Chapter

The Effect of Implant Surface Design and Their Decontamination Methods in Peri-Implantitis Treatment

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Abstract

Different titanium implant surfaces are prone to microbial colonization and dental plaque accumulation contributing to peri-implantitis pathogens adherence and growth. In conjunction with systemic, local, and implant-based factors such as micro- and macro-designs, implant location, and region, these pathogens can cause a complex inflammatory response resulting in peri-implantitis and deleterious bone loss. Implant surface decontamination plays a crucial and important step in peri-implantitis therapy. The primary goal of implant surface decontamination is to eradicate bacteria and their products outside of implant pits and grooves reducing inflammation and promoting tissue regeneration and/or reparation. Various implant surface decontamination methods such as mechanical, chemical or physical methods have been proposed to prevent bacterial resistance development or/and surface damage. The chapter aimed to assess if implant microdesign could influence the decontamination method choice.

Keywords: peri-implantitis, implant design, implant surface, decontamination methods, peri-implantitis therapy

1. Introduction

Dental implants have become highly predictable routine therapeutic strategy in daily practice for a missing teeth replacement in the partial or total edentulous patients' treatment.

Osseointegration presents close bone-to-implant contact (BIC) and depends on several factors such as implant micro- and macro-design which play crucial roles in long-term implant survival success rate. Implant macro-construction (implant shape, number and shape of implant threads) is designed to improve osseointegration mechanism and obtain implant primary stability resisting detrimental forces occurring during physiological functions [1–4]. Various implant surfaces were developed to enhance osseointegration mechanism accelerating and strengthening bone formation providing better stability [5]. Additional modification of implant surfaces increases surface roughness with aim to improve bone healing especially in the region with poor bone quantity or quality stimulating bone growth, and enabling immediate or early loading protocols [6].

This modification increases surface roughness as well, making it another important parameter for effective osseointegration.

The mechanism of osseointegration could invert unpredictably into a pathological process leading to inflammatory reactions in soft tissue (peri-mucositis) or a subsequent bone loss around an osseointegrated implant. This process could cause peri-implantitis onset, and as consequence implant failure [7–9]. As a disease of the modern era, peri-implantitis is defined as a plaque-associated pathological condition characterized by clinical signs of inflammation such as bleeding on probing (BOP) with or without suppuration, peri-implant probing depths increase (PPD), and clinical attachment loss (CAL) along with radiographic bone loss [10].

Major aetiological factors in the peri-implantitis development are virulent pathogenetic anaerobic bacteria (*Porphyromonas gingivalis, Prevotella intermedia, A. actinomycetemcomitans, Tannerella forsythia, Treponema denticola)* isolated from dental biofilm around the implant triggering the deleterious immunological reaction of the host tissue, and causing progressive surrounding bone loss [11]. Furthermore, some facultative isolated a gram-positive pathogen (*Staphylococcus aureus*) and fungi (*C. albicans*) are considered to contribute to peri-implantitis onset [12, 13].

In addition, a myriad of patient-related factors (genetic, diabetes mellitus, cardiovascular diseases, genetics, smoking), local factors (periodontitis, residual cement, poor oral hygiene, etc.), and implant-based factors are introduced as risks that could induce onset and severity of peri-implantitis [8, 14–18].

1.1 Implant-based and implant-related factors in peri-implantitis

1.1.1 Implant macro-design associated with peri-implantitis

Specific implant topography, i.e., its macro-design such as body shape, threads number, and collar design as well as micro-design aimed to speed the process of osseointegration enabling a rapid implant loading [19]. However, these dental implant components themselves could be addressed as one of the implant-based risk factors associated with peri-implantitis onset.

A variety of commercially available implants with cylindrical or conical body shape, one-, double- or triple-threads number and different thread shapes are constructed not only to accelerate the osseointegration process but also to minimize a hazard shear force acting instantaneously. Moreover, the implant macro-design aimed to prevent additional further marginal bone loss that could jeopardize implant long-term stability after prosthetic rehabilitation. In contrast, cylindric implants and implants with triple-threads demonstrated the production of greater detrimental shear forces [19] resulting in higher bone loss with implant failure, respectively.

