopment of the maxillary structure are represented by oral breathing, genetic factors, low tongue posture, spoiled habits such as prolonged sucking of the pacifier or finger; it's important to underscore that the size of the airways is fundamentally determined by the soft tissue that covers them and by the skeleton, so an obese patient, with an increase in adipose tissue, is more likely to experience a narrowing of the airways (12,13). This picture compromises the muscular forces (which influence, as already mentioned, the development of the craniofacial skeleton) which can cause, over time, the long and retrusive facial characteristics observed in healthy children with OSAS as they assume an extended head posture to increase the volume of the retroglossal and hypopharyngeal airways as the adenoid tissue hypertrophies and obstructs nasal airflow (14–16). These children also make use of mouth breathing, which involves caudal movement of the tongue and medialization of the buccal muscles against the jaw, which can cause transverse jaw constriction. All these characteristics outline the profile that is commonly described as "adenoid facies"(17,18).

According to precise etiology, the use of RPE will be different; for example, before talking about therapy, it will be necessary to evaluate whether the cross is only a dental problem, therefore caused by an incorrect dental inclination, or of the bone base, where there is a reduced width of the palate, with shortening of the transverse diameters (3). On the other hand, age plays a very important role; in fact, in the presence of growing subjects it will be possible to expand the palate at bone level, in addition to having a dental effect, the separation of the median palatine suture will be obtained, however, in subjects who have passed the peak of pubertal growth, i.e. in adults, only a dental effect will be possible and for the correction of serious bone discrepancies and therefore widening the palate in adults the possibility of carrying out a maxillofacial surgery operation will have to be evaluated (19).

More in detail, the median palatal suture corresponds to the facing of the two palatine processes of the maxillaries. It grows by 1mm per year until 5 years of age; after that period growth corresponds to 0.25 mm per year until the end of puberty. Thereafter the residual growth is 1.5 mm. After the age of 10 years, the first bony digitations have already begun to be seen. The median palatal suture remains at the sinfibrosis stage on average until the age of 12-14 years in female subjects and 14-16 years in male subjects, and then slowly begins to ossify (20).

Once the diagnosis has been made and it is understood whether the contraction is caused by dental or skeletal factors, it will be possible to choose the type of device for the expansion and widening of the palate or, simply, to give the right inclination to the teeth (21,22).

Several types of expanders have been proposed in the literature, with the latest models incorporating smaller expansion screws with a comfortable design and easy hygiene. The reduced size of the latest generation of screws, in addition to improving patient comfort, allows for higher device placement within the palatal vault.

In the literature, three types of protocols have been identified to obtain maxillary expansion in growing patients: rapid maxillary expansion (RME), slow maxillary expansion (SME) and semi-rapid maxillary expansion (23,24). The latter has aroused less interest in the orthodontic field compared to the first two, which have been the subject of more frequent studies and analyses. Despite broad consensus on the importance of correcting posterior crossbites early, there is still a lively discussion on what the optimal therapeutic approach and ideal timing are. Opinions on the matter are many and often conflicting (25,26).

The introduction of the concept of rapid maxillary expansion has had a significant impact on the clinician's ability to treat transverse discrepancies (27,28). In theory, RME applies direct forces to the posterior teeth without allowing time for collateral tooth movements to develop, thus allowing the applied force to transfer to the palatal suture, resulting in

greater suture opening than tooth expansion. Using greater forces, the treatment objectives are to maximize orthopedic expansion and minimize dental expansion, as the latter tends to recur due to buccal tipping movement (11,29).

In contrast, slow maxillary expansion uses lighter forces and requires months to achieve the same amount of expansion that RME achieves in weeks (30). However, some animal experiments have shown that SME allows for more physiological adaptations to suture separation, with a lower potential for recurrence. The biological principle underlying this therapeutic strategy is that the main resistance to be overcome to obtain the opening of the mid-palatine suture does not reside in the suture itself, but in the surrounding tissues, such as the circummaxillary structures and the sutures of the middle third of the face (31).

The advantages and disadvantages of each protocol have been analyzed for many years, but the topic remains controversial and not entirely clear, as different devices and methodologies complicate comparisons (32). Despite the ongoing dispute, the scientific literature agrees that both therapeutic protocols guarantee maxillary expansion. However, slow expansion appears to be associated with more physiological effects on sutural tissues, greater tooth movement, and fewer orthopedic effects than rapid expansion (33,34). Both protocols, RME and SME, cause lateral flexion of the alveolar process and buccal displacement of the anchoring teeth, although with variable degrees of inclination. Displacement of teeth beyond the anatomical alveolar limits can damage the periodontium, compromising the longevity of the tooth. Both expansion modes produce an increase in the transverse diameter at the molar level, which can be evaluated in the three planes of space (35). Therefore, in the absence of solid scientific evidence, the choice between rapid and slow maxillary expansion must be based primarily on accurate diagnosis and appropriate treatment design. Therapeutic planning to resolve a transverse deficit must also consider the various etiological moments, the extent of the discrepancy between the maxilla and mandible and the transverse diameters of the dento-skeletal structures (36,37).

Rapid palatal expansion using skeletal anchoring (MARPE) can be used in patients in advanced stages of skeletal development to avoid adverse dentoalveolar consequences and maximize the potential for skeletal expansion. In recent years, maxillary expansion has undergone notable evolutions. In 2010, Lee first described the effectiveness of palatal expansion with a hybrid miniscrew and tooth-anchored expander (MARPE) in a single case report of a 20-year-old (38,39). This hybrid expansion method, which uses two miniscrews and anchoring of the upper first molars, did not show the undesirable effect of excessive dentoalveolar expansion, thus being considered an alternative to SARPE in late adolescents requiring skeletal expansion. After 10 years, a recent meta-analysis confirmed that mini-implant-assisted rapid expansion (MARPE) could reduce buccal alveolar bone loss compared to conventional tooth-supported palatal expansion (38,40,41) (Fig.1).

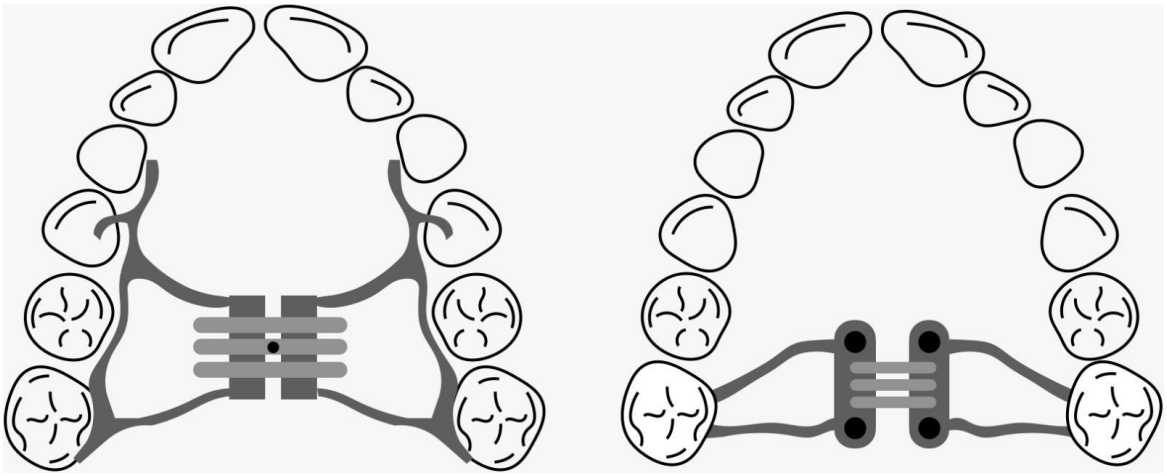

Fig. 1. *Conventional REP on the left and MARPE on the right.*

There are a number of adverse effects to be aware of. The primary adverse impact is an excessive growth of the dentoalveolar bone. The alveolar process bends during RPE if the posterior teeth, which act as anchors, tilt too much laterally. This movement has the potential to harm the periodontium, resulting in issues like recession of the gums, loss of periodontal attachment, and shrinkage of the alveolar bone. This fast swelling of the palate often causes pain and discomfort. When the midpalatine suture is forced apart, headaches, nasal discomfort, and jaw and tooth pain might result. Additionally, a brief increase in tooth movement may be experienced by some patients, which may add to their discomfort (42,43). The development of diastemas, or spaces between the front teeth, is another common adverse effect. These gaps arise from the palate's expansion dividing the two hemimaxillae and creating a space between the top central

incisors. Even while these gaps eventually close on their own, more orthodontic treatment could be necessary to completely fix them.

Phonation and swallowing may be momentarily impacted by rapid palate expansion. When the palate is reshaped, it can affect how sounds are produced and how the tongue aligns itself while swallowing. This can lead to speech difficulties and swallowing issues, which often go away after treatment is finished (44,45).

The palatal sutures and nearby structures may sustain damage from the force used during the RPE in fewer and more severe instances. If the pressure is applied too much or in the wrong place, it may result in problems including bone necrosis or nerve injury. Those with stiffer bones or those whose palatal suture has already partially calcified are more likely to experience palatal suture fracture or injury to the surrounding soft tissues (46,47).

Finally, following fast palatal extension, there is a considerable probability of recurrence. To ensure the stability of the outcomes, a longer retention phase might be required if the upper jaw has a tendency to revert to its initial position (48,49). The tendency of the periodontal tissues and sutures to realign in their original position may be the cause of recurrence, particularly if the patient fails to wear post-treatment retention devices as directed (50).

CONCLUSIONS

Understanding the anatomy of the palate and teeth is crucial for functions like eating, speaking, and oral health. The palate, located on the roof of the mouth, is divided into the hard palate and the soft palate. The hard palate forms a barrier between the oral and nasal cavities and aids in chewing, while the alveolar processes of the maxilla and mandible house the teeth, which are essential for speech and chewing. Humans typically have 32 permanent teeth, categorized into incisors, canines, premolars, and molars, each designed for specific functions. Orthodontics uses tools like the Rapid Palate Expander (RPE) to correct transverse discrepancies between the upper and lower jaws. RPEs are particularly effective in early childhood, addressing issues such as cross-bites, which can stem from genetic factors, thumb-sucking, or delayed tooth loss. The expansion of the upper jaw helps realign teeth and improve oral health. The application and timing of RPE treatment are critical, with options for rapid, slow, or semi-rapid expansion based on individual needs. Advances such as miniscrew-assisted rapid expansion (MARPE) offer solutions for older patients, minimizing adverse effects. Despite benefits, RPE use can lead to temporary discomfort, phonation and swallowing issues, and the possibility of recurrence, emphasizing the need for accurate diagnosis and careful treatment planning. Through proper use, RPEs play a vital role in correcting maxillary discrepancies and promoting long-term oral health.

Author contributions

Conceptualization, A.D.I., F.I., A.M.I., G.P.,F.B., L.M., E.X. and A.P.; methodology, A.D.N., C.C., P.L., F.C.T.. and A.P. software, F.I., G.D., A.D.I., P.L., F.B., F.S. and L.M.; validation, F.I., A.M.I., G.D., M.C. and P.L., formal analysis, A.D.I., A.M.I., A.L., C.C.. and A.R.; investigation G.D., A.P., M.C., F.I. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.S., F.I., L.M., F.B. and G.D.; data curation, G.P., P.L., C.C., A.P., E.X., A.M. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., C.C. and A.R.; writing-review and editing, F.I., A.P., A.L., A.D.N.; visualization, C.C. A.R., A.D.N., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I., A.D.N. and F.C.T..; project administration, M.C., G.P., C.C, A.M.I. and A.R. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement

Not applicable.

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Not applicable.

Data availability statement

Data are contained within the article.

Conflict of interest

The authors declare that they have no conflict of interest.

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Review

THE THERAPEUTIC POTENTIAL OF CBD IN DENTISTRY: APPLICATIONS, MECHANISMS, AND FUTURE PROSPECTS

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ABSTRACT

The most well-known cannabinoids in cannabis are Δ9-THC, CBD, and CBN, and it has a long history of medical use. Since CBD does not have conventional behavioral effects, it cannot be held accountable for the psychotropic effects of cannabis. In today's world, CBD is becoming more and more popular, and its potential in dentistry is growing. Research has demonstrated that CBD has certain therapeutic benefits, according to a number of subjective findings. On the other hand, there is an abundance of inconsistent data concerning the therapeutic potential and mode of action of CBD. This synopsis offers a synopsis of the molecular mechanism of CBD and the latest findings of potential oral health benefits. It emphasizes the biological characteristics of CBD that make it a good candidate for use in dentistry, even though the primary focus of the industry.

KEYWORDS: *Endocannabinoid System (ECS), Cannabidiol (CBD), CB1 and CB2 Receptors, Anti-inflammatory Properties, Therapeutic Applications*

INTRODUCTION

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GPR55, sometimes referred to as CB3, is another member of the G-protein coupled receptor (GPCR) family that binds to endocannabinoids (ECs). It is believed to affect cognitive function, physical activity, and memory and is widely expressed throughout the brain, particularly the cerebellum (1). Because it is found in osteoblasts and osteoclasts, it also contributes to the metabolism of bone (2). Another cannabinoid receptor, GPR119, is predominantly present in gastrointestinal and pancreatic beta cells. It has a role in diabetes and obesity by directly modulating insulin release and indirectly influencing the generation of glucagon-like peptide 1 (GLP-1).

