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Treatment of peri-implant mucositis: adjunctive benefit of glycine powder air-polishing device to professional mechanical biofilm removal. A randomized parallel arm clinical study

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1. INTRODUCTION

Nowadays, dental implants are considered a valid alternative for the replacement of lost dental elements, as recent evidence demonstrated the high level of predictability of implant-supported restorations and patient satisfaction (Buser et al., 2017). However, implants' long-term success is determined by the maintenance of healthy peri-implant tissues, which relies on effective preventive measures, patient's self-performed oral hygiene practices and adherence to a proper supportive peri-implant care program (SPIC) (Heitz-Mayfield & Salvi, 2018; Herrera et al., 2023).

Biological complications associated with dental implants represent a daily challenge in clinical practice, given that their prevalence is consistently high (Salvi et al., 2019).

The direct causal relationship between the accumulation of biofilm and the occurrence of peri-implant diseases, referred to as peri-implant diseases, has been thoroughly demonstrated (Renvert et al., 2018; Renvert & Polyzois, 2015) and current focus is directed toward their treatment and the implementation of preventive programs.

The findings presented in the present randomized clinical study are the compendium of two years of study and research, conducted at the Unit of Periodontology, UOC of Odontology, of Azienda Ospedaliera Universitaria Senese (AOUS), on the adjunctive effect of glycine-powder air-polishing (GPAP) to full-mouth ultrasonic debridement (Fm-UD) in the treatment of peri-implant mucositis, and on the predictive role of implant and patient-level variables for the achievement of disease resolution.

1.2 PERI-IMPLANT DISEASES

1.2.1 Epidemiology and etiopathogenesis

Peri-implant diseases occur with an estimated subject-based weighted mean prevalence amounting to 43% for peri-implant mucositis and to 22% for peri-implantitis (Derks & Tomasi, 2015; Salvi et al., 2019).

Plaque accumulation around dental implant surfaces elicits an inflammatory process at the implant-mucosa interface, resulting in peri-implant mucositis (Renvert & Polyzois, 2015). However, when compared to their gingival counterpart, peri-implant tissues show a stronger inflammatory response (Riben-Grundstrom et al., 2015) and a slower healing capacity (Heitz-Mayfield & Salvi, 2018; Salvi et al., 2012).

Experimental multispecies in vitro and in vivo biofilm models have demonstrated that biofilm formation on titanium implant surfaces follows similar principles and sequences to that of tooth surfaces, described in 1998 by Socransky et al. (Costerton et al., 1995; Kolenbrander, 1997; Socransky et al., 1998), starting with the formation of an acquired pellicle, due to the adsorption of salivary components, chiefly proteins, subsequently followed by the adherence of early colonizers. Their multiplication, at the level of the salivary film, modifies the microenvironment, determining the progressive colonization of secondary and tertiary colonizers (Sánchez et al., 2014; Schmidlin et al., 2013).

The supramucosal and submucosal microbiota is made up of six complexes (Socransky et al., 1998) :

EARLY COLONIZERS

- BLUE COMPLEX: Actinomycetes (A*. israelii*, A. *gerencseriae*, A. *naeslundii*);
- GREEN COMPLEX: E*. corrodens*, C. *sputigena*, C*. gingivalis*, C. *ochracea*;
- YELLOW COMPLEX: S*. mitis*, S. *oralis*, S. *sanguis*, S. *gordonil*, S. *intermedius,* Streptococcus spp;
- PURPLE COMPLEX: V. *parvul*a, A. *odontolythicus*;

LATE COLONIZERS

- V. ORANGE COMPLEX: P. *intermedia*, P. *nigrescens*, P. *micros*, F. *nuc. nucleatum*, F. *periodonticum,* C. *rectus,* C*. gracilis,* C*. showae,* E*. nodatum,* S*. constellatus*;
- VI. RED COMPLEX: B. *forsythus*, T. *denticula*, P. *gingivalis*.

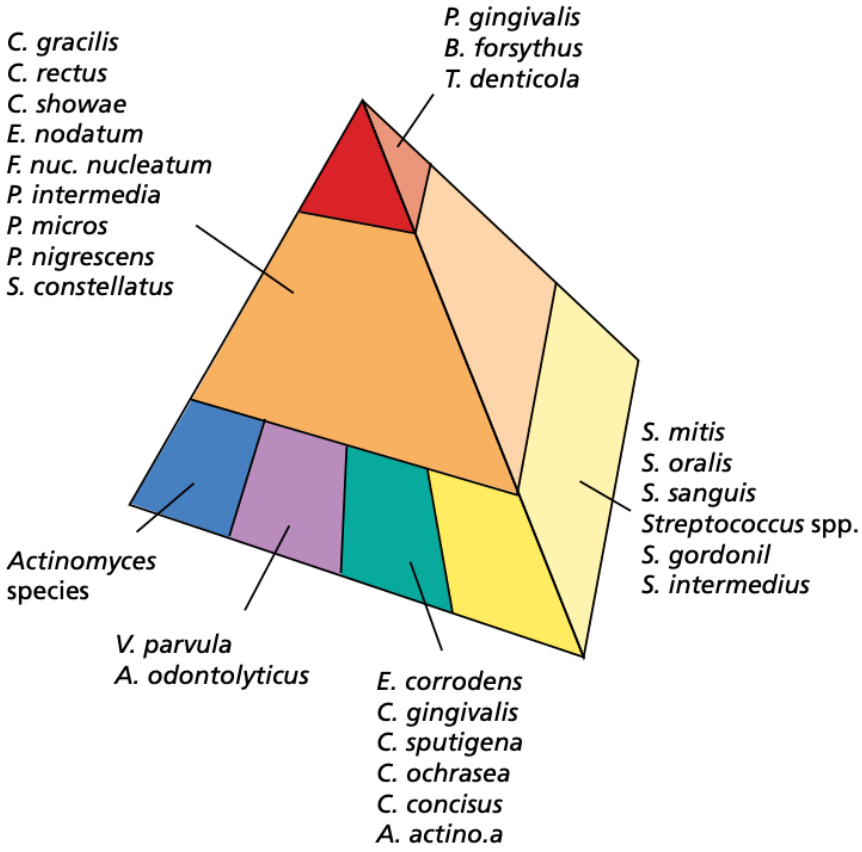


FIGURE 1 Microbiota divided into colored complexes (Lang & Lindhe, 2015)

Regardless of the shared characteristics between biofilm on implant and on tooth surfaces, several distinct traits may be related to implant surface features.

In 1988, Mombelli et al., through the analysis of samples taken from peri-implant sites, identified the microbiota associated with peri-implant health, consisting of Gram-positive cocci (genus Actinomyces and Veillonella), for the most part, and Gram-negative

anaerobic rods (such as spirochaetes and Fusobacteria) in lower percentages (Mombelli et al., 1988). More recently, by means of molecular techniques, such as PCR and/or Checker-board DNA-DNA hybridization, periodontal pathogens such as T. denticola, P. gingivalis, S. intermedius, T. forsythia and A. actinomycetemcomitans have been discovered inside the peri-implant sulcus of edentulous and partially edentulous patients (Lee et al., 2017).

Moreover, numerous investigations have demonstrated that peri-implantitis is associated with species similar to those present in periodontal sites (Botero et al., 2005; Persson et al., 2006): mixed anaerobic microorganisms, mostly Gram-negative, and periodontal pathogens, T. *Forsythia*, P. *Intermedia*, P. *Gingivalis* and T. *Denticola*.

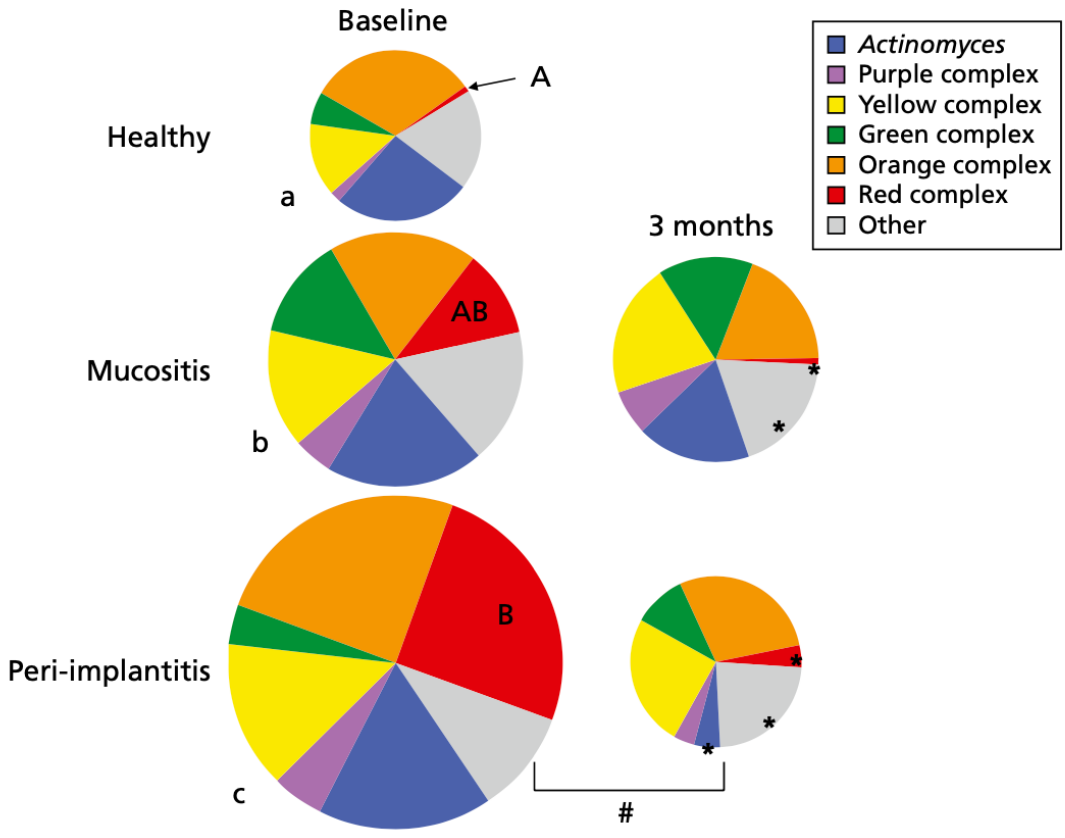


FIGURE 2 Subgingival microbial complexes from samples of biofilm in healthy implant sites, peri-implant mucositis sites and peri-implant sites (Lang & Lindhe, 2015).

According to Maximo et al. (2009), the microbiota composition of peri-implant mucositis sites was very similar to that of sites affected by peri-implantitis; therefore, they hypothesized the evolution from a state of mucositis to that of peri-implantitis. Plaque samples from 13 patients with peri-implantitis and 12 patients with peri-implant mucositis, which were analyzed using checkerboard DNA-DNA hybridization for 40 bacterial species, revealed similar levels of all species. Although, in peri-implantitis sites, lower levels of Actinomyces *gerencseriae* and Campylobacter *ochracea* and higher levels of T. *forsythia* were detected (Máximo et al., 2009)

1.2.2 Classification of peri-implant diseases

Peri-implant diseases are inflammatory processes that, following the accumulation of bacterial plaque, affect the health of the soft and hard tissues surrounding dental implants. The 2017 World Workshop on Classification of Periodontal and Peri-Implant diseases and Conditions proposed a new classification of peri-implant diseases and provided case definitions for peri-implant health, peri-implant mucositis, and peri-implantitis (Caton et al., 2018).

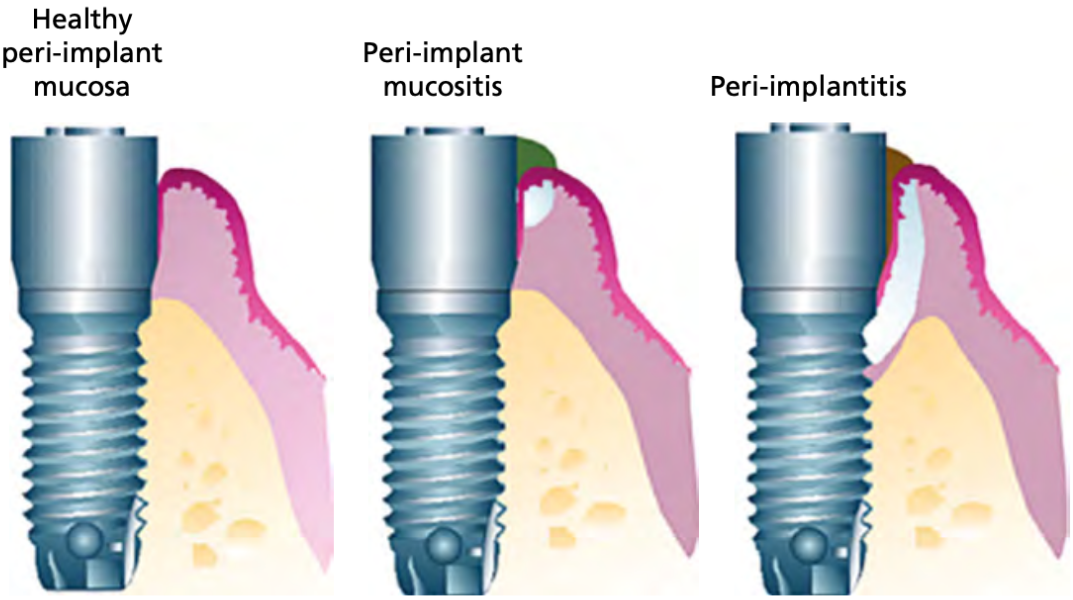


FIGURE 3 Healthy peri-implant mucosa, peri-implant mucositis, peri-implantitis (Lang & Lindhe, 2015).

Healthy peri-implant mucosa

At the microscopic level, the healthy peri-implant mucosa is characterized by the:

- presence of a barrier, formed thanks to the presence of hemidesmosomes, in the interface between the non-keratinized oral epithelium and the implant;
- presence, in the underlying connective tissue, of groups of inflammatory cells that constitute the main response of the host to the presence of bacterial biofilm.

Besides, macroscopically:

- the height of the epithelium, measured from the free gingival margin to the apical portion of the junctional epithelium, has a value of around 2 mm;
- the height relative to the area where the connective tissue is attached has a value between 1 and 2 mm.

As far as the clinical setting is concerned, to determine the peri-implant health status it is necessary to refer to the following parameters:

- absence of signs attributable to inflammatory processes such as: oedema, erythema and suppuration;
- absence of bleeding on probing, the pressure of which should not exceed 0.25 N (Araujo et al., 2018);
- there must be a seal between the peri-implant mucosa and the trans-mucosal component of the implant (Renvert et al., 2018);
- PPD (probing pocket depth) ≤ 5 mm;
- absence of bone resorption, detected through radiographic investigations. Clearly, during the first year following implant insertion, a certain degree of bone resorption is accepted, which however must not exceed 2 mm, and this can be determined by various factors such as the original size of the bone and/or the location of the screw (Tomasi et al., 2010).

However, according to the recently published international consensus report, the "Implant Dentistry Core Outcome Set and Measurement (ID-COSM)", the definition of peri-implant health allows for the presence of a single site bleeding upon probing (≤ 1 BOP positive site, not line nor profuse bleeding) (Tonetti et al., 2023).

Hard and soft tissue implant site deficiencies

A reduction in alveolar process dimensions is the consequence of the normal healing process following tooth loss. However, greater ridge deficiencies may be related to:

- iatrogenic extraction trauma;
- injury to the maxillary sinuses;
- pathological processes such as peri-implantitis, periodontitis, endo-perio lesion and endodontic infections;
- systemic diseases that affect bone mineral density and bone mass
- factors of a mechanical nature such as: prosthetic overload or bad positioning of the implant;
- root fractures.

The presence of one or more of these factors influences the criticality of the clinical condition (Hämmerle & Tarnow, 2018).

Peri-implant mucositis

According to the 2018 classification, peri-implant mucositis is referred to as a bacterial biofilm-induced inflammatory lesion of the soft tissues around dental implants, whose main clinical and visual signs include bleeding on probing, edema, erythema, and no additional loss of supporting bone, after the initial bone remodeling. (Berglundh et al., 2018). Perhaps, due to swelling or decreased probing resistance, peri-implant mucositis can be accompanied by an increase in probing pocket depth. However, the definition has been updated following the ID-COSM consensus (Tonetti et al., 2023). The updated definition states that peri-implant mucositis is characterized by the presence of bleeding, either multiple spots, a line of bleeding, or profuse bleeding

The probing allows to measure the resistance of the soft tissues to the pressure of the probe. In healthy periodontal tissues, the tip of the probe stops at the level of the apical cells of the junctional epithelium. Meanwhile, in an inflamed tissue the tip of the probe, going beyond the epithelium, reaches the level of the connective tissue, in contact with the inflammatory infiltrate (Araujo et al., 2018). In a study conducted by Gerber et al. in 2009, since the peri-implant mucosa turned out to be more sensitive than the gingiva, it

was proposed to apply a pressure of 0.15 N during probing to avoid the occurrence of false positives (Gerber et al., 2009).

Histologically, peri-implant mucositis resembles gingivitis in that they both exhibit a distinct inflammatory lesion located near the junctional/pocket epithelium. This lesion in characterized by a dense infiltration of vascular structures, plasma cells and lymphocytes. However, peri-implant mucositis does not spread beyond the junctional/pocket epithelum in the apical direction not it involves the supra crestal area (Heitz-Mayfield & Salvi, 2018).

The etiology of peri-implant mucositis, as well as for gingivitis, is represented by the accumulation of bacterial plaque (dental/implant biofilm); this determines the activation of the host's immune system, which will lead to an inflammatory response within the mucosal connective tissues.

This cause-and-effect relationship has been investigated in various studies. In 1994, Pontiero et al. found that, following the cessation of oral hygiene maneuvers for at least three weeks, the accumulation of plaque determined the development of an inflammatory reaction, which showed similar extension and localization in both implant and dental sites (Pontoriero et al., 1994). In 2001, Zitzmann et al. investigated the response of the peri-implant mucosa at the histological level by observing, following the activation of the inflammatory system due to the accumulation of plaque, a significant increase in T lymphocytes and plasma cells on biopsies (Zitzmann et al., 2001).

In a study conducted on fifteen subjects, with healthy or stabilized periodontal conditions and rehabilitated with dental implants, Salvi et al. demonstrated the reversibility of the inflammation in the gingiva as well as in the peri-implant mucosa. After an experimental period of plaque formation, when oral hygiene was re-introduced, both experimentally induced gingivitis and peri-implant mucositis gradually resolved. However, they shed light upon how, in front of the same bacterial challenge, the peri-implant mucosa demonstrated a greater inflammatory response, compared to dental sites. Moreover, from a clinical point of view, they pinpointed that longer healing times are required because 3 weeks of continued plaque control did not result in pre-experimental levels of gingival and peri-implant mucosal health (Salvi et al., 2012).

Furthermore, peri-implantitis can develop from untreated peri-implant mucositis. According to Costa et al., patients who had baseline peri-implant mucositis and were not receiving regular supportive peri-implant therapy experienced a 44% incidence of peri-implantitis during a five-year period. The incidence of peri-implantitis over 5 years was 18% in a parallel group of patients with peri-implant mucositis who participated in a regular supportive care regimen. This finding emphasizes the significance of peri-implant mucositis detection and treatment to its progression into peri-implantitis (Costa et al., 2012).

Peri-implantitis

When the signs of peri-implant inflammation are associated with progressive alveolar bone loss (≥3 mm) and/or probing depth (≥6 mm), the condition is defined as peri-implantitis (Berglundh et al., 2018).

Peri-implantitis progression is characterized by a non-linear and accelerating pattern (Derks et al., 2016).

Clinically, peri-implant mucositis is diagnosed based on the following parameters:

- tissue inflammation: erythema, edema and suppuration;
- bleeding on probing;
- loss of supporting bone ≥3 mm;
- PPD ≥ 6mm or increased compared to previous examinations.

In an initial phase, the inflammatory process has an extension that remains quite marginal, so that for a long time the stability of the implant is not affected; but later on, due to the loss of osseointegration, a certain implant mobility may occur (Fransson et al., 2010).

In the presence of peri-implant diseases, it is difficult to accurately determine the real probing depth since the junctional epithelium thickens and ulcerates, due to inflammation, there is no longer a mucosal seal around the implant and the tip of the probe reaches the inflammatory infiltrate, at the level of the barrier epithelium (Derks et al., 2016).

There is therefore a risk of overestimating the depth of the pocket. Indeed, through a systematic review, Schwarz et al. have ascertained that with a PD value between 4 mm and 6 mm there was a strong association for both mucositis and peri-implantitis.
Moreover, for PD values ≥ 7 mm the association concerned exclusively peri-implantitis (Schwarz et al., 2018).
Unfortunately, to date, it is not clear which are the clinical and histopathological characteristics that influence the evolution of mucositis into peri-implantitis; we know that the inflammatory lesion does not seem the disease progression follows a linear pattern and that the repair events, following periods of tissue destruction, do not allow a complete restitutio ad integrum (Berglundh et al., 1992).

1.2.3 Risk factors

Smoking (Rinke et al., 2011; Roos-Jansaker et al., 2006), radiation therapy (Máximo et al., 2009b), inadequate compliance (Costa et al., 2012) and susceptibility to periodontitis have been outlined as some of the most significant risk indicators of peri-implant diseases; whereas, recent evidence pinpointed the width of keratinized mucosa (Boynueğri et al., 2013), the excess cement (Linkevicius et al., 2013; Renvert & Polyzois, 2015) and the prosthetic emergence profile as local factors exacerbating peri-implant inflammation (Bollain et al., 2021; Katafuchi et al., 2018; Monje et al., 2019).

Modifiable and systemic risk factors

It has been thoroughly demonstrated that smoking is a risk factor for peri-implant biological complications. In a study conducted by Roos-Janker et al. in 2006, on a sample of 218 patients and 999 loaded implants, the onset of peri-implant pathologies was monitored and a statistically significant association between smoking and peri-implant mucositis was determined (Roos-Jansaker et al., 2006)
Furthermore, in 2011, through a cross-sectional observational study, on a sample of 89 patients, Rinke et al. demonstrated individuals who smoke show a significantly increased risk of developing biological complications associated with dental implants (Rinke et al., 2011).

Karbach et al. have ascertained, through a study conducted in 2009, that radiotherapy could be considered a significant risk factor for the development of mucositis (Renvert & Polyzois, 2015).