The primary psychoactive ingredient in cannabis, Δ9-THC, functions as an agonist for CB1 and CB2 receptors, with a greater preference for CB1. Through research on the pharmacology, toxicity, and therapeutic potential of Δ9-THC during the past 70 years, the endocannabinoid system (ECS) has been discovered and characterized (3). In addition to endogenous ligands like anandamide (AEA) and 2-arachidonoylglycerol (2-AG), the ECS also consists of CB1 and CB2 receptors as well as additional receptors like PPARα, GPR119, GPR55, and TRPV1. Enzymes like FAAH and MAGL metabolize ECs (4,5). The ECS is engaged in many physiological processes; CB1 receptors are involved in immunological response, whereas CB2 receptors are involved in cognitive activities (6).

Although it has not been studied as much as Δ9-THC, CBD is a notable cannabinoid that is known to have effects on pain, anxiety, and cognition without the normal psychoactivity of cannabinoids (7). CBD can control the effects of THC and has a stronger affinity for CB2 receptors. When exposed to heat, cannabinoids that are produced in acidic forms undergo decarboxylation (8). In glandular trichomes, cannabis plants create cannabinoids that shield the plant from herbivores and environmental stressors. The antibacterial qualities of CBD help the plant remain resilient (9,10).

On account of its analgesic, antioxidant, and anti-inflammatory qualities, CBD has medicinal potential for treating a variety of illnesses, including cancer, neuroprotection, epilepsy, anxiety, and bone problems (11). Notwithstanding legal obstacles, CBD research has increased, resulting in forecasts of substantial industry expansion. The potential of CBD in the realms of dentistry and oral health is being highlighted by the exploration of its medicinal applications in these domains. Cannabis has been used historically for medical purposes since ancient times; in fact, references to its use date back to China in 3000 BCE (12).

Numerous ancient societies, such as the Assyrians, Egyptians, Greeks, and Romans, employed cannabis for its therapeutic qualities. However, because of legislative limitations and the popularity of synthetic fibers, its medical use decreased in the 20th century (13,14). Interest in cannabis study was rekindled by the identification of the ECS and the subsequent discovery of THC. The ECS indicates its evolutionary significance in physiology and survival, as it is found in many animal species (15).

In conclusion, the ECS controls a wide range of physiological functions through the interaction of endogenous ligands with CB1 and CB2 receptors. One important cannabinoid is CBD, which has a lot of therapeutic potential, particularly for its anti-inflammatory and neuroprotective properties (16,17). Cannabis has been used medicinally for a variety of reasons throughout history, and current research is still revealing new uses and advantages for marijuana in a number of areas, including oral health (18).

Biological Targets of CBD Action

1. GPCRs

Because of negative allosteric regulation, CBD can counteract the actions of cannabinoid receptors CB1 and CB2, even at low concentrations when its binding affinity is minimal. The main processes of CBD are related to serotoninergic 5HT1a receptors, which CBD favorably regulates (19). These mechanisms are independent of the endocannabinoid system (ECS). Additionally, GPR55, GPR3, GPR6, and GPR12 are among the orphan GPCRs that CBD targets, impacting neuropathic pain and cell survival. Furthermore, CBD interacts with high-affinity D2- and D3-dopamine receptors as well as μ- and δ-opioid receptors (20).

2. Ionotropic Recetors

With a strong affinity for ionotropic receptors, CBD inhibits TRPM8 and 5HT3a receptors while activating TRP channels (TRPA1, TRPV1, TRPV2, and TRPV4). Additionally, it inhibits voltage-gated calcium (Cav3.1/Cav3.2) and sodium (Cav3.3) channels, positively modulating glycine and GABAA receptors as well as cellular ion conductance (21).

3. Transporters

By blocking FABP protein uptake of anandamide, CBD interacts with endocannabinoid transporters to raise anandamide levels and intensify its effects. Additionally, CBD modulates the ABCG2 and ABCC1 transporters, which influences drug resistance and metabolic processes, and prevents adenosine uptake, altering anti-inflammatory responses (22).

4. Enzymes

Members of the cytochrome P450 superfamily are among the enzymes that CBD regulates, affecting drug metabolism. It targets lipooxygenases, COX1 and COX2, as well as FAAH activity, which affects lipid metabolism and inflammatory processes. Additionally, CBD affects enzymes involved in the metabolism of tryptophan and serotonin as well as mitochondrial complexes (23).

5. Nuclear Factors

CBD acts as a mild agonist on nuclear receptors such as PPARγ and modifies the expression of genes linked to inflammation by binding to Nrf2 (24).

6. Inflammatory Mediators

CBD primarily inhibits immune responses without interacting with cannabinoid receptors by regulating inflammation and cytokine production. It inhibits the release of pro-inflammatory cytokines via interfering with the JAK/STAT signaling pathway and the TRPV1 receptor (25). CBD promotes anti-inflammatory actions via the A2A receptor by inhibiting the activation of inflammasomes and regulating adenosine absorption. The use of CBD in the treatment of inflammatory illnesses is supported by our understanding of these mechanisms (26).

CBD in Dentistry

1. Oral Mucosa

CB1 and CB2 receptors are present in the oral mucosa, which is the first tissue to come into contact with cannabis. While CB1 receptors have the opposite effect, CB2 receptors promote the proliferation and development of epithelial keratinocytes (27). Additionally, CB receptors are present in the tongue's taste buds and connective tissue, where pathological circumstances alter how they are expressed (28). Limited evidence indicates that dental pulp CB1 receptors may target dental pain, and that activating these receptors may encourage the formation of dentin. CB1 and CB2 receptors control salivary production in salivary glands (29).

2. Periodontal Tissue

In periodontal tissues, CB1 and CB2 receptors are expressed, with expression patterns varying according to tissue circumstances. In a healthy periodontal ligament (PDL) and epithelium, CB1 receptor activity is higher, whereas CB2 receptor activity rises in the presence of germs. Because it inhibits bone resorption, promotes cell proliferation, and modulates inflammation, CBD has promise as a periodontal therapeutic (30). Additionally, it exhibits antibacterial qualities that help lower bacterial plaque and treat oral mucositis. Because of its osteoinductivity and biocompatibility, CBD may have beneficial effects in dentistry, which could lead to the development of CBD-based dental treatments (20-31).

DISCUSSION

There are a wide range of interesting applications for CBD in dentistry, including periodontology, oral medicine, oral surgery, endodontic therapy, and oral health. Future research questions, patents, and pertinent studies are reviewed in this section (32).

Endodontic Therapy (Direct Hooding)

Inflammation, discomfort, and necrosis can result from trauma or severe cavities that expose essential tooth pulp, which can stop root growth. By interacting with cannabinoid receptors in the dental pulp, CBD has the ability to promote odonto/osteogenic differentiation, which in turn promotes the migration, differentiation, and proliferation of dental pulp stem cells (33). Pulpal vitality is preserved as a result of enhanced collagen synthesis and mineralization. Additionally, CBD reduces pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α by inhibiting its activity. Additionally, by activating CB1 receptors, CBD boosts extracellular Ca2+ entry, which in turn promotes reparative dentin production in odontoblasts (34). Moreover, the expression of angiogenic and odontogenic genes such OPN, RUNX2, VEGFR1, ICAM-1, DSPP, DMP-1, and ALP is increased by activating CB2 receptors and the MAPK pathway.

Periodontal Therapy

Because of its anti-inflammatory characteristics, CBD has demonstrated the capacity to stop the loss of alveolar bone in periodontitis models. By selectively activating CB2 receptors, CBD reduces inflammation and pain without averting the negative side effects of activating CB1 receptors (35)-(36). By antagonistically interacting with NT, CBD prevents the production of interleukins and other inflammatory mediators, such as cytokines, chemokines, and pro-inflammatory growth factors.The NT-kB. Because of its anti-inflammatory properties, less oxidative stress is produced by a reduction in neutrophil and macrophage movement. Moreover, CBD induces TGFβ and raises AEA levels, which stimulate the formation of gingival fibroblasts and may exacerbate gingival fibrosis through cannabinoid and other receptors (37).

Oral Medicine

The effects of CBD on pain and inflammation are dose-dependent. Because of its antioxidant qualities, it may be used to treat oral mucositis, a disorder that causes excruciating ulcerations (38). Compared to traditional antioxidants, CBD may be more effective against pathological conditions like oral mucositis because of its synergistic effects. Though it doesn't quicken wound healing, it has demonstrated potential in enhancing epithelial alterations in ulcer lesions in vivo, thus further research is needed to determine how it affects keratinocytes (39). By inhibiting osteoclastogenesis, CB2 receptors have been shown to mediate the prevention of inflammation and alveolar bone loss in gingival tissues when synthetic analog HU-308 is administered in vivo (40). Large concentrations of CBD also inhibit the growth of important bacterial subpopulations within the subgingival microbiota, which is mainly made up of Gram-positive bacteria seen in dental plaque (41).

Traumatology/Surgery

Due to its promising biological and osteoinductive properties, CBD can be used to promote bone differentiation and cell migration through the ECS. The ECS's presence in skeletal sympathetic nerves and bone cells emphasizes how cannabinoids support bone mass homeostasis. (42,43). Increased collagen maturation, production of bone proteins, and mineralization are the results of CBD's stimulation of the PLOD1 gene. Because of these benefits to bone tissue's biomechanical characteristics and promotion of neobone formation, CBD is a useful therapeutic adjuvant for bone loss brought on by trauma or surgery (44).

Other Comorbidities

Because of its antioxidant qualities, CBD may be able to cure radiation and chemotherapy-induced oral mucositis. It works well to lessen nausea and vomiting, which lessens the harm these side effects have to the oral cavity (45,46). The anti-inflammatory and antioxidant properties of CBD are also beneficial for arthritic disorders, especially those affecting the temporomandibular joint. Additionally, CBD has demonstrated efficacy in lowering seizure frequency in epilepsy, which lowers the risk of oral injury during seizures. These two benefits are relevant to the management of hyperglycemia-associated oral health concerns (47).

Current Scientific and Technological Knowledge

The use of CBD in dentistry has garnered increasing attention; yet just one patent has been supported by research. The majority of patents center on formulations for oral care as opposed to illness treatment (48). The inexpensive cost of plant-derived substances and the inclination towards natural products make CBD a viable option for dental applications. There are, however, a few restrictions. Significant issues arise from the variability in CBD quality caused by environmental factors, the absence of established analytical methodologies, and potential contaminations (49). Consequently, to guarantee consistent therapeutic benefits and optimize the potential of CBD in dentistry, better regulation and standardization are required.

In conclusion, the talk emphasizes the wide range of dental uses for which CBD has potential (50). Because of its anti-inflammatory, analgesic, antibacterial, and osteoinductive qualities, it is a strong contender to improve oral health therapies. To fully reap its benefits, though, more study and legislative changes are necessary (27,19).

CONCLUSIONS

Even while CBD is becoming more and more popular for medical purposes, there isn't much research on the topic and not many patents for its use in dental health. The potential of CBD as an analgesic, antibacterial, anti-inflammatory, and osteoinductive agent in periodontology and dentistry is highlighted by current research. However, dental floss, mouthwash, and toothpaste are the main topics of the patents that are currently in existence.

The medical potential of Cannabis sativa for a range of illnesses has increased interest in the plant. There are now more study prospects because of the DEA's categorization of CBD for uncommon epileptic syndromes. Cannabinoids, such as CBD, show promise in treating pain and may be able to prevent the overuse of opioids. Numerous studies demonstrate that pure CBD has little side effects.

Many unlicensed CBD products are now on the market without any standards, making unsubstantiated health claims. Products made from cannabis have anti-inflammatory qualities, but it's not clear how well they work in addition to or instead of conventional pain care. Although oils high in CBD are thought to be safe, one should be aware of any adverse effects and drug interactions.

Healthcare providers need to understand that not everyone is a good candidate for CBD products, just like with other drugs. Although CBD has been shown to be effective in treating seizures, its wider therapeutic recommendation is limited by its variable pharmacological and clinical effects as well as the profiles of the products that are sold.