The association between diabetes mellitus and periodontitis is well documented throughout the literature. It has been demonstrated that, at the level of the gingival tissues, the accumulation of the products of catabolism determines dramatic changes in the periodontal tissues, leading to an increased susceptibility to periodontal infections and to a decrease in healing capacity (Matsha et al., 2020). Such changes prompted researchers to investigate what could be the relationship between diabetes mellitus and peri-implant disease: Ferreira et al., in 2006, conducted a transversal study, highlining a statistically significant association between diabetes and the probability of developing peri-implant mucositis (odds ratio = 1.2) (Ferreira et al., 2006).

Non modifiable and systemic risk factors

It can be stated that periodontitis has a strong genetic component, as 50% of the susceptibility to the disease is linked to hereditary conditions, such as the polymorphism of the genes that promote the transcription of inflammation factors (essentially interleukins IL-1β69 and IL -1α) (Zoheir et al., 2022).

Due to these polymorphisms a hyper-inflammatory state is established, determining an increased susceptibility to periodontitis and a greater degree of destruction of the periodontal tissues.

However, Lachmann et al., in 2007, did not identify any correlation between the development of peri-implantitis and interleukin IL-1 (Lachmann et al., 2007).

Moreover, Casado et al., in 2013, studied the association between the gene polymorphism that promotes interleukin IL-6 and the increased susceptibility to peri-implantitis and periodontitis; however, despite the results highlighted that the frequency of the IL-6 174GG genotype and of the G allele were different between peri-implantitis patients and healthy subjects, they failed to demonstrate a statistically significant association (Casado et al., 2013).

Thus, multiple studies present in the literature have failed to establish a strong relationship between genetic polymorphisms and the development of peri-implant diseases (Renvert & Polyzois, 2015).

Modifiable and local risk factors

The onset of peri-implant mucositis is closely associated with the accumulation of plaque at implant sites (Heitz-Mayfield & Salvi, 2018).

Pontoriero and Zitzmann observed how the abolition of oral hygiene maneuvers led to an accumulation of plaque around the implant which determined the development of an inflammatory response in the peri-implant tissues (Pontoriero et al., 1994).

The strong correlation between mucositis and bacterial biofilm accumulation was also demonstrated by Ferreira et al., in 2006 (Ferreira et al., 2006).

Supportive mechanical peri-implant therapy plays a fundamental role in the prevention of peri-implant pathologies. Costa et al., demonstrated that regular compliance during peri-implant maintenance reduces the occurrence of peri-implant diseases and that a significant incidence of peri-implantitis was linked to the lack of preventative maintenance in people with pre-existing peri-implant mucositis (peri-implant mucositis not accompanied by supportive therapy was associated with a 44% incidence of progressing to peri-implantitis) (Costa et al., 2012).

Wennerberg et al., through a study on the early inflammatory response of the peri-implant mucosa in relation to abutments with different degrees of roughness, hypothesized that there was a direct correlation between surface roughness and the amount of accumulated plaque, but not between surface roughness and the development of peri-implant mucositis per se (Wennerberg et al., 2003).

Furthermore, it has been demonstrated that following resorption of the crest margin, a greater accumulation of plaque can be ascertained, also facilitated by the roughness of the implant surface, and consequently a greater probability of developing peri-implant biological complications (Lang & Berglundh, 2011).

It is very important that the prostheses supported by the implants are easily cleansable through daily home oral hygiene procedures, in order to prevent and/or manage peri-implant pathologies (Ferreira et al., 2006; Tapia et al., 2019).

Indeed, due to the anatomical variants, which can influence the features of the prosthetic restoration, the oral hygiene instructions must be customized and adapted for each patient. After the therapy, it has been seen that implants with prosthetic restorations with supra-mucosal margins show lower probing depth values compared to those with sub-mucosal margins (Heitz-Mayfield & Salvi, 2018).

Regarding the morphology of the prosthetic restoration, it was observed that a restoration emergence angle higher than 30 degrees can be accounted as a significant risk indicator for peri-implant biological complications. Moreover, a convex rather than a concave contour of the prostheses profile represents an adjunctive risk, mainly in the presence of bone-level implants, in posterior areas (Katafuchi et al., 2018).

Wilson et al., in 2009, studied how implants rehabilitated with a single crown, presenting excess of cement developed signs of mucositis more frequently than single prosthetic rehabilitations without cement excess (Wilson Jr., 2009).

In support of this study, a retrospective case analysis conducted on a sample of seventy-seven patients and 129 implants established that peri-implant mucositis occurred with a higher prevalence in implants with cemented prostheses than in those with screwed prostheses (Linkevicius et al., 2013).

Indeed, excess cement is a considered risk factor for the development of peri-implant diseases. Therefore, it is of crucial importance to ensure that the prosthetic margin does not invade the peri-implant soft tissues. Moreover, after cementation, careful removal of the excess is recommended (Staubli et al., 2017).

Non modifiable and local risk factors

The oral microbiota greatly affects the formation of the biofilm: some cross-sectional studies have shown that the composition of the microbiota in the peri-implant sulcus is the same in the dental sites (Quirynen & Van Assche, 2011).

It has been observed that deeper periodontal pockets can become a reservoir for the colonization of implant sites (Mombelli et al., 1995); therefore, the persistence of sites

in which periodontitis has not been treated can represent a risk factor for the adjacent implant surfaces (Lang & Berglundh, 2011).

With the healing of the peri-implant soft tissues, following the surgical insertion of the implant, the formation of mucosa is obtained, which can be keratinized or not; this is due to the degree of extension of the masticatory mucosa at the level of the alveolar process and to the reabsorption that the alveolar process has undergone. The presence of an adequate dimension (≥ 2 mm) of the keratinized mucosa around the implant is necessary to prevent soft tissue recession and facilitate oral hygiene maneuvers by the patient (Moon et al., 1999)

A systematic review, conducted by Wennstrom et al. in 2012, demonstrated an association between an inadequate size of keratinized mucosa (< 2 mm) and the increased accumulation of plaque, as patients experienced discomfort when performing brushing maneuvers. However, no correlation has been demonstrated between the lack of keratinized mucosa and the onset of peri-implant mucositis (Wennström & Derks, 2012)

1.2.4 Non-surgical treatment of peri-implant diseases

Peri-implant tissue health, peri-implant mucositis and peri-implantitis exist on a spectrum. This continuum is influenced by inflammatory processes that occur due to the maturation and nososymbiocity of microbial biofilm. Effectively managing inflammation by removing plaque is essential for maintaining overall health and preventing as well as treating peri-implant diseases.

Since peri-implant mucositis can be effectively treated, resulting in the restoration of peri-implant tissue health, it plays a crucial role in preventing the onset of peri-implantitis, indeed it can be accounted as a preventive strategy. However, once peri-implantitis has developed, it is widely recognized that treatment alone cannot fully restore the original support of peri-implant tissues, even if inflammation is effectively managed (Jepsen et al., 2015).

The interventions for managing peri-implant mucositis, such as self-administered or professionally administered, implementation of mechanical and/or antiseptic maneuvers, aim to decontaminate the affected sites from plaque and calculus deposits,

in order to rebalance the sub-mucosal microbiome. However, it is important that these plaque and calculus removal maneuvers do not affect the surface of the abutment or implant, which could therefore be damaged.

It is recommended to assess treatment outcomes after two or three months, and if the desired results have not been achieved, retreatment is advised (Herrera et al., 2023). These outcome measures indicate the restoration of peri-implant health.

Mechanical debridement

Professional mechanical biofilm removal, associated with adequate home plaque control, is documented as the standard of care for the treatment of peri-implant mucositis and the most indicated preventive measure to limit its conversion to peri-implantitis (Barootchi et al., 2020; Berglundh et al., 2018).

However, conventional surface debridement reduces clinical signs of inflammation, although it revealed a limited efficacy in achieving complete resolution of BoP on the subject level (Jepsen et al., 2015) and biofilm elimination from implant surface (Costa et al., 2012; Salvi et al., 2012; Sánchez-Martos et al., 2020), making clear that a complete resolution is not achieved.

There are different instruments that could be used for the debridement of plaque and calculus deposits.

Curettes can be classified according to the material of which they are made of:

- titanium: during instrumentation there is no risk of scratching, having a similar hardness to that of the implant;
- stainless steel: they have a higher hardness than the previous curettes; therefore, during the instrumentation they can create irregularities on the implant surface;
- carbon fiber: with a much lower hardness than titanium, they do not damage the implant during instrumentation but can, however, easily break;
- plastic: like the previous ones, there is no danger that they could scratch the implant surface, but they easily break.

Ultrasonic tips are characterized by a coated stainless-steel core, mostly with PEEK (polyether ether ketone), a polymer with mechanical properties able to avoid any

damage to the implant surface. In a study by Karring et al., comparing instrumentation performed with carbon fiber curettes and ultrasound, a reduction in major bleeding index was found at sites treated with ultrasound (Karring et al., 2005)
Cups are devices used mainly for the removal of bacterial plaque and for the polishing phase.

Antimicrobial agents

According to the currently available shreds of evidence, the use of topical antiseptics and local or systemic antimicrobials does not provide additional beneficial effects to sole mechanical cleansing. (Heitz-Mayfield & Salvi, 2018; Jepsen et al., 2015; Thöne-Mühling et al., 2010).
In order to prevent new bacterial colonization in the treated sites, many therapeutic protocols have suggested the introduction of antimicrobial agents as adjunctive therapy to mechanical debridement.
In 2010, Thöne-Mühling et al. compared the effects of one-stage full-mouth scaling with or without chlorhexidine. In the test group, chlorhexidine gel (1%) was brushed on the back of the tongue for one minute and was applied sub-gingivally, tonsils were spray for four times with chlorhexidine spray (0.2%) and subjects were asked to daily rinse, for one minute, with chlorhexidine mouthwash (0.2%). After 8 month follow up, no inter-group difference was found in terms of improved clinical parameters (Thöne-Mühling et al., 2010).
Similarly, in 2011, a randomized clinical trial was published by Heitz-Meyfield et al. where, following the mechanical therapy of the implants affected by peri-implant mucositis the test group performed, twice a day, brushing maneuvers with a chlorhexidine-based gel and the control group applied a placebo gel, twice a day.
Participants allocated to both groups had been taught home hygiene maneuvers. At the end of the protocol, both test and control groups showed a significant reduction in the clinical signs of peri-implant mucositis. Therefore, the efficacy given by the simple combination of mechanical debridement and oral hygiene instructions was confirmed.
Moreover, a systematic review conducted by Jepsen et al., in 2015, confirmed that local antiseptics and antimicrobials add no adjunctive beneficial effects to the sole

mechanical debridement (Jepsen et al., 2015). Anyhow, home oral hygiene instructions submitted to the patient and mechanical debridement performed with mechanical tools are effective in reducing the signs of inflammation, although complete disease resolution seems not achievable.

However, in order to maintain the stability of the tissues around the implant for a long time, it is necessary to implement the treatment plan with supportive care (Heitz-Mayfield et al., 2020; Staubli et al., 2017)

Additional therapies

According to the current evidence, the use of topical antiseptics, local or systemic antimicrobials and lasers does not provide additional benefits to sole mechanical debridement (Dommisch et al., 2022; Ramanauskaite et al., 2021; Atieh et al., 2022; Lin et al., 2018).