Author contributions

Conceptualization, F.S., A.D.I., F.I., A.M.I., F.B., L.M., G.D. and A.P.; methodology, A.D.N., B.F.P.P., R.V.G., F.C.T. and A.P. software, B.F.P.P., G.P., A.D.I., R.V.G., L.M., F.B. and F.S.; validation, F.I., A.M.I., G.D., M.C. and B.F.P.P.; formal analysis, A.D.I., A.M.I., L.M., B.F.P.P. and R.V.G.; investigation, G.D., A.P., M.C., F.l. and F.C.T.; resources, A.M.I., A.P., A.D.I., F.I., F.S. and G.D.; data curation, G.P., B.F.P.P., R.V.G., A.P. and F.C.T.; writing-original draft preparation, A.D.I., A.M.I., G.D., B.F.P.P. and R.V.G.; writing-review and editing, F.I., A.P., F.S., A.D.N. and G.P.; visualization, B.F.P.P., R.V.G., A.D.N., A.P., F.S. and A.D.I.; supervision, G.D, F.I., A.D.I., A.M.I., F.B., L.M., A.D.N. and F.C.T.; project administration, M.C., G.P., B.F.P.P., A.M.I. and R.V.G.. All authors have read and agreed to the published version of the manuscript.

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Review

OPTIMAL SKELETAL ANCHORAGE IN ORTHODONTICS: A SCOPING REVIEW

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ABSTRACT

The purposes of this paper was to compare the relevant findings in the literature regarding different orthodontic anchorage, the biologic background for a desired control of anchorage and the different kinds of techniques depending on the movement that must be obtaine. A scoping review of the literature on orthodontic anchorage has been done on US National Library of Medicine on Medline database (www.ncbi.nim.nih.gov/ pubmed), Scopus, Livivo, Google Scholar, and international books relevant to the topic. The keywords chosen were skeletal orthodontic anchorage and (miniscrew). Fifteen articles, focused on the quality of anchorage and biological basis, were selected. The traditional notion of a linear relationship between force and tooth displacement is challenged by individual variations and the phenomenon of hyalinization. Strategies for maintaining anchorage include distributing forces over multiple teeth to avoid excessive pressure and traumatic effects. Different anchorage methods, such as reinforced, stationary, and cortical anchoring, aim to control tooth movement while minimizing unwanted side effects, emphasizing the importance of optimal force application for effective orthodontic treatment. This review provides orthodontists with a comprehensive guideline to optimize skeletal anchorage.

KEYWORDS: *Orthodontic anchorage; skeletal anchorage; miniscrew; dental anchorage, tooth movements, TADs*

INTRODUCTION

Orthodontic anchorage has been a subject of significant debate in the literature, establishing itself as a fundamental requirement for effective treatment (1,2).

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Edward Angle introduced the concept of orthodontic anchorage, defining it as the resistance to undesired tooth movement. The aim is to maximize desired tooth movements and minimize the unwanted ones. Opting to promote the movement of a tooth inevitably triggers a corresponding and opposing impact on adjacent structures (3,4).

In the history of skeletal anchoring, the earliest studies date back to the 1980s/90s and refer to the studies in maxillofacial surgery of Costa and Raffaini; these techniques involved wire fixation, which consisted of drilling the bones by passing a wire through them, which was then clamped between two drilled bones (5,6).

This was followed by rigid fixation using surgical screws, which later became purely orthodontic (7). Skeletal anchorage-supported systems are usually proposed in complex cases that otherwise would be impossible to treat unless by orthognathic surgery treatment (8–11).

Temporary Anchorage Devices (TADs) in orthodontics are small titanium screws or mini-implants used to provide a stable anchorage point for moving teeth with precision. These devices are inserted into the jawbone through a minimally invasive procedure, usually under local anesthesia. Once in place, TADs serve as a fixed point around which teeth can be moved, allowing for more controlled and efficient orthodontic treatments.

One of the primary advantages of TADs is that they offer a stable anchorage independent of other teeth, which means they don't rely on patient compliance and don't cause unwanted movement of surrounding teeth. This stability allows for complex tooth movements that might be difficult or impossible with traditional braces alone. For example, TADs can be used to move teeth vertically (intrusion) or horizontally (distalization or mesialization), correct dental midline discrepancies, and manage other complex movements with greater ease (8,11,12).

Another significant benefit is the potential reduction in overall treatment time. Because TADs provide a fixed anchorage point, they can make tooth movements more efficient, often leading to faster treatment results. Additionally, TADs are temporary and can be easily removed once their purpose has been served, typically with minimal discomfort and no lasting impact on the jawbone. This combination of precision, efficiency, and ease of use makes TADs a valuable tool in modern orthodontics (13).

Orthodontists, during treatment planning, must take into consideration the anchorage calculation, the stable anchorage, which is a fundamental requirement for successful orthodontic treatment and an essential part of therapy that expands the options available in orthodontic practice (14,15).

A precise treatment plan must consider that, when a force system is applied to one or more dental elements, two different systems are created: the tooth-bone reaction, i.e. the active force applied to the teeth and the reactive force of the bone that opposes movement, and the periodontal reaction (5).

Skeletal anchorage, whether lost or acquired, can be considered a method for the correction of malocclusions (16–18).

To better understand the mechanism of action of skeletal anchorage, it is useful to re-member the difference with dental anchorage and its relative classifications: it can be classified according to displacement and available space; it can therefore be of four types: maximum if the anchorage unit presents no displacement or less than 1/3 of the available space, medium if the anchorage unit presents a displacement of 1/3 to 2/3 of the available space, minimum if the anchorage unit presents a displacement of more than 2/3 of the available space and absence of anchorage when the dental elements move by the same amount (19,20).

Skeletal anchorage opened the doors to innovative and avantgarde orthodontic treatments; indeed, temporary skeletal anchorage provides for a rigid system allowing the orthodontists to move teeth without using other teeth as reactive unit. Sometimes the insertions of miniscrews need a strong interaction between the orthodontists and the oral maxillo-facial surgeon.

The main applications of anchorage are related to:

- Expansion (MARPE and SARPE)
- Mesialisation/distalisation
- Space closure
- Molar Uprighting
- Intrusions/extrusions (21,22)

These movements can also be performed simultaneously (23).

If the objective is to avoid or minimize tooth anchorage, it is possible to rely on palatal expanders anchored on miniscrews (Miniscrew Assisment Rapid Palatal Espansor, MARPE), therapy indicated between the ages of 15 and 25 (24,25) (Fig.1).

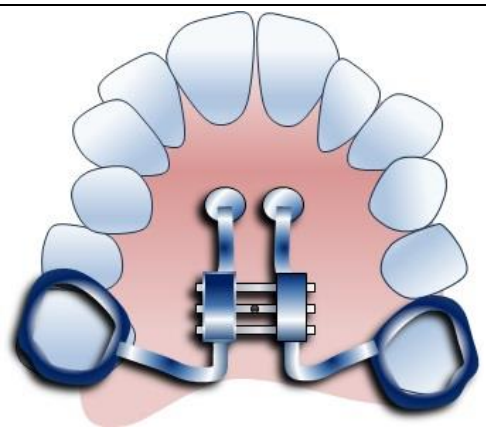

Fig. 1. *Schematic image of MARPE device.*

This device involves the insertion of two or four miniscrews in the palate, usually located lateral to the medial palatine suture, and may be hybrid anchored if it has bands on the molars or fully skeletal anchored if there is no dental support; it also has the advantage of avoiding anchoring on the dental elements, which is useful if these are compromised or not present, and it is also useful for avoiding the dento-alveolar reaction to expansion forces, even if this is minimal (26–28).

Through SARPE (Surgical Assisted Rapid Palatar Espansor) it is possible to separate the palatine suture with a possible increase in transverse diameter and nasal volume; the age at which this treatment is indicated is over 25 years (29–31) (Fig.2).

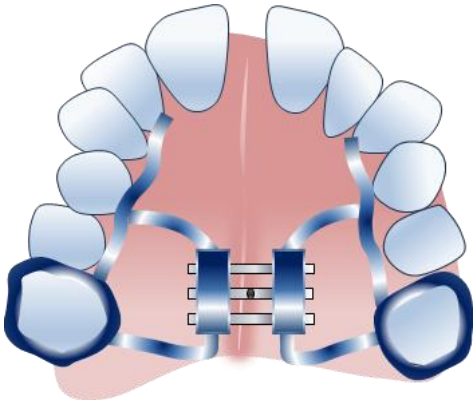

Fig. 2. *Schematic image of SARPE device.*

As far as the mechanics of distalisation are concerned, these can take place:

(a) By means of fixed rails, in which the miniscrews are positioned on the midline through a rigid structure located at the level of the tooth's center of resistance; there is then a connection with a molar band and compressed springs with small screws that tighten and prevent the spring from unloading forward (32–34).

(b) Using distalisation arms: these cases utilize non-cooperative mechanics, i.e. mechanics that do not require the patient's cooperation (35,36).

The springs, depending on their type, support opening or closing movements (16).

Mini screws are also widely used in pre-prosthetic orthodontics; by connecting a spring to a temporary crown placed on the implant, in fact, it is possible to determine the up righting of the element (37).

There are countless publications on orthodontic anchorage. Sometimes, precisely because of this, the clinician gets confused (38,39).

The aim of this study is to scrutinize the optimal orthodontic anchorage systems, iden-tifying those currently in use and those obsolete, assessing anchorage from a biological standpoint, and exploring the influence of orthodontic and occlusal force systems on the cellular response of the periodontium supporting dental anchorage.

MATERIALS AND METHODS

Protocol and Registration

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.

Search Processing

With a restriction on English-language studies published between 1 January 2014 and April 2024, PubMed, Scopus, and Web of Science Medline, LILACS, Open Grey and Cochrane Library databases were screened. To undertake an evaluation+ that is current with the recent 10 years, this time frame was selected. The search approach included the following Boolean keywords: (skeletal orthodontic anchorage) AND (miniscrew).

Eligibility Criteria and Study Selection

It has been chosen to analyze studies with patients aged between 7 and 20 years. Studies included patients with mixed or permanent dentition.

The two steps of the selection process were the appraisal of the title and abstract and the complete text. Any article that fit the following requirements was taken into con-sideration: (a) clinical trials including human intervention; (b) comparison of the therapy to other interventions; (c) English language complete text. Publications (such as me-ta-analyses, research methods, conference papers, in vitro, or animal experiments) that lacked original data were not included. Titles and abstracts from the preliminary search were retrieved and evaluated for relevance. Full articles from pertinent research were acquired for further analysis. The retrieved studies were assessed for inclusion using the aforementioned criteria by two different reviewers (A.M. and G.S.).

Data Processing

A.M. and G.S., two reviewers, independently evaluated the studies' quality based on selection criteria after doing a database search to extrapolate the findings. To use with Zotero, the chosen articles were downloaded in the 6.0.15 version. A senior reviewer (F.I.) was consulted in order to address any disagreements between the two writers.

PICOS Requirements

The PICOS (Population, Intervention, Comparison, Outcome, and Study Design) criteria, which are used in this evaluation, encompass population, intervention, comparison, outcomes, and study design (Table I).

Table I. *PICOS criteria.*

Category	Details
Population	Children, adolescents, and adults (age range 7–20 years)
Intervention	Use of skeletal anchorage and miniscrews
Comparisons	Before and after treatment using the most common skeletal anchorage techniques and their comfort
Outcomes	Different results obtained by the most commonly used skeletal anchorage techniques
Study Design	Clinical Trials
Keywords	"skeletal orthodontic anchorage" AND "miniscrew"

Study selection

A total of 217 articles on the topic were identified within the Pubmed database and 512 within the other search databases. All articles found were entered into EndnoteWeb® to eliminate duplicates. The first phase consisted in reading the titles and eliminating all those that were not strictly relevant: many of them (446) were therefore excluded due to wrong topic be not suitable for eligibility criteria chosen. For titles that were not clear enough to determine with certainty whether to include or exclude the article, we decided to read the abstract.

Inclusion and exclusion criteria were considered for studies selection; the inclusion criteria were entered according to the acronym PICO and are as follows:

- Studies whose patients presented an age range between 7 to 20 years
- Studies whose patients presented mixed or permanent dentition.
- Studies performed from 2014 to the present (april 2024)
- Systematic reviews and meta-analyse were excluded.

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyzes) guidelines were used for the review.

This operation permitted 128 studies, whose materials and methods were screened. 112 of these were excluded because they did not meet the previously established selection criteria (wrong out-come, population and study design). Finally, 16 articles were included for qualitative synthesis.

Two reviewers independently took care of data collection and data confirmation was undertaken by a third reviewer; using an Excel spreadsheet, all the parameters analyzed, useful for the review, were entered.

In particular, the items selected in the calculation table were divided as follows: title, year of publication, journal, author, abstract and keywords.

RESULTS

The included articles that met the selection criteria were randomized clinical trials, prospective clinical trials and retrospective clinical trials.

The studies were conducted within hospital and clinical facilities.

The study sample concerns young male and female patients between the ages of 11 and 23 undergoing orthodontic treatment in which the various anchoring methods were monitored. The studies reported in this article were conducted within hospital and clinical facilities.

In the selected articles, the use of the following anchoring systems has been reported: hybrid mini-implant-supported rapid maxillary expansion (MARME), intermaxillary Class III elastics (C3E) anchored by a hybrid hyrax (HH), MGBM System (MGBM) and the Distal Screw appliance (DS), miniscrew, transpalatal arch, MARPE and Hyrax, FRS, Hessix appliance, miniscrew-anchored maxillary protraction, elastics (C3E) anchored by a hybrid hyrax (HH), Herbst appliance with miniscrews, Miniscrew and molar blocks, rapid palatal expansion (RPE) and miniscrew-assisted RPE (MARPE), Forsus Fatigue Resistant Device. The main applications for which miniscrews were used in these studies are correction of class III malocclusion, distalization and palatal expansion.