Lin et al. demonstrated, through a meta-analysis based on eleven studies, that by applying

laser as an adjunctive therapy, this has little benefit regarding probing pocket depth reduction, clinical level attachment gain and plaque index. While, in the short term, a reduction in the bleeding index can be observed. For this reason, to date, it is believed that the adjunctive use of lasers does not bring, in the long term, any additional benefits compared to mechanical debridement, in the treatment of peri-implant mucositis (Lin et al., 2018).

Air polishing

Furthermore, the use of air polishing devices as an adjunctive method in the treatment of peri-implant mucositis has been investigated in several publications (Schwarz et al., 2015).

Among the powders associated with this treatment modality it is worth mentioning Sodium bicarbonate, no longer used today since its harmfulness to soft tissues has been discovered (Figuero et al., 2014), and glycine, that represents a less abrasive alternative to bicarbonate, it is water-soluble and, above all, biocompatible (Simon et al., 2015)

Pre-clinical studies shed light upon the significant decontamination efficacy of air abrasive devices, without detrimental effects on implant surfaces (Moharrami et al., 2019); notably, the use of glycine powder air polishing in adjunction to ultrasonic debridement has been proven to significantly reduce artificial biofilm deposits (Discepoli et al., 2022). De Siena et al., in an observational clinical trial, support the GPAP greater potential in reducing probing pocket depth, compared to debridement performed with ultrasound and curettes, referable to a glycine-induced trophic effect on peri-implant mucosa; however, regarding BI and PI, almost negligible superior effects are revealed (De Siena et al., 2015). Accordingly, recently published randomized clinical trials failed to demonstrate any superior effect of air abrasive devices, over professional oral hygiene alone, in reducing clinical signs of inflammation (i.e. BOP), either investigated as adjunctive therapy (Ji et al., 2013) or as an alternative to sole mechanical debridement (Riben-Grundstrom et al., 2015)

Photodynamic therapy

Mainly used in the dermatological field, photodynamic therapy is also recently gaining ground in the dental field. This type of therapy is based on the use of light and a photosensitizing substance, in the form of cream or powder. When applied to the sites to be treated, the photosensitizing substance binds to the bacteria and once activated by light, initiates a chemical reaction that leads to the destruction of the pathogen.
Unfortunately, this system may have some limitations which are mostly linked to the reduced application surface and the difficulty of reaching the bottom of the pocket; for this reason, it is used more as an adjunct to mechanical debridement than as an alternative therapy for mucositis. Furthermore, there are still not enough studies that can attribute real advantages and/or disadvantages to it.

Non-surgical treatment of peri-implantitis

As for the treatment of peri-implant mucositis, the therapeutic strategy of choice for the non-surgical management of peri-implantitis involves the use of mechanical

debridement performed with suitable ultrasonic tips (PEEK coated) or curettes (in carbon fiber or titanium) (Liñares et al., 2023).

In a randomized study, Renvert et al., investigated which instrument, between ultrasonic tips and titanium curettes, was more effective in the treatment of peri-implantitis; however, in terms of plaque and bleeding index reduction, no differences were found between the two instruments (Renvert et al., 2009).

Moreover, it has been demonstrated that the adjunctive use of glycine powder air polishing devices for the non-surgical treatment of peri-implantitis shows the same effects of mechanical instruments in terms plaque removal and reduction of bleeding on probing, again failing to achieve complete disease resolution (Schwarz et al., 2015).

For what concerns the use of lasers, no scientific evidence demonstrating any additional benefits of this tool, compared to traditional mechanical biofilm removal, is available (Lin et al., 2018).

Furthermore, it has been seen that, in terms of Bop and probing pocket depth reduction, the use of antibiotics in sites affected by peri-implantitis, in addition to mechanical therapy, shows some beneficial effects (Graziani et al., 2012).

Through the data presented in the literature we can, therefore, conclude that the non-surgical treatment of peri-implantitis, of a moderate or severe degree, is not entirely conclusive; this even if the mechanical treatment is assisted with antibiotics for topical use, air polishing or laser systems (Graziani et al., 2012).

2. EXPERIMENTAL PROTOCOL

2.1 OBJECTIVES OF THE STUDY

Since none of the investigated clinical protocols appears to be more effective than others in achieving complete resolution of peri-implant inflammation and given the lack of adequate data in this regard, further in-depth analysis is needed to assess the therapeutic effects of air polishing as an additional treatment for peri-implant mucositis. The main objective of the current research protocol is to investigate the clinical efficacy of glycine-powder air-polishing as an adjunctive measure to full-mouth ultrasonic debridement for the treatment of peri-implant mucositis.

The secondary objective was to highlight the predictive role of implant and patient-level clinical and radiographic variables, for the partial and complete resolution of the peri-implant disease.

2.2 MATERIALS AND METHODS

2.2.1 Study design

The present study is a single-centre, randomized, parallel-group, double-blind, University-based, superiority clinical trial. In accordance with the ethical principles enshrined in the Declaration of Helsinki and with the approval of the University Hospital of Siena Ethics committee (Siena, Italy) (Sezione Area vasta Toscana Sud Est n°22044), all enrolled patients were informed about the study protocol and were asked to read and sign the informed consent.

2.2.2 Participants

Eligible subjects were recruited from the Unit of Periodontology, UOC of Odontology, of Azienda Ospedaliera Universitaria Senese (AOUS), between July 2020 and November 2022.

Each patient was required to meet the following inclusion criteria: (I) age between 18 and 70 years old; (II) presence of one implant loaded at least one year prior to their referral; (III) presence of bleeding and/or suppuration after gentle probing of the peri-implant mucosa; (IV) pain and/or tenderness of the peri-implant mucosa (V) good general health conditions; (VI) ability to give written informed consent.

Patients with one or more of the following characteristics were excluded from the study: (I) radiographic bone loss ≥ 2 mm around the implant; (II) intake of anti-coagulants, anti-aggregation, antibiotic or cortisone drugs during the preceding three months; (III) inability to perform oral hygiene maneuvers.

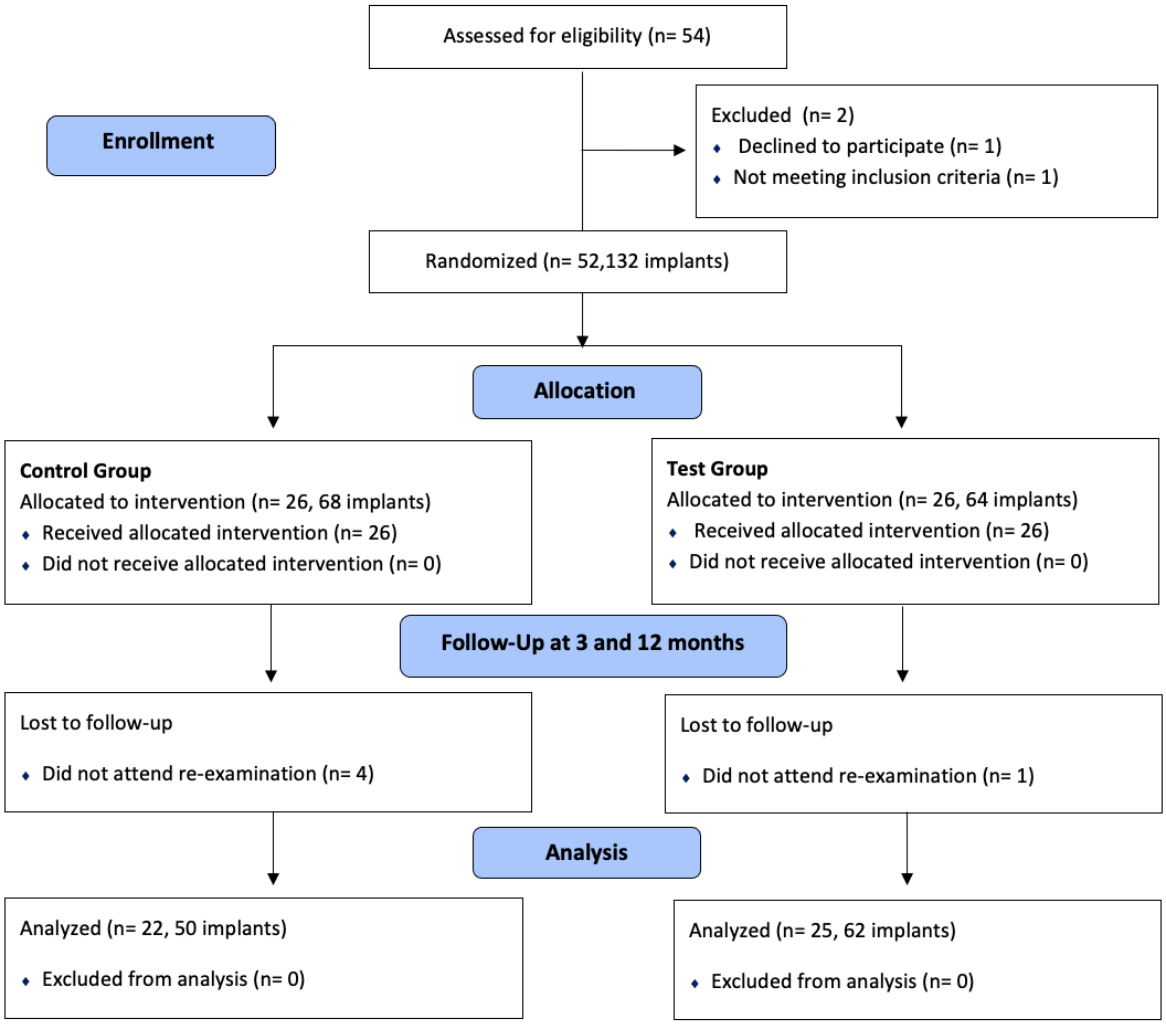


FIGURE 4 CONSORT Flow Diagram

2.2.3 Pre-therapeutic phase

Screening and anamnesis

Information about the patient's age, gender, smoking status and oral hygiene habits was recorded. Furthermore, during the anamnesis, the presence of familiarity and comorbidities influencing the subject's susceptibility to periodontal diseases was investigated.

The following details about implant-specific features were also reported: brand and number of the implants per patient, implant distribution (sextants, maxilla, mandible), radiographic emergence angle, type of restoration (single or multiple crowns) and type of retention (screwed or cemented).

Radiographic variables

To be deemed suitable for inclusion, once having ascertained the presence of peri-implant inflammation by clinical variables, an intraoral radiograph of the experimental unit was performed, to evaluate the peri-implant radiographic bone level. Subsequently, the prosthetic emergence angle was calculated.

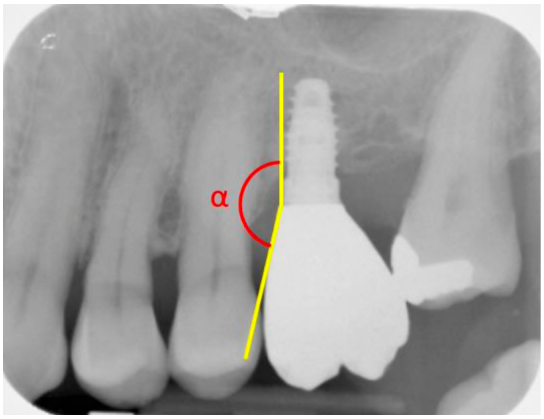


FIGURE 4 Prosthetic emergence angle (α), calculated on the periapical radiograph as the angle between the straight line passing through the abutment-implant junction and the straight-line tangent to the profile of the prosthetic crown.

Clinical variables

At baseline, all enrolled subjects received a full periodontal chart. Clinical parameters were recorded using a UNC 15 periodontal probe and a pressure of 0.25 N, six sites per tooth (Lang et al., 1991).

FMPS and FMBS were calculated as the proportion of all tooth and implant surfaces that presented plaque and that bled when probed (O'Leary et al., 1972; Tonetti & Claffey, 2005). The number and proportion of all BoP + implant sites were recorded (N BoP; % BoP implants). The number and the proportion of pockets ≥ 5mm with BoP were also obtained. Moreover, the mean and the maximum probing pocket depth of all included implant surfaces were calculated (PPD mean; PPD max; Mean PPD implants).

Furthermore, the distance between the mucogingival junction and the margin of the peri-implant mucosa was measured to assess the keratinized tissue width (KT).

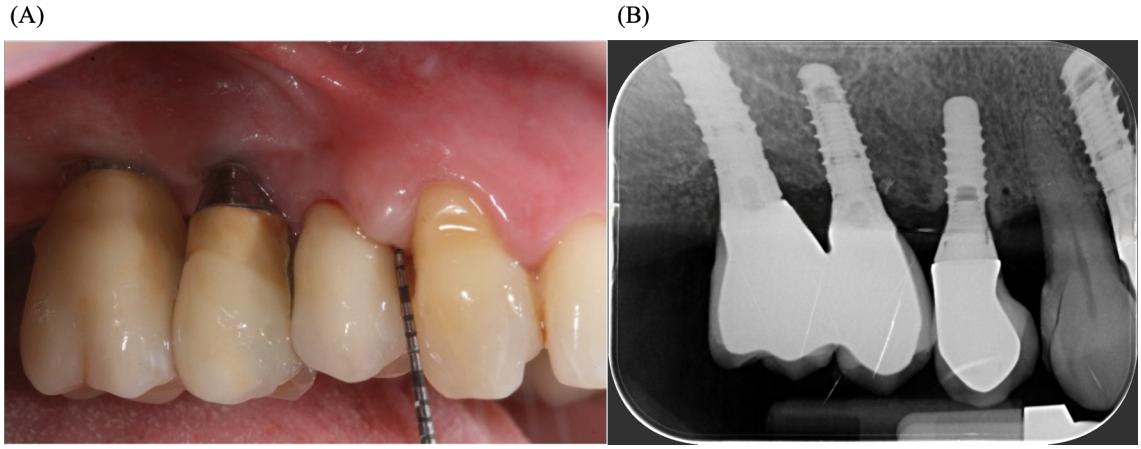


FIGURE 5 Clinical finding of bleeding on probing (A) and absence of radiographic bone loss (B), allowing the diagnosis of peri-implant mucositis.

2.2.4 Therapeutic phase

Following baseline variables collection, both groups received Full-mouth ultrasonic debridement (Fm-UD) (Wennstrom et al., 2005), using a magnetostrictive device (Cavitron Select SPS®, Dentsply Sirona), without the administration of plexus anesthesia. Therefore, fine ultrasonic tips with a silicone insert (SlimLine 30k insert, SofTip implant 30k insert, Dentsply) were used at all sites for plaque and calculus debridement.

The patients assigned to the test group received an additional debridement, exclusively on the experimental units, carried out with a glycine powder air polishing device (StarJet®, Mectron). The subgingival nozzle was applied around each experimental unit (mesial, oral, distal and buccal), allowing the glycine powder (Glycine Powder, Mectron) to exit for 5s within the probable sulcus (Riben-Grundstrom et al., 2015), as recommended by the manufacturer.

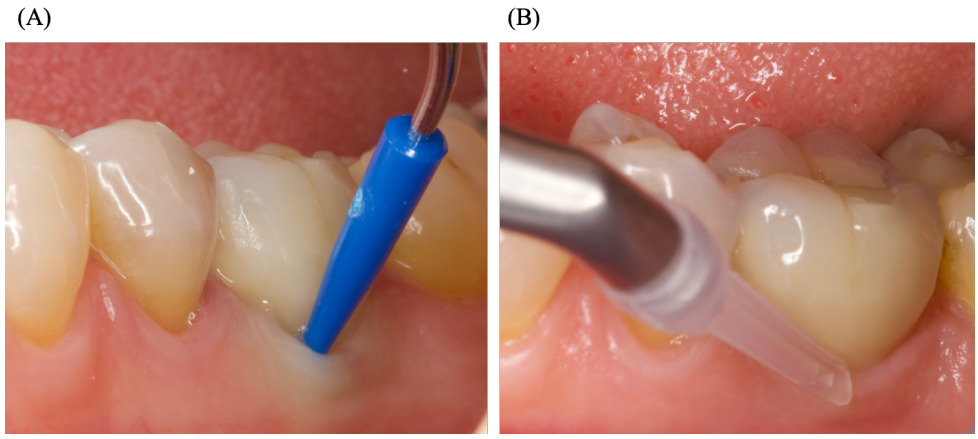


FIGURE 6 Fine ultrasonic tips with a silicone insert (A), used for plaque and calculus debridement; glycine powder air polishing device (StarJet®, Mectron) (B).

At the end of the instrumentation, the participants were asked to assign a score to the discomfort felt during the treatment session, using the visual-analog pain scale (VAS).

2.2.5 Post-therapeutic phase

Follow-up visits

One month after therapy, standardized professional oral hygiene instructions were provided to the participants, with the use of manual toothbrushes, individualized inter-dental brushes or dental floss and a toothpaste containing sodium fluoride.
Two months following the intervention, a second recall visit was scheduled. Patients received re-enforcement of OHI. Based on the adherence to the planned appointments, the compliance of the participants was dichotomously measured (Compliance yes/no). The non-attendance at one or both the follow-up visits, or a delay in the chronogram, defined the patients as erratic (Compliance no).

Re-evaluation visits

Re-evaluation appointments were set at three and twelve months after therapy. During these visits, participants received a full periodontal chart to re-assess all the clinical variables. Besides, the patients were asked to report on the VAS scale the discomfort felt during brushing of the experimental units.

2.2.6 Study outcome

Clinical Implant variables

One calibrated investigator, unaware of the experimental procedure performed, recorded the following clinical outcomes at six sites around the selected implant, with the use of a periodontal probe (UNC 15, HuFriedy, Chicago, IL, USA): (I) BOP was recorded as present or absent at each site (Jepsen et al., 2015); (II) Modified plaque index (mPII) (Mombelli et al., 1987); (III) PPD was measured, to the nearest millimeter, as the distance between the gingival margin and the clinical extent of the gingival sulcus/pocket; (IV) REC was calculated as the distance between the incisal portion of the crown and the mucosal margin at the mid-buccal site.

Clinical Patient variables

The following clinical variables were recorded for patient-level analysis: (I) Plaque and bleeding on probing were assessed dichotomously, six sites per tooth, in order to obtain the FMPS and FMBS (Ainamo & Bay, 1975; O'Leary et al., 1972); (II) PPD; (IV) REC was measured from the gingival margin to the CEJ and (V) CAL was measured as the sum of PPD and REC.

The degree of disease resolution (DR) at the patient level was measured as the proportion of implants with either no BoP + sites (DR1) or <2 BoP + sites (DR2). At the implant level, IDR was assessed dichotomously (yes/no). Resolution of peri-implant inflammation was considered achieved when the implant presented either no BoP + site (IDR1) or <2 BoP + sites (IDR2), in accordance with the recently published ID-COSM consensus report (Tonetti et al., 2023).

Calibration was obtained in double session measurements on 5 randomly selected patients within one week. The kappa score (K) was 0.81-0.85 for dichotomous variables; the intra-class correlation coefficient (ICC) for continuous variables was 0.91-0.95.

Radiographic variables

The prosthetic emergence angle was calculated on the digital radiograph, as the angle between the long axis of the implant and the average tangent of the transitional contour ("The Glossary of Prosthodontic Terms," 2017). The measurement was performed with the software ImageJ, version 1.53e, by the same calibrated examiner.

2.2.7 Sample size calculation

Bop reduction at implant site was selected as the primary outcome variable. The mean difference in the reduction between test and control group was considered clinically relevant at 20% with a common SD of 20% (Pulcini et al., 2019; Ramber et al., 2009). Keeping the latter estimation with an alpha risk of 5% and a statistical power of 90%, the total sample size resulted in 44 individuals. Assuming a potential dropout of 20%, a target experimental sample of 52 participants was determined.

2.2.8 Randomization and allocation concealment

Randomization and allocation concealment were guaranteed by an operator who was not involved in any part of the clinical trial. Participants were randomly assigned to each of the two intervention groups (test/control) by means of a computer-generated sequence created by a software (Stata IC15, "rndseq" command). Each identification number was placed in a sealed, opaque envelope and opened only after the Full-mouth ultrasonic debridement session (Fm-UD).

2.2.9 Statistical analysis

Analyses were conducted using a dedicated software (STATA IC, version. 15, StataCorp LP, TX, USA). The statistician was blinded to the experimental treatments carried out.
Continuous data were reported as mean and confidence interval at 95% (CI 95%, Wilson) and categorical variables were presented as proportion and 95% CI (CI 95%, Wilson).
The test of Shapiro Wilk was applied to evaluate the normal distribution of the variables. Inter-group comparisons were assessed using the paired two-sample Student t-test for continuous variables and with the chi-squared test for categorical variables. Intra-group differences were analyzed by One way analysis of variance (ANOVA test) with Bonferroni post hoc.
A predictive model for disease resolution (nBop <=1 or nBop<=2) as the dichotomic dependent variable was modeled. Baseline Implant (n°Bop at Implant; Group of treatment; Site and position (Mandible/maxilla) of Implant; Type of prosthetic connection; Keratinized mucosa; Radiographic prosthetic angle; mean Ppd; Maximum Ppd) and the patient-level characteristics (Group of treatment; Gender; Smoking habit; Diabetes; Familiarity; Compliance; Full mouth bleeding score) were introduced and the final predictive model was selected through the “all possible equation “(Command “allsets”, Stata. 15C). The Akaike information criterion (AIC) was used to classify the models proposed.
Eventually, to preserve the prognostic balance afforded by randomization, an Intention to treat analysis (ITT) was applied.

3. RESULTS

3.1 Study population

A total of 52 patients (26 test and 26 control) and 132 implants (64 test and 68 control) were included. Five patients, four allocated to the control group and one to the test group, were lost during follow-up for reasons unrelated to the study (FIGURE 4).

3.2 Demographic and clinical variables

The descriptive statistics of demographic and clinical variables assessed at baseline, at the subject level, are displayed in Table 1. Patients were homogenously distributed for age, gender, presence of comorbidities (i.e., Diabetes), family history of periodontal disease, mean number of implants, compliance, oral hygiene habits and VAS score. Test and control groups were comparable in terms of FMPS [test group 53 (47.60 - 58.40); control group 47.27 (39.26 - 55.28)] and FMBS [test group 30.76 (24.31 - 37.21); control group 24.72 (19.75 -29.70)]. The mean number of pockets ≥ 5mm was 11.28 (6.68-15.88) in the test group and 6.41 (3.50-9.31) in the control group (p value>.05).