DISCUSSION

Biologically, the best anchorage involves a periodontium without any change in tissue turnover (40). The periodontal ligament and the surrounding alveolar bone are characterized by a turnover determined by local and systemic factors (5,41). In approximately 2 days the number of osteoblasts and osteoclasts increases and, if the vascularization of the periodontal ligament is maintained, the alveolar wall begins to resorb in the direction of the applied force (5,12).

Anchorage maintenance was traditionally based on a hypothesis, as claimed by Quinn and Yoshikawa, about the existence of a linear relationship between force and the degree of tooth movement. This hypothesis, however, does not remain valid. Weinstein in 1967 demonstrated that the displacement of a single element is possible with a force even lower than 4 g. Subsequently, several authors demonstrated that there is no relationship between the amplitude of the force and the degree of dislocation and that individual variations overwhelm the variations in force (42–44). Furthermore, Brudvik and Rygh reported that even mild forces may be able to generate hyalinization around the active unit. Therefore, it is as if the level of force acting on the reactive unit corresponds to the force necessary for the displacement and leads to a loss of anchorage (45). The minimum threshold of the level of force necessary to produce tooth movement is not yet known but we know that this depends on the individual response to the interaction between orthodontic and occlusal forces. Therefore, the hypothesis that more teeth automatically offer more resistance to tooth movement cannot be supported (46).

In approximately half of the selected articles, results were reported in which a significantly relevant difference compared to the control group was not highlighted.

The biological background of the miniscrew anchoring

A good anchorage, whether skeletal or dental, reflects the stability of the reactive unit and depends on the cellular activity of the periodontium (5). This is possible if the forces acting on the periodontal ligament and surrounding bone remain below the threshold that promotes tooth movement. A stable occlusion is characterized by a balance of forces acting on the dental elements. In an ideal anchoring situation this balance is maintained (47).

The application of orthodontic forces displaces the teeth embedded in the viscoelastic periodontal ligament (5).

Subsequently the surrounding bone is deformed, and this is recorded by the osteocytes. Through a complex cell-to-cell communication system, osteocytes promote stem cell differentiation along the alveolar surface and in adjacent bone (48).

If the vessels are completely compressed, then the cells will die from ischemia and hyalinized areas will develop. During the hyalinization period, the cells lining the alveolar surface will disappear and, at the same time, the osteoclasts

will differentiate into medullary spaces to begin the removal of bone through an erosive process. No tooth movement can occur until the bone is stripped of its lining cells (48).

It follows that the use of more elements in the reactive unit compared to the active unit al-lowed for greater load distribution, thus maintaining the force below the threshold of each single tooth present in the anchoring unit.

Considering the duration of the stimulus, it has been shown that even the positioning of a band and a short-term mechanical load are sufficient to activate the cell population of the periodontal ligament (5). Various 'anchoring devices' are used both for preparing the anchor and for maintaining it. These are generally inserted prior to the onset of active mechanics. When treatment begins with the 'preparation for anchoring' phase cellular activity is initially stimulated at the anchoring unit (36). When retraction begins, the cellular activity in the periodontal tissue of the active unit will decrease, while the cellular population located in the anchoring unit will be intensively activated. Since it is the cellular activity of the periodontium that facilitates tooth movements, it is recommendable, from a biological point of view, to increase cellular activity at the level of the elements that will be necessary to move and keep the cell population found in the anchoring unit quiescent. Therefore, the principle regarding the preparation of the anchoring is in complete contradiction with the idea to keep cellular activity as inert as possible in the reactive unit to achieve maximum anchoring (5,49).

Risks of Losing Anchorage

An alternative strategy to improve anchoring is to increase the stiffness of the arches inserted into the reactive unit. In this regard, transpalatal and lingual arches are recommended (10,50,51). The insertion of a rigid arch can be the final step, following leveling, after a gradual increase in size and rigidity of the wires. Paradoxically, this procedure would increase anchorage loss. In fact, it is rarely possible to produce a totally rigid and passive wire, as even minor activations could alter the cellular balance and lead to a loss of anchorage. There are two possible solutions to avoid this loss: either you adapt the wire to the study models and bond the brackets directly to the wire before bonding, or you solder the baseplate wire directly and then proceed with bonding. The second solution is recommended if subsequent leveling or intra-arch movements are not planned (52).

The loss of Anchorage, however, is a method of correcting malocclusions when reciprocal movements are desired.

Sometimes the front teeth act as anchors, sometimes the back ones. They include:

- the loss of total anchorage posteriorly on the two maxillae in cases where the anterior relationships are aesthetically good on the horizontal plane, but it is desired to reduce the posterior vertical motion;
- the loss of total anterior anchorage on the two maxillae in cases of bi-protrusion;
- the loss of antero-superior anchorage, which allows the reduction of the upper proalveolia when the lower arch is well organized, even if the upper molars are in II;
- the loss of antero-superior and postero-inferior anchorage in cases of Class II div. 1 with extraction.
- the loss of antero-inferior anchorage in Class III cases.

Naturally, combinations of the different anchorage losses are possible based on the skeletal and dental characteristics (53,54).

Reciprocal Tooth Movement

In a reciprocal situation, the forces applied to the teeth or to segments of the arch are equal in intensity and distributed similarly along the periodontal ligament (55). The essentially identical teeth are subjected to the same force distributed similarly along the periodontal ligament and move towards each other for an identical amount of space (55). An example of mutual dental anchoring occurs when two upper central incisors, separated by a diastema, are brought into contact through the application of an active spring (5). The anchoring capacity of a tooth is related to the root surface and therefore to its periodontal ligament area. The larger the root, the larger the surface over which the force will be distributed, and vice versa (5,31).

Reinforced Anchoring

When more teeth or an extraoral structure are involved in the anchoring, the reaction force to the movement is distributed over a larger surface of the periodontal ligament (44). This helps avoid subjecting the periodontal fibers of a single tooth to excessive and sometimes harmful pressure loads, thereby reducing the pressure on the anchor units (56).

For example, following the extraction of a first lower premolar, strengthening the anchorage by adding the second molar to the posterior dental segment modifies the existing relationship between the root surfaces involved (38).

This redistribution of pressure minimizes trauma and pain, creating an advantageous anchor by making use of different areas in the anchor sectors (5,57).

Stationary Anchoring

The term refers to the advantage gained by contrasting the bodily movement of one group of teeth with the tipping movement of another group (57).

For instance, if a lower premolar has been extracted, orthodontic equipment can be used to close the space created by the lack of the dental element through the lingual version movement of the anterior sector and the bodily movement of the rear sector (51).

The realization of this strategy requires the use of light forces (5,58).

Using heavy forces severely compromises this method of anchorage control, as excessive movement of the anchoring sector occurs, making the movement of the anterior dental elements inferior (59).

Differential Effects of Very Heavy Forces

If tooth movement is hindered by the application of very heavy forces, it is possible to use an an-choring method in which the movement of the tooth segment with the greatest periodontal ligament surface occurs (48). However, traumatic effects can occur, so this type of anchoring management is inadvisable.

Cortical Anchoring

Orthodontic bone anchoring has undergone strong growth in recent years. The cortical bone is much more resistant to resorption, and tooth movement is significantly slowed down when a root encounters it (49,57).

Some authors have suggested applying a torque to the roots of the posterior teeth to bring them against the cortical plates (60).

However, continuous forcing of a root against the cortical plate can lead to very slow movement and root resorption, with possible perforation of the cortical bone (61).

Bone anchoring represents a synchrony in induced tooth-bone movement (5).

Anchorage refers to a resistance applied against unwanted tooth movement (44).

Since the aim of biomechanics is to minimize unwanted side effects and maximize desired tooth movements, the most obvious solution for controlling anchorage is to concentrate the forces necessary to produce tooth movement at the desired point and dissipate the reaction forces by distributing them on as many teeth as possible, keeping the pressure as low as possible on the periodontal ligament of the anchoring teeth (51).

Dental response to different pressures, where higher pressure produces greater tooth movement than that induced by lighter pressure, allows some teeth to move more than others, even if some unwanted movement is observed (6).

The dental elements undergo a movement initially proportional to the intensity of the pressure exerted on the periodontal ligament (50). The pressure on the periodontal ligament is determined by the force used, divided by the area of the ligament itself, over which the force is distributed (55).

Tooth movement increases proportionally to the pressure up to a certain level of force, beyond which it remains constant, creating a plateau of effective orthodontic pressure and decreasing when the pressure level is too high (5). The optimal force for orthodontic movement is therefore the lightest force capable of producing a pressure that induces a maximal response (62–65).

The application of greater forces, although equally effective in producing tooth movement, would be excessively traumatic and would unnecessarily stress the anchorage.

CONCLUSIONS

The present review permits to conclude that a good anchorage reflects the stability of the reactive unit and depends on the cellular activity of the periodontium. This is possible if the forces acting on the periodontal ligament and surrounding bone remain below the threshold that promotes tooth movement. A stable occlusion is characterized by a balance of forces acting on the dental elements. In an ideal anchoring situation this balance is maintained.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Review

THE EVOLUTION OF UPPER ARCH DISTALIZATION SYSTEMS: A SYSTEMATIC REVIEW

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ABSTRACT

II Class malocclusions may be skeletal or dentoalveolar and are considered for treatment high priority. They cannot always be solved with an extractive therapy and the arch space must be created or modified with orthodontic devices. Distalization of the upper arch is a technique to gain space that can help to solve a II Class malocclusion from maxillary overshoot or dental mass in the upper arch. This study aims to analyze the current knowledge in the literature on the treatment of II classes by distalization of the upper arch, to clarify which is the most effective method and therapy for the resolution of the orthodontic case, when it is not possible or desirable to recover space exclusively with the help of extractive therapy.

KEYWORDS: *Molar distalization, Orthodontics, Aligners*

INTRODUCTION

Knowledge of the biology and genetics of splanchnocranium growth is the main means of understanding how the alterations in the growth and development of the craniofacial complex often are at the root of malocclusions (1).

Facial growth is closely linked to genetic factors responsible for the individual's genetic heritage. Other factors that may influence genetic expression are environmental factors, such as health status, diseases, pathologies, or syndromes, nutrition, and physical activity. Positively, malocclusions are not exclusively the prerogative of genetic heritage, and it is possible, in several cases, to intervene with orthodontics.

In the physiological growth of the splanchnocranium, a balance is formed between the genetic equipment and the environment which condition each other: when this balance is not established, the harmony between the interconnected structures is also gradually established, which will eventually lead to the establishment of a skeletal malocclusion (2).

Class II is a high-priority malocclusion, and a significant percentage of patients are classified with this kind of problem, whether skeletal or dentoalveolar. The high priority of treatment depends on the complexity of the class

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rehabilitation starting from a maxillary problem and the link between the right age to exploit the patient peak growth. A Class II malocclusion can result from a skeletal problem and an excessive growth of the upper maxilla; or from a dento-alveolar problem, that needs retraction and rehab of the superior arch space. The case can't always be solved with extractive therapy and the arch space must be created or modified with orthodontic devices. Molar distalization is a method of space rehabilitation recommended for normodivergent, hypodivergent subjects, and deep bite cases. Molar distalization can cause, as a consequence of the extrusion of the posterior dental elements, an increase in the vertical dimension, and changes in the occlusal plane and the mandibular position. Distalization is contraindicated in subjects with hyper-divergent profiles or even open skeletal bites. The extra-oral traction was the first device used for the Class II molar distalization treatment. The extra-oral traction must be worn for 12-14 hours per day to be effective and implies that the outcome of the therapy depends on the patient's compliance (3,4).

The clinician can also use the trans-palatal bar, a device that is fixed close to the palate does not require collaboration from the patient and can help the activity due to molar rotation. However, it is difficult to manage, as the activations require some manual skills by the clinician (5,6).

There are other therapeutic alternatives that do not require patient compliance to ensure the effectiveness of treatment and easier activation, such as distal-screw and distal-jet devices fixed on palatal mini-screw (7–11); Pendulum (8,9); Locasystem, a device that uses the nickel-titanium characteristics, as well as the springs in nickel-titanium with Nance appliance (12,13).

Other distalization devices use the "sagittal first" protocol, such as the Carrier® Motion device, that treats malocclusion on the sagittal plane to rehab the malocclusion using dental-alveolar compensation in head-to-head II Class, 1 division cases, for growing subjects and adults (9,14–20).

The aim of this study was to analyze current literature knowledge about upper arch distalization devices to establish the most functional and efficient equipment and therapy for II-class malocclusion rehabilitation.

MATERIALS AND METHODS

To conduct this study, the keywords "molar distalization" and "orthodontics", connected by the logical connective AND, were entered in the PubMed search engine. This search yielded 516 results. The screening phase is continued using as a first filter the publication date not earlier than 5 years, to obtain the most up-to-date results on the subject.