Implants were equally divided between groups for implant distribution, type of restoration, KT and emergence angle (Table 2). Most of the implants under study were in the posterior area. Cemented prostheses were more frequent in the control group (69% versus 37%, p = 0.005). The mean PPD was 3.08 (2.90 - 3.26) for test group implants and 3.24 (3.05 - 3.42); while the mean of BOP+ sites was 3.23 (2.83 - 3.63) and 3.28 (2.92 - 3.64) for the test and control group, respectively.

Table 1 Baseline demographic and clinical variables, patient level

Variable		Control (*n*=26)	Test (*n*=26)	*p* value
Gender (P [95%CI])	MALE	**15%** *(6% - 35%)*	**31%** *(16% - 51%)*	0.19
	FEMALE	**84%** *(65% - 94%)*	**69%** *(65% - 94%)*	
Age (Mean [95%CI])		**60.96** *(55.89 - 66.04)*	**57.92** *(54.39 - 61.45)*	0.32
Smoking (P [95%CI])	NS	**42%** *(25%-62%)*	**58%** *(38%-75%)*	0.43
	CS	**23%** *(0.11 - 0.43)*	**12%** *(0.04 - 0.31)*	
	FS	**35%** *(19%-55%)*	**31%** *(16%-51%)*	
Diabetes (P [95%CI])	NO	**85%** *(65%-94%)*	**96%** *(76%-99%)*	0.16
	YES	**15%** *(6%-35%)*	**4%** *(1%-24%)*	
Family History of Perio (P [95%CI])	NO	**42%** *(25%-62%)*	**42%** *(25%-62%)*	1
	YES	**58%** *(38%-75%)*	**58%** *(38%-75%)*	
N Implants (Mean [95%CI])		**3.31** *(2.37 - 4.25)*	**2.73** *(2.14 - 3.32)*	0.29
Compliance (P [95%CI])	NO	**35%** *(19%-55%)*	**31%** *(16%-51%)*	0.77
	YES	**65%** *(45%-81%)*	**69%** *(49%-84%)*	
Toothbrush (P [95%CI])	MANUAL	**50%** *(31% - 69%)*	**54%** *(0.35 - 0.72)*	0.78
	ELECTRIC	**50%** *(31% - 69%)*	**46%** *(28%-65%)*	
Interproximal devices (P [95%CI])	NO	**15%** *(6%-35%)*	**23%** *(11%-43%)*	0.48
	YES	**85%** *(65%-94%)*	**77%** *(57%-89%)*	
VAS (treatment) (Mean [95%CI])		**3.5** *(2.70 - 4.30)*	**3.28** *(2.03 - 4.53)*	0.76
% PPD ≥ 5 mm with BoP (Mean [95%CI])		**4.7** *(2.57 - 6.83)*	**8.4** *(4.96 - 11.84)*	0.07
N PPD ≥5 mm with BoP (Mean [95%CI])		**6.41** *(3.50 - 9.31)*	**11.28** *(6.68 - 15.88)*	0.08
FMPS (Mean [95%CI])		**47.27** *(39.26 - 55.28)*	**53** *(47.60 - 58.40)*	0.22
FMBS (Mean [95%CI])		**24.72** *(19.75 -29.70)*	**30.76** *(24.31 - 37.21)*	0.14
Mean PPD implants (Mean [95%CI])		**3.26** *(2.95 - 3.57)*	**3.30** *(3.02 - 3.57)*	0.87
% BoP implants (Mean [95%CI])		**56.31** *(47.19 - 65.42)*	**56.96** *(47.53 - 66.40)*	0.92

Abbreviations: NS, non-smoker; CS, current smoker; FS, former smoker; N implants, number of implants; VAS (treatment), visual analogue scale of pain assessed at treatment; % PPD ≥ 5 mm with BoP, proportion of probing pocket depths ≥ 5mm with bleeding on probing; N PPD ≥ 5 mm with BoP, number of probing pocket depths ≥ 5mm with bleeding on probing; FMPS, full mouth plaque score; FMBS, full mouth bleeding

score; Mean PPD implants, mean probing pocket depth among implants; % BoP implants proportion of BoP + implant sites.

Table 2 Baseline demographic and clinical variables, implant level

Variable		Control (*n*= 68)	Test (*n*= 64)	*p* value
Implant distribution (P [95%CI])	MANDIBLE	**40%** *(29%-53%)*	**46%** *(33%-59%)*	0.77
	MAXILLA	**60%** *(46%-72%)*	**54%** *(41%-67%)*	
Site (P [95%CI])	ANTERIOR	**9%** *(4%-20%)*	**14%** *(7%-26%)*	0.67
	BICUSPID	**49%** *(36%-62%)*	**46%** *(33%-59%)*	
	MOLAR	**42%** *(29%-55%)*	**40%** *(28%-54%)*	
Prosthesis (P [95%CI])	CEMENTED	**69%** *(56%-80%)*	**37%** *(25%-50%)*	0.0
	SCREWED	**31%** *(20%-44%)*	**63%** *(50%-75%)*	
Single crown (P [95%CI])	YES	**45%** *(33%-59%)*	**37%** *(25%-50%)*	0.43
	NO	**55%** *(41%-67%)*	**63%** *(50%-75%)*	
KT (Mean [95%CI])		**2.01** *(1.67 - 2.36)*	**1.78** *(1.39 - 2.17)*	0.37
Emergence Angle M (Mean [95%CI])		**22.81** *(19.83 -25.80)*	**21.38** *(17.78 - 24.98)*	0.54
Emergence Angle D (Mean [95%CI])		**25.76** *(22.18 -29.33)*	**23.66** *(19.79 - 27.52)*	0.43
N BoP (Mean [95%CI])		**3.28** *(2.92 - 3.64)*	**3.23** *(2.83 - 3.63)*	0.87
PPD mean (Mean [95%CI])		**3.24** *(3.05 - 3.42)*	**3.08** *(2.90 - 3.26)*	0.22
PPD max (Mean [95%CI])		**4.37** *(4.09 - 4.64)*	**4.22** *(3.96 - 4.48)*	0.43

Abbreviations: KT, keratinized tissue width; Emergence Angle M, emergence angle mesial; Emergence Angle D, emergence angle distal; N BoP, number of sites positive to bleeding on probing; PPD mean, mean probing pocket depth; PPD max, maximum probing pocket depth.

3.3 Clinical outcomes

3.3.1 Subject-level analysis

Subject-level clinical outcomes at baseline, three and twelve months are shown in Table 3.

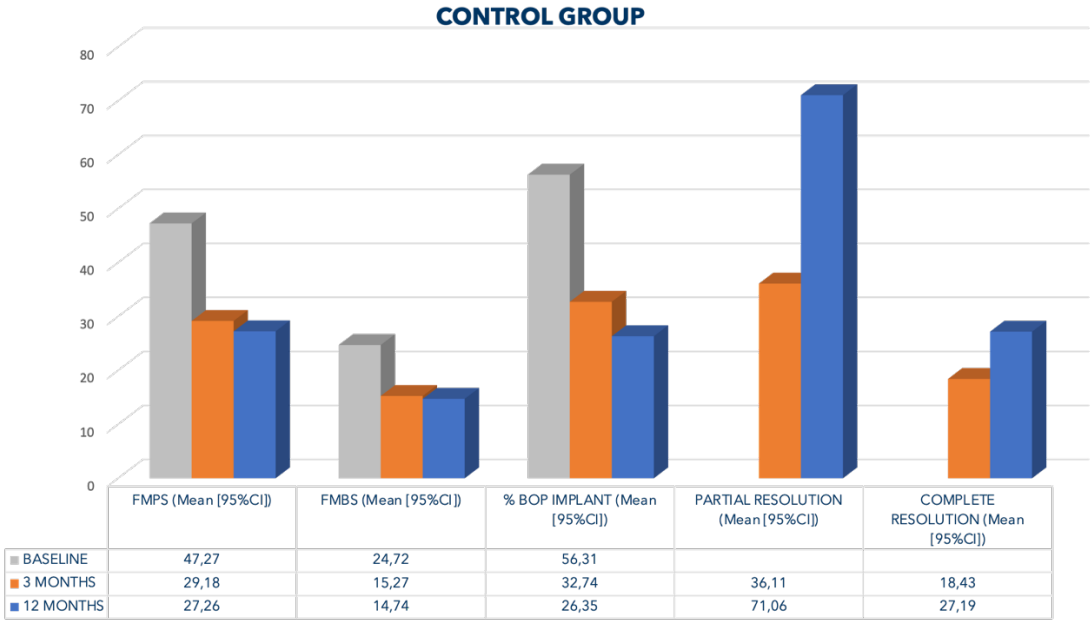
Intra-group analysis demonstrated statistically significant clinical improvements in terms of both FMPS and FMBS after three and twelve months, in both groups. The percentage of all BoP + implant sites (% BoP implants) showed a significant reduction through the months.