From these data, all articles that were not available in English and that had not been carried out on humans were excluded: it was thus possible to exclude 145 titles. All articles that did not have the free full text available were then excluded, thus obtaining 142 articles. In the last phase, studies considered off-topic were excluded: since they did not focus on the problems of molar distalization and revisions; articles dealing with invisible aligners were also excluded, as not considered in this study as a pure distalization device. Finally, 11 articles were selected satisfying the search criteria (Fig.1).

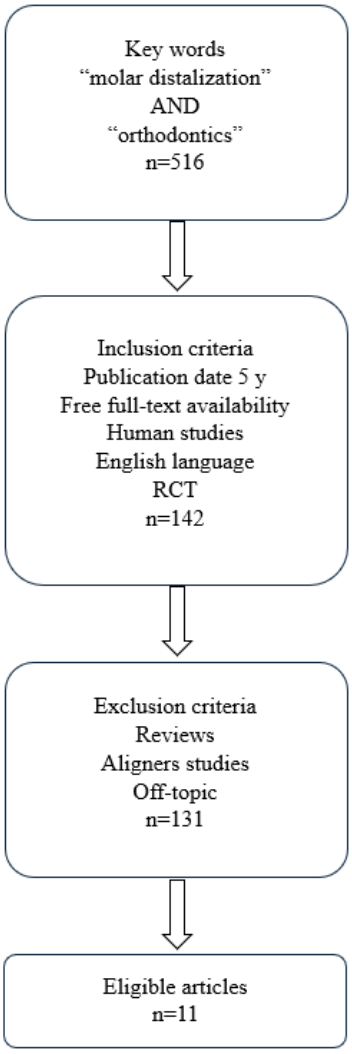

Fig. 1. *Screening and eligibility of the research.*

DISCUSSION

Vilanova et al published a retrospective study on the molar distalization performed by three different devices: Jones Jig, Distal Jet, and First Class appliance. The sample consists of 71 subjects and by cephalometric analysis studied the distalization degree of the first upper molar. The collected data indicate that the best performance is due to the use of the First Class appliance. In addition, the device is also the one that allows for the shortest therapy. An average of 2.48 mm is a satisfactory solution to the problem II class. However, there are also side effects in the use of all three devices such as mesialization of the premolars, mesial and distal angle of the first molars, and increased overjet. The First Class appliance is the device that produces the greatest distalization and with less time for treatment (21).

Jung et al, conducted a study on 40 patients comparing the use of two modified C-palatal plates. The study compares two groups of subjects with II Class malocclusion, hypo-divergent and hyperdivergent, by cephalographic analysis. The best distalization is in favor of hypodiverging patients. Also, the therapy time is shorter for these patients. Hypodiverging patients have more side effects in terms of tipping and distal angle of the first upper molars (22).

Hashem et al published a study with a sample of 60 patients, where they were treated orthodontically for the resolution of II Class malocclusion by molar distalization using the Carrier® Motion device and differentiating between subjects with second upper molar and subjects who do not have the second upper molar in the upper arch yet. Data analysis is done through a CBCT study. The greatest distalization appears to happen with the Carrier® Motion device when the second upper molar is not erupted, also leading to a reduction in treatment time. There is also no apparent difference in terms of side effects such as mesial and distal angle, tip, or torque of the first upper molar (23).

Kinzinger et al presented a pilot study, carried out on a sample of 10 patients, who were treated for II Class malocclusion using the Pundulum K device for molar distalization. All subjects have solved malocclusion obtaining an

average distalization around 3 mm. Side effects such as mesial and distal angle, as well as loss of anchorage of the first upper molar were also found in this study (24).

Schmid-Herrmann et al, in this retrospective study of 16 patients, analyze the effectiveness of Carrier® Motion distalization in achieving II molar class. The device in this study seems to solve malocclusion mildly by pure distalization; with only 0.96-0.80 mm of average. In addition, the use time is higher than in other studies, about 11.85-4.70 on average. There are many undesirable effects, like lower arch expansion, tipping, mesialization, extrusion of the first lower molar, and protrusion of the lower incisors (25).

Areepong et al, carried out a study on 59 patients to solve the II Class malocclusion with the Carrier® Motion device, dividing the sample into I Class skeletal malocclusion and II Class skeletal malocclusion. The devices achieve treatment goals, with similar time treatment in both groups, but there are more side effects in the skeletal II Classes. The side effects found are distal tipping and rotation of the upper canine, and mesial tipping and rotation of the first lower molar. The side effects are mainly due to the use of elastic bands, above all the mandibular teeth (26).

Poghosyan et al, treated II Class malocclusion on 17 patients with a customized orthodontic device for molar distalization with palatal mini-screws that prevent molar anchorage loss. There are side effects in the upper molars, like intrusion, rotation, distal tipping, distal premolar tipping, and central incisors palatal tipping. Also, data reported a clear upper intermolar distance increasing, due to the dental-alveolar device effects (27).

Vilanova et al conducted a study of 20 patients with palatal mini-screw cantilevers. The device achieves the treatment goals, and also an "overtreatment". Data also showed an intermolar distance increasing due to dentoalveolar device effects, such as upper first and second molar and premolar distal tipping, molar intrusion and rotation, and upper incisors tipping (28).

Taylor et al conducted a study on 35 patients, with two different therapies: Herbst and Pendulum. Both therapies achieved goals also due to skeletal effects in growing subjects, which compensate the skeletal II Class, especially with Herbst. The distalization with the Pendulum is slightly more effective than Herbst. There were side effects in both devices: lower molar mesialization, lower incisor proclination, upper incisor palatal inclination, upper molars mesial angulation with Herbst, and upper molars distal angulation with Pendulum (20).

Wilson et al published a study with 50 patients with II Class malocclusion, divided into a short Carrier® Motion therapy group and a standard Carrier® Motion therapy group. Both therapies are effective in molar distalization. There were also mandibular arch side effects, such as lower molar mesialization, distal molar, and premolar upper tipping. The short Carrier® obtained more upper molar rotation, canines distal tipping, and fewer overjet variations, compared to the standard Carrier® Motion (29).

Li et al, presented a case report with cervical-pull headgear therapy, followed by a fixed orthodontic device, to solve a II dental Class in an adult patient. Data were collected from model, photo, and cephalometric analysis. The treatment achieved the I Class producing a 5 mm molar distalization. Also, without side effects development such as tipping or molar rotations (30) (Table I).

Table I. *Summary table of selected articles for review.*

	Sample	Treatment time	Evaluation system	Appliance	Amount of distalization	
Vilanova et al, 2020	30 25 16	0.8 y 1.06 y 0.69 y	Cephalometric study	Jones Jig, Distal Jet, First Class	1.82 1.52 2.48	Best distalization
Jung et al, 2020	20 20	15.4 ± 1.3 months 14.9 ±1.5 months	Cephalometric study	modified C-palatal plates (MCPPs)	2.7 hyper-divergent 4.3 hypo-divergent	Best distalization
Hashem, 2021	30 30	19.2 ± 1.6 weeks 23.3 ± 2.3 weeks	CBCT study	Carrier® before 2nd molar eruption Carrier® after 2nd molar eruption	3.9 ± 0.8 mm 3 ± 0.6 mm	Best distalization
Kinzinger et al, 2021	10	17.2 weeks	Cephalometric and cast study	Pendulum K	3.28 ± 0.73 mm	Anchorage loss
Schmid-Herrmann et al, 2022	16	11.85 ± 4.70 months	Cephalometric and cast study	Carrier®	0.96 ± 0.80 mm	Mild distalization
Areepong et al, 2020	27	4.9 months	CBCT study	Carrier® for Skeletal Class I,	1.92 mm ± 0.80 mm	Best distalization

	32	4.2 months		Carrier® for Skeletal Class II	1.67 mm ± 1.56 mm	
Poghosyan et al, 2023	17	6.8 months	Cephalometric and cast study	Customized distalizator with mini-screw	3.8 mm	No anchorage loss
Vilanova et al, 2023	20	0.43 ± 0.13 years	Cephalometric and cast study	Miniscrew-anchored cantilever	4.54 mm	Overcorrection
Taylor et al, 2019	17	2.8 ± 0.8 years	CBCT study	Herbst	0.6 ± 1.7 mm	
	18	2.5 ± 0.7 years		Pendulum	0.2 ± 3.4 mm	Best distalization
Wilson et al, 2021	25	12.66 ± 1.05 years	CBCT study	Shorty Carrier®	1.83 ± 2.11 mm	
	25	12.73 6 1.07 years		Standard Carrier®	2.14 ± 1.34 mm	Best distalization
Li et al, 2021	1	31 months	Cephalometric, photo, and cast study	Cervical-pull headgear	5 mm	

RESULTS

In this study, we analyzed the current literature about distalization devices to establish the effectiveness of Class II malocclusion therapy with upper molar distalization. Class II is high-priority malocclusion treatment, which means that must be treated once discovered.

Detecting malocclusion means making a correct diagnosis and establishing the right therapy. The best therapy is customized to the individual patient and based not only on the malocclusion characteristics but also on the age of the patient and his compliance. The clinician's ability will be to understand all these characteristics to arrive at the most appropriate and functional therapy for the individual case. The malocclusion treatment of II Class can be complex when the choice falls on extractions or devices that require the use of mini-screws: both options are often considered invasive. When the patient refuses treatment with extractive therapy, space arch rehabilitation must be entrusted to specific and effective devices, for crowding or Class rehabilitation.

The articles selected for this study offer an overview of the possible alternatives for achieving a Class I. The selected studies show how different appliances can achieve the same result but differ in performance and treatment timing. The different treatment choices have in common the result achievement and the development of side effects: each type of device produces side effects, mainly due to the use of elastic bands (26), which can aid the achievement of I Class or become undesirable effects, such as anchorage loss (24,27,28).

It is not sufficient to analyze the Class you must consider the profile and muscles of the patient before embarking on an orthodontic path: hypercorrection (28) is a choice that the clinician adopts to prevent the risk of relapse and is an effective method of orthodontics. In addition to the side and dental-alveolar effects, the skeletal effects of equipment are highlighted. In the growing subjects the effects on the mandible arch joined with the dental effects represent forms of compensation that help to reach the I Class, underlining the importance of the growth factor when choosing a device (20,29,30).

Schmid-Herrmann et al carried out a study on Carrier® Motion that seems to show poor effectiveness of the device: among all articles considered in this research, it is the study where the least distalization is recorded, despite the therapy is still a success because the I Class is reached. Numerical data can be explained by combining it with data on three-dimensional effects. The I Class is reached not only by distalization but also through the distal rotation and tipping of the first upper molars. Also, as dental effects, there are compensations in the lower arch, such as the molar mesialization and lower incisors proclination. It is stressed, in fact, the greater presence of tipping, rather than body movements of the molars. At the skeletal and three-dimensional level, it is noted that the effects of distalization in the upper arch and mesialization in the lower arch can compensate for the Class. The side effects of compensation, both dental and skeletal, are important and become relevant in growing patients (25).

CONCLUSIONS

The articles in this review analyze the characteristics and effectiveness of the therapy of II Class with distalization. The operation of these appliances is based on biomechanical principles: the development of an action force necessarily involves the development of a reaction force. In addition, forces that do not develop near the tooth's resistance center

produce non-body movements of the tooth itself. Various studies show that II-class orthodontic appliances are effective in reaching the I Class.

Orthodontic appliances are not standard and their choice and use depend on the patient's characteristics: a growing patient will have different characteristics and possibilities than an adult patient: can be only dental in adults and both dental and skeletal in growing patients.

Each device will produce side effects and the knowledge of their limits and possibilities can be exploited as compensation mechanisms and help to achieve I Class.