Table 3 Intra- and inter-group comparisons, patient level

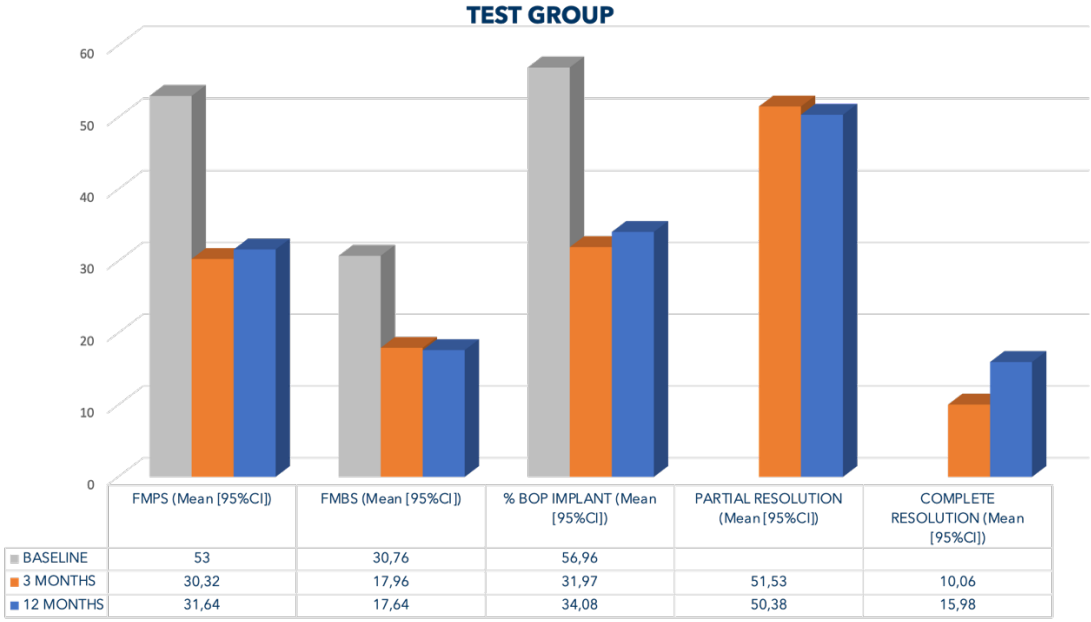
Variable	Control			Test		
	Baseline	3 months	12 months	Baseline	3 months	12 months
% PPD ≥ 5mm with BoP (Mean [95%CI])	**4.7** *(2.57 - 6.83)*	**3.64** *(1.90 - 5.38)*	**3.90** *(1.93- 5.86)*	**8.4** *(4.96 - 11.84)*	**6** *(3.08 - 8.92)*	**5.82** *(2.76- 8.88)*
N PPD ≥ 5mm with BoP (Mean [95%CI])	**6.41** *(3.50 - 9.31)*	**4.90** *(2.40 - 7.41)*	**5.6** *(2.96 - 8.24)*	**11.28** *(6.68 - 15.88)*	**8.24** *(3.95 -12.53)*	**7.5** *(2.81 - 12.19)*
FMPS (Mean [95%CI])	**47.27** Δ *(39.26 - 55.28)*	**29.18** Δ *(23.08 - 35.28)*	**27.26** Δ *(20.51 - 34.01)*	**53** Δ *(47.60 - 58.40)*	**30.32** Δ *(25.59 - 35.04)*	**31.64** Δ *(26.36 - 36.91)*
FMBS (Mean [95%CI])	**24.72** Δ *(19.75 -29.70)*	**15.27** Δ *(11.70 - 18.84)*	**14.74** Δ *(10.57 - 18.90)*	**30.76** Δ *(24.31 - 37.21)*	**17.96** Δ *(14.24 21.68)*	**17.64** Δ *(11.58 - 23.69)*
Mean PPD implants (Mean [95%CI])	**3.26** *(2.95 - 3.57)*	**3.08** *(2.77 - 3.38)*	**3.08** *(2.73 - 3.44)*	**3.30** *(3.02 - 3.57)*	**2.90** *(2.63 - 3.17)*	**2.96** *(2.59 - 3.33)*
% BoP implants (Mean [95%CI])	**56.31** Δ *(47.19 - 65.42)*	**32.74** Δ *(24.39 - 41.08)*	**26.35** Δ *(14.76 - 37.93)*	**56.96** Δ *(47.53 - 66.40)*	**31.97** Δ *(23.62 - 40.32)*	**34.08** Δ *(21.56- 46.59)*
VAS (Mean [95%CI])	**3.5** *(2.70 - 4.30)*	**1.31** *(0.87 - 1.74)*	**1.13** *(0.68 - 1.58)*	**3.28** *(2.03 - 4.53)*	**1.47** *(0.96 - 1.98)*	**1.35** *(0.82 - 1.88)*
Partial resolution (Mean [95%CI])		**36.11** Δ *(20.45 - 51.78)*	**71.05** Δ *(53.12 - 88.98)*		**51.53** *(35.53 - 67.53)*	**50.38** *(30.81- 69.95)*
Complete resolution (Mean [95%CI])		**18.43** *(8.32 - 28.56)*	**27.19** *(12.23 - 42.15)*		**10.6** *(1.90 - 19.30)*	**15.98** *(3.60 - 28.38)*

Abbreviations: % PPD ≥ 5 mm with BoP, proportion of probing pocket depths ≥ 5mm with bleeding on probing; N PPD ≥ 5 mm with BoP, number of probing pocket depths ≥ 5mm with bleeding on probing; FMPS, full mouth plaque score; FMBS, full mouth bleeding score; Mean PPD implants, mean probing pocket depth among implants; % BoP implants proportion of BoP + implant sites.

Δ, p-value < 0.05 for intra-group comparisons.



	FMPS (Mean [95%CI])	FMBS (Mean [95%CI])	% BOP IMPLANT (Mean [95%CI])	PARTIAL RESOLUTION (Mean [95%CI])	COMPLETE RESOLUTION (Mean [95%CI])
BASELINE	47,27	24,72	56,31		
3 MONTHS	29,18	15,27	32,74	36,11	18,43
12 MONTHS	27,26	14,74	26,35	71,06	27,19



	FMPS (Mean [95%CI])	FMBS (Mean [95%CI])	% BOP IMPLANT (Mean [95%CI])	PARTIAL RESOLUTION (Mean [95%CI])	COMPLETE RESOLUTION (Mean [95%CI])
BASELINE	53	30,76	56,96		
3 MONTHS	30,32	17,96	31,97	51,53	10,06
12 MONTHS	31,64	17,64	34,08	50,38	15,98

FIGURE 7 Intra- and inter-group comparisons, patient level

3.3.2 Implant-level analysis

Implant-level clinical outcomes at baseline, three and twelve months are reported in Table 4.

Intra-group comparisons demonstrated statistically significant differences in terms of number of sites bleeding upon probing (N BoP), after three and twelve months, in both groups.

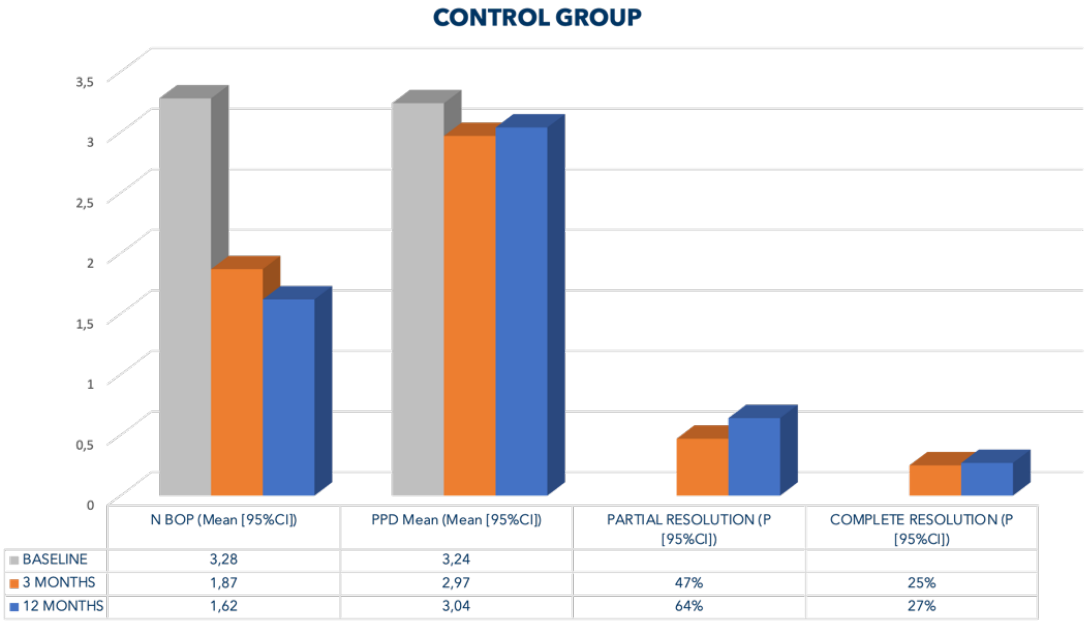
Table 4 Intra- and inter-group comparisons, implant level

Variable	Control			Test		
	Baseline	3 months	12 months	Baseline	3 months	12 months
% PPD ≥ 5mm with BoP (Mean [95%CI])	**4.7** *(2.57 - 6.83)*	**3.64** *(1.90 - 5.38)*	**3.90** *(1.93- 5.86)*	**8.4** *(4.96 - 11.84)*	**6** *(3.08 - 8.92)*	**5.82** *(2.76- 8.88)*
N PPD ≥ 5mm with BoP (Mean [95%CI])	**6.41** *(3.50 - 9.31)*	**4.90** *(2.40 - 7.41)*	**5.6** *(2.96 - 8.24)*	**11.28** *(6.68 - 15.88)*	**8.24** *(3.95 -12.53)*	**7.5** *(2.81 - 12.19)*
FMPS (Mean [95%CI])	**47.27** Δ *(39.26 - 55.28)*	**29.18** Δ *(23.08 - 35.28)*	**27.26** Δ *(20.51 - 34.01)*	**53** Δ *(47.60 - 58.40)*	**30.32** Δ *(25.59 - 35.04)*	**31.64** Δ *(26.36 - 36.91)*
FMBS (Mean [95%CI])	**24.72** Δ *(19.75 -29.70)*	**15.27** Δ *(11.70 - 18.84)*	**14.74** Δ *(10.57 - 18.90)*	**30.76** Δ *(24.31 - 37.21)*	**17.96** Δ *(14.24 21.68)*	**17.64** Δ *(11.58 - 23.69)*
Mean PPD implants (Mean [95%CI])	**3.26** *(2.95 - 3.57)*	**3.08** *(2.77 - 3.38)*	**3.08** *(2.73 - 3.44)*	**3.30** *(3.02 - 3.57)*	**2.90** *(2.63 - 3.17)*	**2.96** *(2.59 - 3.33)*
% BoP implants (Mean [95%CI])	**56.31** Δ *(47.19 - 65.42)*	**32.74** Δ *(24.39 - 41.08)*	**26.35** Δ *(14.76 - 37.93)*	**56.96** Δ *(47.53 - 66.40)*	**31.97** Δ *(23.62 - 40.32)*	**34.08** Δ *(21.56- 46.59)*
VAS (Mean [95%CI])	**3.5** *(2.70 - 4.30)*	**1.31** *(0.87 - 1.74)*	**1.13** *(0.68 - 1.58)*	**3.28** *(2.03 - 4.53)*	**1.47** *(0.96 - 1.98)*	**1.35** *(0.82 - 1.88)*
Partial resolution (Mean [95%CI])		**36.11** Δ *(20.45 - 51.78)*	**71.05** Δ *(53.12 - 88.98)*		**51.53** *(35.53 - 67.53)*	**50.38** *(30.81- 69.95)*
Complete resolution (Mean [95%CI])		**18.43** *(8.32 - 28.56)*	**27.19** *(12.23 - 42.15)*		**10.6** *(1.90 - 19.30)*	**15.98** *(3.60 - 28.38)*

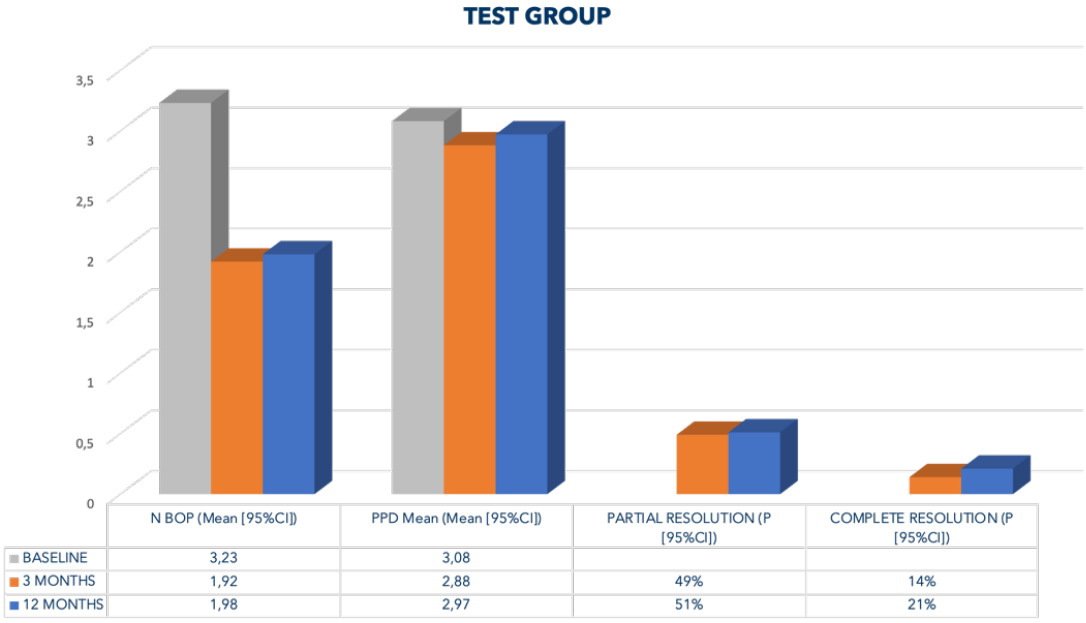
Abbreviations: N BoP, number of sites positive to bleeding on probing; PPD mean, mean probing pocket depth; PPD max, maximum probing pocket depth.