Author contributions

Conceptualization, A.D.D., A.D.I.,M.C., C.M., F.I., A.M.I., G.D., S.C. and A.P.; methodology, A.P., F.I., G.D., A.M.I., A.D.I., D.D.V., S.C. and A.P. software, A.D.D., A.D.I., A.P., A.M.I., G.D. and F.I.; validation, F.I., A.M.I., G.D., S.C., N.C., M.C. and A.P.; formal analysis, A.D.I., A.M.I., G.D. and F.I.; investigation, G.D., A.P., A.M.I., F.l. and A.D.I.; resources, A.M.I., A.P., A.D.I., F.l. and G.D.; data curation, G.P., A.P. and F.I.; writing-original draft preparation, A.D.I., A.M.I., G.D., A.P. and D.D.V.; writing-review and editing, F.I., A.P., A.M.I., A.D.I. and G.D.; visualization, F.I., G.D., A.P. and A.D.I.; supervision, G.D, F.I., A.D.I.,A.M.I. and A.P.; project administration, G.D., A.M.I. and A.D.I.. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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Original Article

THE IMPORTANCE OF TERRITORIAL EMERGENCY MEDICINE THE ROLE OF ITALIAN SET-118 DURING THE COVID-19 PANDEMIC, A MULTIDISCIPLINARY APPROACH TO FACE THE NEXT PANDEMIC CATASTROPHE

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ABSTRACT

Aim: This study aims to evaluate the critical role of the 118 emergency service in Italy during the COVID-19 pandemic, highlighting the challenges faced, the strategies implemented to ensure continuity of care, and the lessons learned for future emergency healthcare improvements. *Materials and Methods:* The analysis focuses on the operations of the SET 118 service in the city of Taranto. Data were collected from reports and case studies documenting the service's response to emergencies during the pandemic. Key issues examined include resource availability, staff expertise, hospital reorganization, and the efficiency of the pre-hospital care network. Particular attention was given to the training and performance of first responders, as well as the integration of advanced medical equipment in emergency operations. *Conclusions:* The findings underscore the strategic importance of the 118 emergency system, particularly during a global health crisis. Despite the challenges of limited resources, reduced personnel, and increased demand, the service adapted through targeted interventions, such as optimizing resource allocation, enhancing staff training, and developing a hierarchical emergency network. Post-pandemic, these adaptations remain crucial, especially in addressing emerging health conditions like "long COVID." The case of SET 118 in Taranto illustrates the need for continued investment in high-level equipment and specialized personnel to ensure equitable access to emergency care across the country.

KEYWORDS: *118 SET Taranto ASL; Emergency Medicine; COVID-19; SARS-CoV-2; single nucleotide polymorphisms-SNPs; Long Covid*

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INTRODUCTION

This study highlights the critical role of the 118 National Units as key players in territorial emergency healthcare and frontline emergency medicine. Despite their importance, these services are still not fully recognized by local authorities or the central government. Additionally, collaboration between academic institutions and the 118 system remains limited, particularly in terms of data sharing and joint initiatives (1). To ensure readiness for future emergencies, it is essential to foster strategies aimed at improving the quality and efficiency of these services. The COVID-19 pandemic has posed one of the most significant challenges to global healthcare systems in recent years. The sudden surge of patients suffering from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposed the Italian healthcare system's lack of preparedness to handle such an unprecedented crisis (2). Healthcare workers faced numerous challenges simultaneously during the pandemic: providing care for a large number of patients with a novel, highly contagious disease; managing the needs of individuals with chronic illnesses, emergencies, or other conditions; and minimizing their own risk of exposure to SARS-CoV-2. To curb the spread of the virus, maintaining a sanitized work environment was critical (2,3). This involved employing automatic disinfection systems or atomizers with disinfectant solutions, along with frequent and meticulous cleaning of surfaces, particularly high-contact areas such as doorknobs, light switches, and workstations (4). During the early stages of the COVID-19 pandemic, healthcare workers had limited certainty about the disease. Patient outcomes were often unpredictable, and concerns about the pathogen's transmissibility dominated. Early studies indicated that more than 40% of hospitalized patients might require supplemental oxygen, with up to 15% needing mechanical ventilation. These procedures carried a well-documented risk of disease transmission to healthcare workers due to the generation of infectious aerosols (5).

Infection and death rates among healthcare workers, doctors, nurses and paramedics, caring for patients with COVID-19, reached shocking values in the first months of the pandemic (6,7).

This risk of infection was also caused by the extreme difficulties of providing care in a pre-hospital environment: these areas were difficult to control, patients were undifferentiated, personal protective equipment (PPE), resources were limited, and information was scarce.

During the lockdown period, the number of recorded home infection events also increased significantly (6,7).

However, there is little scientific data on the impact of the lockdown on COVID-19-related out-of-hospital deaths.

Major changes made in the EMS organization during the pandemic did not cause a significant increase in major trauma mortality in our large study population (6–8).

Context

The Taranto Provincial Operations Center "118" Territorial Emergency System (SET 118) is the publicly funded provider of ground ambulance and medical/paramedic services for the municipalities of the city of Taranto and its provinces in the Puglia region, which collectively comprise a mixed suburban and rural geography of 2467.35 km2, with a population of approximately 600,000 residents. The service employs over 700 paramedics and primary and advanced care physicians who operate a total of 65 ambulances and eight rapid response units during peak hours (9) (Fig.1).

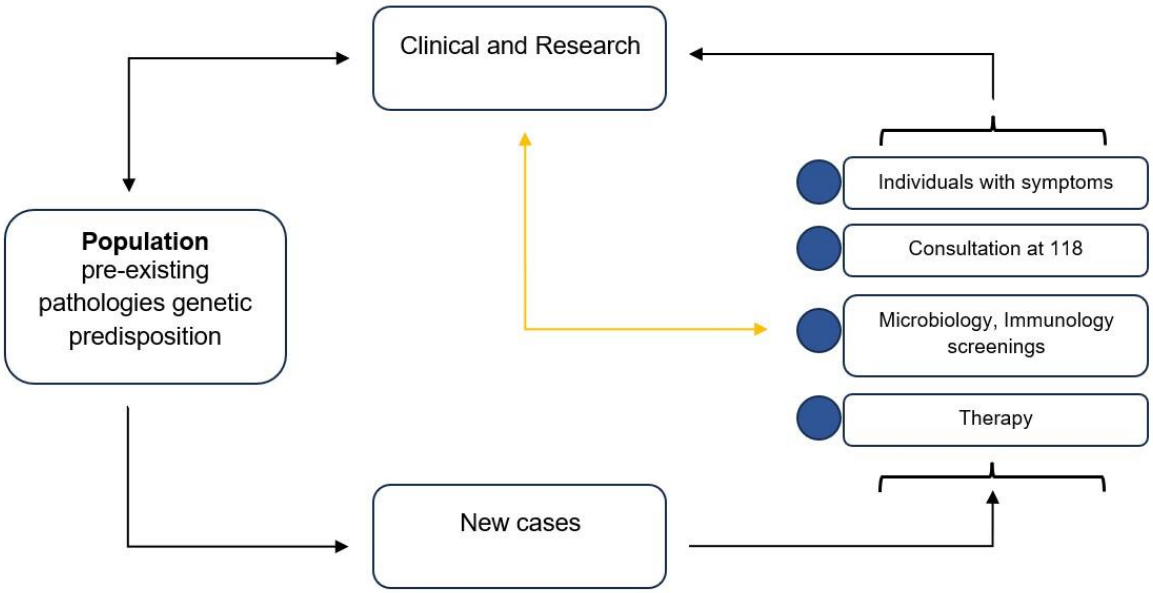

Fig.1. *The gate model proposed by Taranto's SET 118 assigns a special role of protection of the territory both to the 118 doctors and to the GPs, according to the Anglo-Saxon logic of entrusting the specialist reception unit of the hospital: the GPs and the doctors of the 118 have been proposed as the diagnostic vanguard to face and solve the first problems acting as filters before being directed to specialist cares. By this way it was emphasized a new management procedure with the intent of coordinating territory care and hospital care for implementing a systematic therapeutic plan.*

The province of Taranto is geographically divided into 6 health districts, each with a centralized headquarters from which crews start their shift in a "hub-and-spoke" and are then required to move to the territories or points requested by calling 118.

Ambulances are staffed by two paramedics and a doctor in PCP or ACP configuration and rapid response units are equipped with a single PCP. On average, 118 can respond to approximately 130,000 emergency calls per year (9–11).

As of April 2020, 118 was operating under a declared state of emergency throughout Italy, while SET 118 Taranto mobilized a joint union and management task force under the Incident Management System framework to develop local rescue.

Our task force included representatives with experience in medical and paramedical education, occupational health nurses, and safety professionals, with an immunology team serving as a liaison to the Emergency Operations Center and the Taranto Central Health Department service response to the crisis (9).

SET 118 Taranto continued to be one of several “hotspots” in the province for the care of community transmission of COVID-19, in part due to essential emergency personnel and territorial units (9,12).

MATERIALS AND METHODS

In April 2020, in the Puglia region, the local hospital SG Moscati and the 118 SET, were operating in a state of emergency for which they mobilized a joint union and management task force establishing a filter unit under the 118 management system framework to develop emergency first aid prior to hospital admission (13–15).

The task force included paramedics, nurses and physicians, medical immunology researchers and service operations with the leadership acting as a link with the Emergency Operations Center of the Province and the Region (12).

Over 1500 patients were admitted to our COVID-19 SET 118 emergency unit of the SG Moscati hospital in Taranto from March 2020 to November 2020 (16–20).

The majority were male [61%], 17 deceased [5%] with an average age of 72 years.

In that period, over 10,000 calls were collected by the Pre-hospital Health Service 118 operating in the province of Taranto. Patients who reported symptoms attributable to possible respiratory diseases were managed or who claimed to have had contact with people with suspected or confirmed SARS-CoV-2 infections (21,22).

RESULTS

The results of retrospective cohort studies from March to November 2020, which assessed the mortality rate in over 1300 ICU patients with confirmed SARS-CoV-2 infection, reported a higher mortality rate in male patients (12.5%) compared to female patients (9.6%) (9,12).

We promptly highlighted the phenomenon known as "happy hypoxia", coined by J. Couzin-Frankel (9,11,23). "Happy hypoxia" was an event that many patients experienced characterized by a sudden decline saved by high-flow oxygen support performed in intensive care. The etiopathogenesis was then related to a severe endothelitis considered as the main causal factor affecting the microcirculatory mechanism, followed by a silent and rapid necrosis process linked to a generalized increase in uncontrolled inflammatory processes leading to microvascular thrombosis, coma and then death (9,23,24). By monitoring many patients who showed rapid deterioration, we started to implement the use of arterial blood gas (ABG) analysis: it helped us to clarify some specific dynamics of the infection functional to the adoption of more effective therapies and treatments (25–28).

The ABG results were atypical, sign of an acute hypocapnic respiratory state accompanied by a hypoxemic condition with a compensatory alkalosis.

DISCUSSION

The multidisciplinary approach adopted by SET 118 demonstrated the importance of integrating emergency care, immunology, and diagnostics to manage COVID-19 effectively. The innovative operational model, including pre-hospital triage and the creation of specialized units, ensured effective allocation of resources and reduced hospital congestion. Findings such as the role of IL-6 and other inflammatory markers emphasized the need for targeted therapies.

The study also highlighted the role of genetic predispositions and immune dysfunction in disease progression, supporting the need for personalized medicine in pandemic responses. Observations of long COVID symptoms, including respiratory and neurological effects, underscored the complexity of post-infection management. With regard to gender: 40.96% of the calls came from female patients while 59.04% involved male patients (12,29).

The reported symptoms were fever, cough, general malaise, difficulty breathing, headache, cold, sore throat, conjunctivitis, alterations in taste and/or smell, gastrointestinal symptoms; a large percentage of these reported having had contact with patients affected by SARS CoV-2 without showing symptoms of infection.

Furthermore, patients who reported symptoms were divided into different age groups: 0-9 years, 10-19 years, 20-34 years, 35-59 years, 60-69 years, 70-79 years, 80-89 years, ≥ 90 years.

The dynamic development of hospital preparedness and the SET 118 response were essential to ensure the right effectiveness of healthcare due to COVID-19, to reduce the spread of infection and prevent hospitals from being overwhelmed due to the large number of severely ill patients infected with COVID-19 (9,12,29).

A key consideration was the resilience of 118 and its ability to adapt and manage beyond what was normally possible to provide pre-hospital clinical treatment, as COVID-19 resulted in a short period of rapid growth in demand. Therefore, the Taranto SET 118 was required to take proactive measures to manage emergency care requests, identify gaps in territorial intensive care and identify maximum case admission capacities (9,12).

Our model used data that included city performance indicators such as types of daily emergency calls, clinical priority level, ambulance types (Dual/ALS/BLS), and EMT/paramedic or physician crew data that were often collected during the previous non-pandemic period.

Second, we addressed possible limitations found by other Covid studies that may include the recognition and reporting of early signs and parameters of symptoms (fever, cough, difficulty breathing, loss of taste and smell, extreme tiredness, etc...) (9,12,29,30).

The overall program goal for SET 118 Taranto was primarily to prevent COVID-19 infections in the community while continuing to ensure high-quality care while minimizing the risk of hospital congestion.

For all that we can afford, we have identified three specific program goals: (1) Limit physician and paramedic exposure to the virus within the service to the extent reasonably possible; (2) Ensure hospital services and safety through frequent exposure to high-risk patient types and procedures; (3) Provide high-quality resuscitation care to critically ill patients, including performing aerosol procedures where they were typically indicated while avoiding overloading hospital care units (9).

With these intentions, we tried to solve the underlying medical intervention and logistics problems, based on some previous studies and our experiences before the COVID-19 pandemic.

The first step was to estimate and predict the travel or response times of ambulances using a coordinated system of information that changes between the camps and the Central Operations Quarter (COQ).

A specific intervention time interval was established based on the relationship between the number of calls or counts and the duration (the time elapsed between calls) with the data collected and the symptoms described by the patients.

Between each call and intervention, ambulances and responders were dispatched to each event, recording the critical times of each intervention (Fig.1).

An Innovative Operational Plan

At the beginning of the pandemic, the regulatory bodies that govern SET 118 practices in Puglia issued a regulation that recommended limiting ordinary tasks in all but extraordinary circumstances.

Included in this file were: limiting the use of nebulized drugs, continuous positive airway pressure, bag-mask ventilation, and high-flow oxygen administration, among others (9,12,29,30).

The SET 118 emergency response system to the COVID-19 pandemic consisted of multiple interconnected components, such as: the creation of a special pre-hospital COVID-19 unit that functioned as inpatient clinical treatment, the creation of an emergency management plan that included the infection prevention and control program, the creation of a special research unit to collect data, numbers, and scientific information to support clinical case management, coordination of communications, laboratory and diagnostic services (9,12,29,30). We conducted a systematic narrative review of emerging literature, supported by extensive medical research, to develop innovative diagnostic and therapeutic approaches. This effort allowed us to quickly gain a comprehensive understanding of the pleiotropic effects of SARS-CoV-2 and to formulate recommendations for managing COVID-19. These included guidelines for cardiopulmonary resuscitation and preventive measures for both confirmed or suspected cases and the general population. This research enabled us to establish a clear protocol that guided our operations in the field and within the COVID-19 Unit. While most of these recommendations were implemented, certain advanced procedures, such as the use of video laryngoscopes for intubation, could not be adopted due to their absence in our standard equipment. Our approach drew inspiration from high-performing emergency medical systems in Europe, incorporating best practices in human factors, such as pre-procedure checklists and crisis resource management. The task force responsible for developing these operational protocols relied on emerging evidence and consensus-driven methodologies. Regular team meetings, collaboration with ambulance staff, paramedics, and supervisors from critical departments (including intensive care, pulmonology, and infectious diseases), as well as simulated trials, helped refine these procedures and address potential weaknesses (25,31–35).

The SET 118 COVID-19 Pre-Hospital Filter Unit

We established a dedicated COVID-19 Special Unit equipped with a negative pressure system to manage the high influx of patients at the SG Moscati Hospital's 24-hour facility. Unlike standard operations, this unit operated autonomously, triaging patients based on physical and diagnostic parameters to prioritize those with severe conditions requiring aerosol-generating procedures and immediate medical intervention. The crew was mobilized via text alerts from ambulance or field teams for cases involving life-threatening conditions, such as dry cough, fever, cardiac arrest, altered consciousness, severe respiratory distress, or significant comorbidities. In addition, physicians and nurses in the admissions room could request the COVID-19 Special Unit's intervention when needed. The COVID-19 Special Unit was a "first-in" response that arrived promptly. The medical crew discussed the risk assessment with the paramedics already present while it was anticipated that patients would require the required full testing and diagnostic procedure (36–39).

A special "COVID zone" was created divided into two designated wings, "area A" where only our special staff were present during patient care and a "B or hot zone" area where ICU patients with PPE transported by air would remain and require high flow O2 masks.

Once the aerosolization procedures were completed, the staff on scene would assist with mask removal and the patient would be transported to the main hospital wards.

In COVID-19 SET 118, the physician in charge was responsible for liaising with the staff of the receiving facility to arrange the transfer procedure along with a detailed care plan before the patient was removed from the facility (40–42) (Fig.2,3).

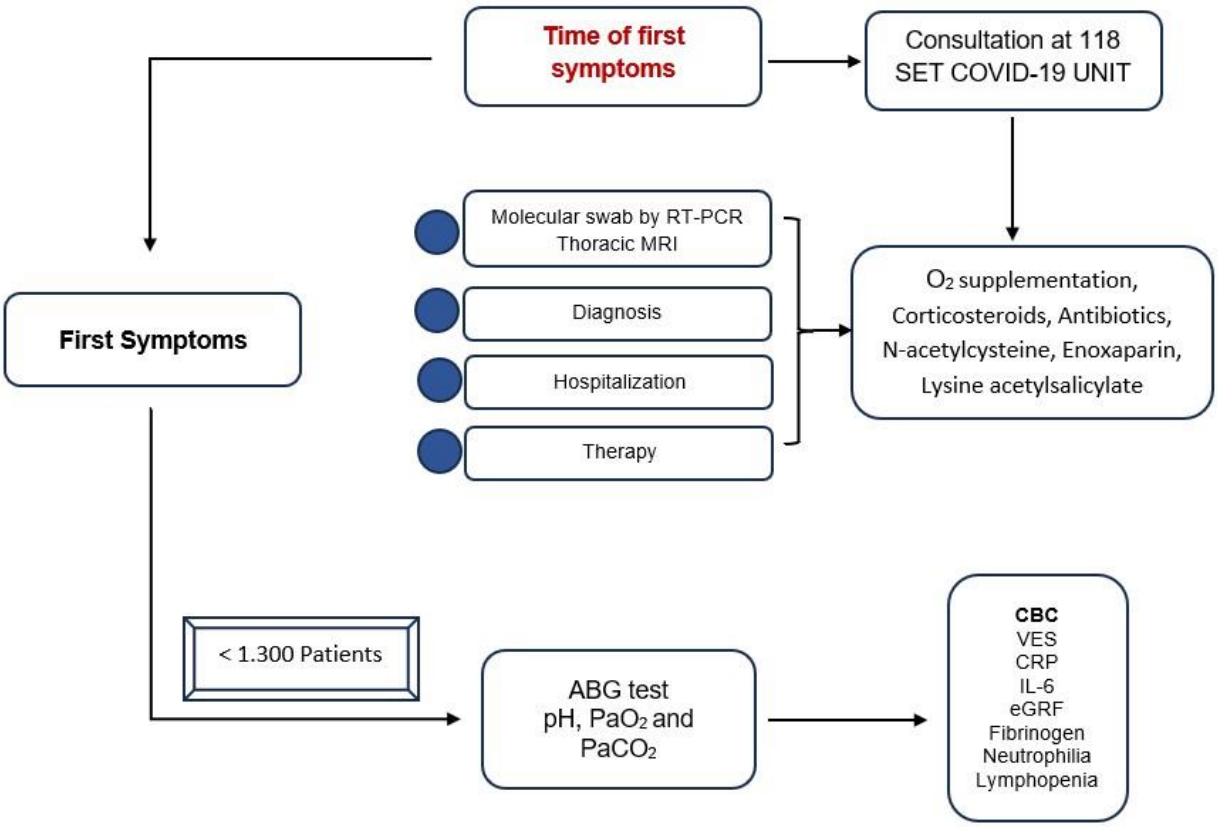

Fig.2. *The above algorithm allowed the 118 SET to reach tremendous results proceeding with a multi-disciplinary approaches by setting up a multi-centered therapy that combined O2 support, antioxidants, antiretroviral, cortisone and antibiotics to arrest systemic inflammation and prevent multi organs decay, model that was posing the base of an epidemic preventing action for the upcoming winter season.*

Prehospital emergency care of suspected COVID-19 patient with acute respiratory failure

Objective

Ensure the patient classified as a suspected or full-blown case with an initial clinical picture of acute respiratory failure and/or shock the appropriate and continued emergency therapeutic support during the phases of protected transport and temporary management pending the taking charge of the dedicated hospital units.

Methodology

At home and in a mobile station (ambulance) SET-118 → acute respiratory failure → therapeutic protocol

Oxygen therapy, as needed (SpO2> 90%):

- low flow (P/F > 300 mmHg): with nasal goggles: 2 - 4 L/min
- high flow (P/F < 300 mmHg): with face mask with reservoir: 15 L/min

Non-Invasive Mechanical Ventilation (Sp02< 90% or P/F < 200 mmHg + severe dyspnoea, use of accessory respiratory muscles - sternocleidomastoid, scalenes, paradoxical breathing-, RR > 35 breaths/min, pH < 7.35, pH> 7.2, Kelly 1-2) → CPAP: 5 - 10 cm H2O, with FiO2 of 60 - 90%

In more severe cases

In the presence of severe hypercapnia, altered mental status, hemodynamic instability, invasive mechanical ventilation IMV → ETI is indicated.

If the clinical picture compatible with bilateral interstitial pneumonia:
dexamethasone: 6 mg iv (associated with gastroprotection with pantoprazole 40 mg iv)
acetylcysteine f1300 mg iv: 2 flev in 250 ml of saline
enoxaparinafl: 1 fl4000 IU sc (in the absence of specific contraindications)

Intravenous drip with 5% glucose solution for nutritional purposes, in case of prolonged hospitalization.

Where an emergency vehicle with a non-medicalized but nursed crew intervenes on an unstable COVID-19 patient, the 118 Operations Center can guarantee remotely, through the CO118 doctor or even through the SET doctor specifically dedicated in service at the CO118 to carry out operations of "medical control online", real-time medical support for the administration of emergency therapy.

Fig.3. *The admission to the pre-hospital unit was created to avoid the overload into the hospital of the Taranto area. The admission phases were based on the clinical condition of each patient at the moment of 118 COVID-19 Unit acceptance. Based on symptoms and ABG parameters the therapies could be delivered home or organized and performed at the site.*

Measures, analysis and research, what we have achieved

We did not find much evidence on how measures were managed by area and population as the pandemic progressed, although some researchers and laboratories have already reported changes during the evolution of covid and during the advanced stages of the pandemic, for example, cases of long Covid (43–47).

Therefore, our evaluation, screening and research program was based on a manual review of all patient electronic health records (ePCR) data, convincing laboratory results conducted with a careful peer-review search of published works in viruses, microbiology and immunology regarding similar viral infections.

The data we focused on most was the percentage of calls involving high-risk COVID-19 with the intention of predicting, preventing and treating COVID-19 infection (30,48,49) .

To provide a contextualized basis for comparison, we also manually examined ePCRs for all admissions where COVID-19 patients were performed in the first and second waves (February-May 2020 and September-November 2020) of the pandemic that led to the drafting of articles for international publication (50–54).

We subsequently continued to explore both the scientific hypothesis related to the unique pleiotropism of SARS-CoV-2 and to create a new RT-PCR diagnostic method (1,26,55–57).

To do so, a collaboration was established with several departments, laboratories and universities (national and international) such as Aldo Moro University of Bari (Italy), Phan Chau Trinh University of Medicine (Vietnam) and

Lincoln University (Oakland California-USA). This teamwork allowed us to collect critical information that gave us a clearer picture of the situation (26,58–63).

SARS-CoV-2 pathogenic traits emerged slowly, helping us to assess a faster diagnosis, and realize a more effective therapy.

The results confirmed the distinctive patterns of the virus' mode of infection and its ability to evade immune surveillance and host responses (30,48). From our research, we learned about gender-based differences in COVID-19:

male patients were at higher risk of developing severe disease with increased mortality rate, and the time to intervention was crucial, 36 hours maximum from the first signs (25,64–68).

This picture suggested a progressive pulmonary microembolism, specular to an ongoing internal hypercoagulability with endothelial activation as a consequence of an uncontrolled increase in proinflammatory cytokines, the infamous "cytokine storm" (69,70).

The hypoxemic state has been described as an increase in minute ventilation leading to an uncontrolled hypocapnia, due to the rapid diffusion of CO2 into the tissues, CO2 moving about 20 times faster than O2.

This allowed us to understand the pathoanatomical and pathophysiological basis of COVID-19 respiratory failure, characterized by the presence of progressive and widespread damage to multiple organs and tissues and alveoli with interstitial thickening, deep vein thromboembolisms and impaired gas exchange. A scenario that was often accompanied by atelectasis and lung consolidations clearly visible on CT images with typical ground-glass opacities (9,12). Eventually, the combination of ABG analysis (partial saturation level of oxygen and carbon dioxide - PaO2 and PaCO2) and CT proved to be a better tool in the diagnosis of COVID-19 than RT-PCR swab alone (9,12).

The complete blood count of COVID-19 patients performed immediately after ABG tests indicated the presence of an infectious-inflammatory condition with involvement of lungs, heart and kidneys.

The most common picture was a high total white blood cell count (WBC > 10,000 cells/mcL), with marked neutrophilia and lymphopenia (71–76).

Laboratory results confirmed low levels of eGFR and 25OH-vitamin D, increased levels of troponin, IL-6, D-dimer and ESR and an increased level of fibrinogen. At that time, we were able to highlight a secondary phase of the infection triggered by aggressive bacteria, later confirmed also by other teams around the world.

The rapidity of multiorgan involvement with contextual septic course was in fact related to the presence of several pathogens identified in the BALF and blood culture, such as *Klebsiella spp, Candida albicans, Aspergillus, Pseudomonas spp,* which have proven to be a prerogative feature of the final phase of SARS-CoV-2 infection (9,12).

The mechanism of Sars-CoV-2 infection affects all cell types (epithelial, neuronal, myocyte) via the angiotensin-converting enzyme-2 (ACE2), followed by the cleavage of S by the transmembrane serine protease 2 (TMPRSS2) (77–83).

This explains the multiplicity of symptoms that characterize COVID-19 disease (9,12,23,24,38,69).