Δ, p-value < 0.05 for intra-group comparisons;

§, p-value < 0.05 for inter-group comparisons.



	N BOP (Mean [95%CI])	PPD Mean (Mean [95%CI])	PARTIAL RESOLUTION (P [95%CI])	COMPLETE RESOLUTION (P [95%CI])
BASELINE	3,28	3,24		
3 MONTHS	1,87	2,97	47%	25%
12 MONTHS	1,62	3,04	64%	27%



	N BOP (Mean [95%CI])	PPD Mean (Mean [95%CI])	PARTIAL RESOLUTION (P [95%CI])	COMPLETE RESOLUTION (P [95%CI])
BASELINE	3,23	3,08		
3 MONTHS	1,92	2,88	49%	14%
12 MONTHS	1,98	2,97	51%	21%

FIGURE 8 Intra- and inter-group comparisons, implant level

3.3.3 Regression models

At patient level analysis (Table 5), considering the partial resolution of the disease as an independent variable, the number of implants (N implants ≤1) and FMBS <25% resulted statistically significant (OR=4.09, p=0.04 and OR=4.59, p= 0.02, respectively).

The best predictive models for implant level variables are reported in Table 6. The complete resolution of the disease at twelve months (nBop=0) was best predicted by the number of BoP sites at baseline (nBop, OR=2.7, p=0.04), the position of the implant (Implant distribution Max, OR=2,1, p=0.15), the type of prostheses (Screwed prosthesis, OR=0.5, p=0.11) and the greatest PD value (PPDmax, OR =2.7, p=0.05). For the partial resolution (nBop<2) the type of prostheses (Screwed prosthesis, OR 2.59, p=0.02) and the mean value of PD (PPD mean, OR=2.23, p=0.04) resulted statistically significant.

Table 5 Logistic multivariate regression model, patient level

Partial Resolution (AUC = 0.7 ; AIC = 64.7 ; BIC = 72.5)						
LR chi²	**Prob > chi²**	**Pseudo R²**				
11.55	0.01	0.17			**95% CI**	
Partial Resolution	**OR**	**SE**	**Z**	***p* value**	**Lower**	**Higher**
N Implants ≤ 1	4.09	3.17	1.82	**0.04**	0.90	18.63
FMBS Baseline < 25	4.59	3.02	2.31	**0.02**	1.26	16.70
Compliance	2.40	1.83	1.15	0.25	0.54	10.75
_cons	0.10	0.08	-2.89	0.0	0.02	0.48
Complete Resolution (AUC = 0.8 ; AIC = 64.7 ; BIC = 72.5)						
LR chi²	**Prob > chi²**	**Pseudo R²**				
0.9	0.36	0.07			**95% CI**	
Complete Resolution	**OR**	**SE**	**Z**	***p* value**	**Lower**	**Higher**
N Implants ≤ 1	4.33	6.73	0.94	0.35	0.21	90.85
_cons	0.08	0.08	-2.47	0.01	0.01	0.59

Abbreviations: N implants, number of implants; FMBS Baseline, full mouth bleeding score recorded at baseline.

Table 6 Logistic multivariate regression model, implant level

Partial Resolution (AUC = 0.7 ; AIC = 148.3 ; BIC = 159.2)						
LR chi²	**Prob > chi²**	**Pseudo R²**				
12.69	0.01	0.08				
Partial Resolution	**OR**	**SE**	**Z**	***p* value**	**95% CI Lower**	**Higher**
Screwed Prosthesis	2.59	1.05	2.35	**0.02**	1.16	5.75
Single crown	2.04	0.85	1.71	0.09	0.90	4.63
PPD mean > 3 mm	2.23	0.92	1.94	**0.04**	0.99	5.02
_cons	0.44	0.17	-2.15	0.03	0.21	0.93
Complete Resolution (AUC = 0.7 ; AIC = 122.7 ; BIC = 136.3)						
LR chi²	**Prob > chi²**	**Pseudo R²**				
10.98	0.03	0.08				
Complete Resolution	**OR**	**SE**	**Z**	***p* value**	**95% CI Lower**	**Higher**
N BoP < 3	2.70	1.45	1.85	**0.04**	0.94	7.75
Implant distribution Max	2.06	1.03	1.44	0.15	0.77	5.50
Screwed Prosthesis	0.47	0.22	-1.58	0.11	0.18	1.02
PPD max < 4 mm	2.69	1.35	1.96	**0.05**	1.00	7.25
_cons	0.08	0.05	3.77	0.0	0.02	0.30

Abbreviations: PPD mean, mean probing pocket depth; N BoP, number of sites positive to bleeding on probing; implant distribution Max, implant distribution maxilla; PPD max, maximum probing pocket depth.

4. DISCUSSION

The current clinical trial demonstrated that professional mechanical biofilm removal, irrespective of the adjunctive use of glycine powder air polishing, resulted in a statistically significant diminution of bleeding (FMBS, % BoP implants, N BoP) and plaque levels (FMPS) at twelve months re-evaluation. At patient level, according to the predictive model, the number of implants (N Implants ≤ 1) and the proportion of bleeding sites (FMBS<25%) can increase the likelihood to resolve the inflammation. Similarly, at implant level, the number of bleeding sites, the initial depth of the sulcus and the type of prosthetic connection (screwed/cemented) can play as prognostic variables. Both treatment strategies are positively accepted by the patients (VAS scale).
The present outcomes align with the results of several studies investigating the efficacy of GPAP for the treatment of peri-implant mucositis. Ji et al. identified a significant reduction in PPD and BI through the treatment, although they failed to outline any adjunctive benefit of GPAP as compared with conventional ultrasonic debridement (Ji et al., 2014). Similarly, Riben-Grundstrom et al. demonstrated steady improvements in PPD and BoP, but suggested a limited superior effect of air polishing as an alternative to mechanical debridement (Riben-Grundstrom et al., 2015).
In line with the previously argued findings, evidence about the efficacy of adjunctive measures used to treat peri-implant mucositis (i.e., laser, aPDT, antiseptics, local and systemic antibiotics, probiotics) reported negligible additional effects in terms of BoP and PD diminution compared to the mechanical debridement alone (Dommisch et al., 2022; Ramanauskaite et al., 2021).
At twelve months of follow-up, the complete absence of bleeding (DR1) (Sanz et al., 2012) was achieved only in 16% (test group) and 27% (control group) of individuals. The latter is a common finding throughout the literature: recent evidence, indeed, highlighted that none of the investigated NST protocols of peri-implant mucositis reported a complete resolution of peri-implant inflammation (Barootchi et al., 2020; Philip et al., 2021; Ramanauskaite et al., 2021; Schwarz et al., 2015).
Such clinical results, corroborate the idea that several anatomical and iatrogenic factors, still not fully understood, jeopardize the accomplishment of a complete resolution of the peri-implant disease.

Interestingly, in the current sample, the proportion of patients who have completely resolved the inflammation increased alongside the 12 months. In line with the present findings, a previous experimental peri-implant mucositis model (Salvi et al., 2012) demonstrated the slower reversibility of peri-implant mucositis, compared to gingivitis. At implant level, a probable peri-implant sulcus less than 4 mm influences the efficacy of mechanical treatment, fostering the resolution of peri-implant mucositis by 3 times (OR 2.69; IC 1,00-7,25). Accordingly, an in vitro experiment demonstrated that peri-implant sulci deeper than 4 mm hinder the accessibility of mechanical and air-polishing devices, limiting the percentage of artificial biofilm removal (Discepoli et al., 2022). Moreover, Chan and co. have clinically outlined the role of a "mucosal tunnel" deeper than 3mm in terms of response to mechanical peri-implant mucositis therapy. Implant with deeper peri-implant mucosal tunnel displayed a delayed and incomplete resolution of clinical inflammation after professional cleaning (Chan et al., 2019). From a clinical standpoint, the current results, and the background available, raise some doubts about the need to submerge the implant platform in a deeper sub-crestal position. Such a clinical approach, indeed, could increase the risk of developing biological complications, especially in patients susceptible to periodontal disease.

Screw-retained implant restorations resulted to be significant predictors for DR2 ($p= 0.02$). This finding reflects the evidence that cement-retained prostheses often leave extra-coronal residual cement, offering a retentive surface for biofilm accumulation. The role of cement remnants as a predisposing factor in the pathogenesis of peri-implant diseases has been extensively documented (Heitz-Mayfield & Salvi, 2018; Linkevicius et al., 2013; Pesce et al., 2015).

The subject-level analysis demonstrated that, whenever the patient had no more than 1 implant and a baseline FMBS < 25%, the odds of reaching partial resolution after twelve months increased by 4 times. This finding is in line with the results of a previous investigation, in which a higher number of implants increased the risk of biological complications (Vignoletti et al., 2019). Indeed, multiple implants can challenge the control of the biofilm by both the professional and the patient (Gurgel et al., 2017; Karoussis et al., 2003; Pimentel et al., 2018). Moreover, the number of implants, interpreted as a measure of the extent of tooth loss even due to periodontitis, can be considered an indirect indicator of the individual's susceptibility to periodontal disease.

In this perspective, the history of periodontitis has been extensively linked to a higher risk of peri-implant biological complications (Derks et al., 2016a; Karoussis et al., 2003; Roccuzzo et al., 2010).

Such findings sustain the importance of implementing interventions at the treatment plan stage, defined as 'primordial' interventions (Herrera et al., 2023), and of performing an individual implant-disease risk assessment (IDRA) (Heitz-Mayfield et al., 2020). Detecting modifiable risk factors prior to the beginning of implant therapy can minimize the chances of developing biological complications (Herrera et al., 2023). Furthermore, the IDRA, through the identification of systemic and local risk factors, allows to improve the outcomes of peri-implant disease treatment and to establish a proper supportive peri-implant care program (SPIC) (Heitz-Mayfield & Salvi, 2018; Herrera et al., 2023).

However, for the correct interpretation of the current results, it should be acknowledged that the experimental sample displayed a certain degree of erratic compliers. One third of the individuals failed to regularly attend the periodontal support visits scheduled. This feature could have influenced the level of plaque (FMPS) that was, indeed, slightly higher than expected. Therefore, the proportion of implants and individuals able to obtain complete resolution of the disease might have been negatively affected.

5. CONCLUSIONS

In conclusion, the present study demonstrated that, regardless of the adjunctive use of GPAP, and despite significant improvements of clinical signs of peri-implant inflammation, DR may not be expected from non-surgical peri-implant therapy; additionally, the initial levels of bleeding and probing depth have a strong impact on the achievement of the treatment endpoint (DR).

It is therefore fundamental to reduce compromises related to the early phases of implant therapy, in terms of inadequate implant positioning and deep MT, as they increase the chance of occurrence of biological complications. Moreover, a prevention program in accordance with the risk profile of the patient should begin "ab initio".

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