Our investigation allowed us to explain a very unusual phenomenon consisting of the aberrant increase in erythroid progenitors together with an anomalous decrease in platelet circulation both in critical hospitalized cases and after receiving the vaccine injection. Such observations together with hypoxia, hypocapnia, alkalosis, iron deficiency anemia and coagulopathies were seen highly correlated with an alarming degree of risk of death (69).

We were able to highlight the increased mean platelet volume (MPV) and platelet hyperactivity that we often found in COVID-19 patients with a reduced level in overall platelet count, since erythroid and myeloid lineage progenitors appear to be the only cell types expressing both ACE2 and TMPRSS2 among the cells present in the bone marrow (37,69,70,84–86).

Events that ultimately demonstrated the contamination of the erythroid lineage by the virus during the differentiation phase and the reduced number of platelets due to the autoimmune attack by T cells, neutrophils and NK cells (37,70,84–86) (Fig.4).

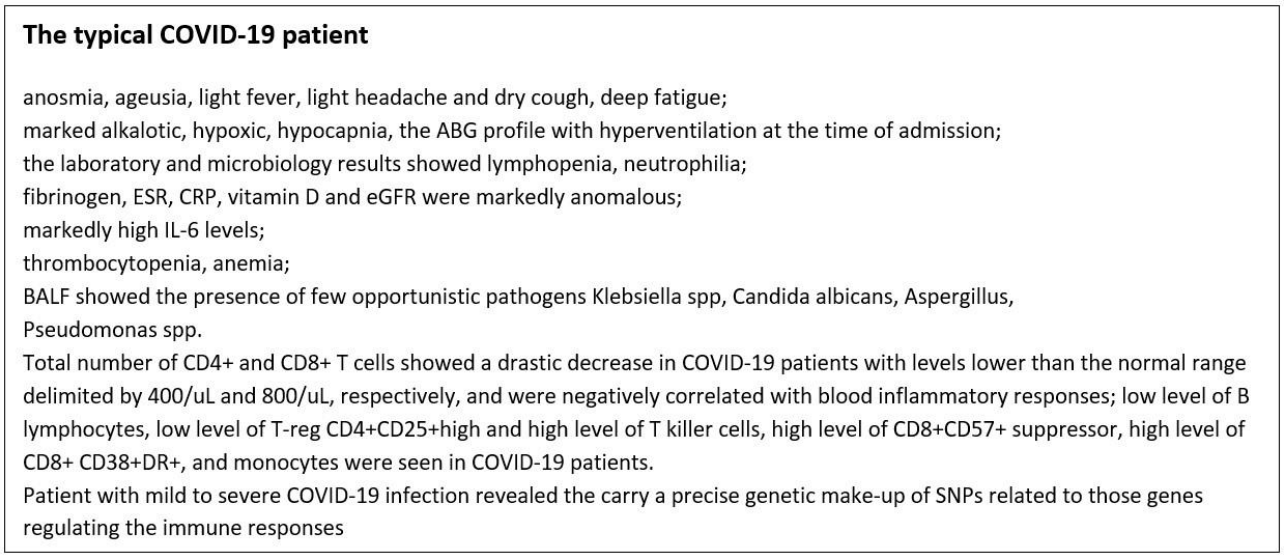

Fig.4. *The overall picture of affected patients was a result that we reached gradually based upon the clinical, laboratory and investigative approaches.*

The panel of cytokines considered also revealed an association with hospitalization time, age and sex.

Patient-associated cytokine signatures were partially and included molecules that have been implicated in the pathogenesis of COVID-19 such as IL-6, eGFR, vitamin D3, fibrinogen, as well as molecules that are more generally associated with inflammation/infection, such as ESR, D-dimer, CRP and iron (75,87–91).

Thus, the cell-mediated immune response is significantly increased in COVID-19 cases, compared to other patients. In this case, we assumed the necessary existence of a lung-kidney-heart crosstalk; this simultaneously explains the whole complexity of COVID-19 disease and its mechanism of progression along with uncontrolled autoimmune responses under the guidance of IL-6 leading to the well-known "cytokine storm" (1–3,5,6,23,24,48,69).

The data obtained from our analysis was in line with the results of observational studies which confirmed that a reduced level of vitamin D, in a concentration lower than 20 ng/mL, was a distinctive feature in COVID-19 patients and was related to a poor prognosis (84).

Regarding our main clinical findings, a clear reduction of platelets and erythrocytes was observed, an event related to the deficit found in the immune system response towards its own affected cells infected by SARS-CoV-2 (92–97).

Initially all the focus was on containing the spread of autoimmune reaction and uncontrolled inflammatory flare-ups, providing a therapy based on both anti-inflammatories, antioxidants and two types of antibiotics to stop a secondary type of bacterial infection often associated with COVID-19 to meet the increasing need for lost immune modulation as a consequent reduction of the lack of immunoregulatory cells and cytokines (3,5,8,12,29,30).

The findings revealed a significantly impaired immune system during SARS-CoV-2 infection. Key characteristics observed in COVID-19 patients included lymphopenia (64%), reduced levels of B lymphocytes (60%) and CD4+CD25+high regulatory T cells (37.8%), as well as elevated levels of cytotoxic T cells (73.3%), CD8+CD57+ suppressor cells (64.44%), CD8+CD38+DR+ cells (80%), and monocytes (28.9%). As lung capacity begins to decay due to the lack of microvascular homeostasis, cardiovascular functions also worsen, affecting the reuptake of filtered 25-hydroxyvitamin D in renal proximal tubules (37,85,87). Vitamin D has endocrine, paracrine and autocrine functions. RAS is inhibited by vitamin D due to its involvement in preventing angiotensin II (Ang-II) accumulation via inhibition of renin release, a very common event in COVID-19 patients (87,98). Increased Ang-II in cholesterol plaque accumulation along arteries, veins and visceral glomerular epithelial cells (podocytes) is a well-known phenomenon that induces cholesterol metabolism dysfunction leading to renal and cardiovascular injury (87). In this context, we evaluated the heightened toxic effects of the spike protein, which is associated with Ang II accumulation and its potential role in promoting cardiac hypertrophy and heart failure (25,90,99–105). Specifically: (1) Ang II is synthesized within the myocardium, (2) its activation is observed in hypertrophic hearts experiencing myocardial failure, and (3) the pharmacological inhibition of the RAS pathway and Ang II has demonstrated significant efficacy in both animal models and patients with hypertrophic hearts and myocardial failure (106–109). The significant variability in individuals affected by COVID-19 added complexity to understanding the disease. Viral exposure alone could not account for the wide range of responses, nor the stark differences between those who developed the disease and those who remained asymptomatic despite close contact with infected individuals. It soon became evident that pre-existing health conditions and the state of immune defenses

played crucial roles in determining disease progression. However, further investigation was needed to explore the genetic factors influencing host susceptibility and risk of severe outcomes. Genetic testing conducted on patients revealed that host genetic composition directly impacted susceptibility to infection and the progression of COVID-19 (86,87). One of the best results in this direction was to investigate and highlight the presence of single nucleotide polymorphisms (SNPs) of those genes involved in the immune regulation mechanism. In fact, the degree of severity of the disease was soon observed in relation to the presence of specific SNPs (37). The overall results showed the following: ACE-1 (higher prevalence of I/D in the COVID-19 group), Serpina3 (higher prevalence of G/T in the COVID-19 group), CRP (higher prevalence of G/G in the healthy group), IL6 rs1800795 (higher prevalence of G/G-G/C in the COVID-19 group) and IL10 (higher prevalence of G/A in the healthy group; higher prevalence of A/A in the COVID-19 group) and IL1RN (higher prevalence of C/T-T/T in the COVID-19 group; higher prevalence of C/C in the healthy group), IL6R (lower prevalence of A/A in the COVID-19 group), VDR (higher prevalence of Fok1 TC in the COVID-19 group and higher prevalence of T/T in the healthy group; higher prevalence of Taq1 A/G in the COVID-19 group, higher prevalence of G/G in the healthy group). healthy group), IFNγ (lower prevalence of A/A in the COVID-19 group), IFNγ (higher prevalence ... prevalence in the COVID-19 group, A/T higher prevalence in the healthy group) and TNFα (G/G higher prevalence in the COVID-19 group) (Fig. 3) (37,86).

Final consideration and the problem of the “Long COVID”

One of the lessons of the COVID pandemic is the importance of multidisciplinarity to achieve effective diagnosis, treatment and prevention (109–111).

Cooperation between primary emergency care and secondary care is indispensable, thus cooperation between different departments and disciplines such as emergency medicine, immunology and microbiology departments (112–114).

Many COVID-19 patients had comorbidities at the time of admission, but many others reported long-term effects of the infection, later called long COVID syndrome. These patients showed a very particular clinical picture and were often severely ill (115–122).

Management of patients with comorbidities and long COVID required a multidisciplinary approach and treatment to achieve complete recovery.

Recently, some symptoms have been described in patients a few months after being affected by COVID-19 (123–130).

In the literature, many symptoms recur and vary from foggy thoughts, anemia, neuromyasthenia, vegetative neuritis, post-viral fatigue syndrome, sleep disturbances, raphe nucleus encephalopathy, chronic lung conditions (pulmonary interstitial fibrotic scarring) and chronic mononucleosis syndrome among others.

This virus (RNA-virus) and the vaccines (mRNA) that are analogous can start with uncontrolled immune responses that lead to extreme "central" decay, a picture that also includes a reduction in B lymphocytes, an increase in pro-inflammatory cytokines (IL-6, IL8, TNFα), an increase in glial macrophages (M1) (responsible neural inflammation) and activation of autoreactive T cells (cytotoxic T cells and Th1) (131,132).

From these results we assume that the post-COVID condition will surely represent another challenge for healthcare professionals, since these signs should also be referred to pre-existing comorbidities deeply linked to a higher correlation burden.

The fact that this varied symptomatic picture would indicate a common Long-COVID condition, suggests that the SARS-CoV-2 variants may be connected. We suggest that the pathogenic spike protein of SARS-CoV-2 and the cell-cell mechanisms associated with the Long-COVID syndrome may be similar but not the same among the different SARS-CoV-2 variants (131).

The data and overall outcomes would support this hypothesis: individuals affected by the early variants showed a higher number of post-COVID symptoms, especially respiratory symptoms such as dyspnea, fever, and fatigue, compared to patients infected by the later variants.

Many of them showed lung fibrotic tissues validated by chest CT even after 12 months from COVID-19 infection (50,133).

However, exposure to infection alone failed to support the great variety of each individual's responses to the virus and the huge diversity of signs and symptoms (86).

Consequently, it would be expected that the development of infection and post-infection symptoms would be higher not only in the presence of historical variants and pre-existing conditions, but also with mRNA vaccines.

All of this is influenced by a predisposing genetic environment (50,86,87,133,134).

Proposing innovative, albeit complex, research strategies and clinical procedures to address and solve all the problems mentioned above has not been easy.

However, despite the difficulties, 118 SET demonstrated that this approach was indeed effective in reducing mortality and generating a new effective and deliberate discussion on the COVID-19 pandemic by stimulating new perspectives and concrete actions on future plans, priorities and strategies (50,133–135).

The proposed emergency plan algorithm helped to keep everyone involved, raise awareness and questions, allowing to set concrete goals to be achieved step by step for a wide variety of health problems.

The complex challenges that our health services faced were enormous and could not be achieved without multidisciplinary exchanges and debates.

Teamwork was of great help in standardizing health procedures and improving network governance in the province of Taranto, strengthening the impact of health services on population health, which in the post-COVID era is more necessary than ever.

So, with this article we proposed a new procedure that could become a "Know-how" tool for the formation of well-organized interdisciplinary teams of health professionals.

The effectiveness of this procedure during the pandemic has been tested so we sincerely hope that it will be used in the future to help healthcare professionals solve the next new global challenges.

CONCLUSIONS

This study highlights the critical role of pre-hospital emergency systems in managing large-scale health crises. The integrated response model of SET 118 successfully minimized mortality and improved resource utilization during the COVID-19 pandemic. The findings emphasize the importance of multidisciplinary collaboration, genetic research, and tailored therapeutic strategies in addressing both acute and long-term effects of infectious diseases. The proposed framework serves as a model for managing future global health emergencies, emphasizing the need for innovative solutions and robust healthcare planning.

Author Contributions

C.G.I., M.G.B., D.P., F.I., G.D., A.M.I. and A.S. conceptualization, final editing, and harmonization; C.G.I., L.F., R.D.P., G.D., L.F. A.D.I. and R.L. drew the figures; K.C.D.N. and C.G.I. drafted the manuscript in cooperation; writing—review and editing, T.C.T., A.D.I., R.L., A.S., M.G.B., F.I.; visualization, M.G.B., L.S., A.M.I., F.I., G.D., L.F. and A.D.I.; validation, P.D. and T.C.T.; supervising, A.S., G.D., A.M.I., G.D., L.F. and D.P.; project administration, T.C.T. and L.S. All authors have read and agreed to the published version of the manuscript.

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The authors declare that they have no conflict of interest.

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