To speed up and shorten implant placement by increasing the threads number on the implant body (double- and triple-thread) could, unfortunately, induce more pressure forces [2]. This resulted in increased bone loss, especially at triple-threads compared to single-thread [19]. In a laboratory model, using finite element analysis (FEA), threads shape was used to stimulate and estimate stress distribution between implants and cortical or cancellous bone [20] indicating that "V" shape and a broader-square shape generated less stress in cancellous bone than other examined threads. In contrast, implants with "V" and butter thread shapes generated higher forces that induced bone defect formation [20, 21], and may consequently contribute to peri-implantits. Although these facts arising from *in vitro* and *in vivo* conditions, localisation and bone quality could affect the success of implant therapy associated with implant macro-design. However, a significant incidence of peri-implantitis has been reported in the posterior region of the mandible [22–25]

suggesting that the location and region of implant placement might be associated with peri-implantitis development.

Implant macro-design could also cause excess cement retention that could act as rough surface facilitating an adherence of microorganism and inflammation around peri-implant mucosa with subsequent bone loss. Moreover, other implant-based factors such as implant-abutment connection type, prosthetic rehabilitation, and occlusal overload, could also be taken into consideration as risks for peri-implantitis onset [8, 18, 26–28].

Since the current literature are insufficient in providing evidence whether the implant macrodesign parameters such as implant body shape and dimension, and threads number could be the possible risk factors associated with the initiation and progression of peri-implantitis, further studies are required.

1.1.2 Implant micro-design in correlation with peri-implantitis onset

Over the last few decades, implant surfaces topography has been modified to enhance BIC rates, primary implant stability as well as positive host-to-implant response aiming to attain long-term implant treatment success rates. Bone response to implant topography modification has been specifically related to surface roughness, surface free energy and surface chemistry.

The implant's surface could be "smooth" (machined) or rough. Roughness Average (Ra) or Arithmetical Mean Height (Sa) parameters are used to describe the roughness of dental implant surfaces referring to the height of the surface structure in two or three dimensions. Mostly, implant surface roughness could be divided into four groups: smooth implant surface with Sa roughness value less than 0.5 μm, minimally rough surface (Sa value 0.5–1.0 μm), moderately rough surface (Sa value 1.0–2.0 μm), and rough surface (Sa value more than 2.0 μm). Several methods are reported in the literature to create implant roughness including acid etching, sandblasting, titanium plasma spraying, and hydroxyapatite (HA) coating, contributing to changes in implant physicochemical properties [5, 29, 30]. Currently available dental implant systems could have either moderately rough surfaces such as SLA, TiUnite, OsseoSpeed, and TiOblast implants or a rough surface such as Ankylos, IMZ or TPS implants [29]. Nevertheless, these implant topography features may play a role in peri-implantitis onset [5, 29, 31].

A study by Polizzi and al. demonstrated that peri-implantitis was more commonly detected at implants with a rough TiUnite surface compared with the minimally rough machined surface [32]. Furthermore, the spontaneous and greater bone loss occurred at the implants with a TiUnite surface compared to Turned, SLA or TiOblast surfaces [33–35]. The hazardous effect of TiUnite surface could be explained by its microdesign and the presence of grooves and pits that might encourage bacterial adhesion [35]. Although microbial plaque accumulation had been detected on novel modified anodized surfaces (TiUltra), this surface affected minimal bone loss and inflammation resulting in marginal bone stability [36]. Additionally, zirconium surface promoted plaque reduction *in vitro* conditions compared to Ti-machined, sandblasted and acid-etched surfaces.

Implant roughness and surface free energy influenced the dental plaque accumulation and biofilm formation inducing peri-implantitis [37, 38]. According to a literature review by Teughels et al. [37] increasing surface roughness above 0.2 μm resulted in biofilm formation and bacteria adhesion. Despite differences in surface roughness, another *in vivo* study recorded plaque accumulation on three different titanium disk surfaces (machined, RBM sandblasted and Xpeed) [39]. Additionally, some periodontal bacteria such as *P. gingivalis* could have the ability and greater bacterial viability on titanium compared with zirconium abutments [40]. *S. aureus*,

which is introduced as one of the main harmful bacteria in peri-implantitis development, has an immense affinity to colonize on titanium implant surfaces [41, 42]. Even though the role of *C. albicans* in peri-implantitis disease is still being investigated, this species has also been isolated around implants with diagnosed peri-implantitis. In combination with *Streptococcus* species, *C. albicans* has the ability to grow on titanium surfaces forming a robust mixed biofilm that could cause inflammatory tissue reactions with potential tissue damage [43–45].

The development of bioactive titanium surface coatings with antibacterial properties has been considered as an additional strategy for controlling biofilm formation [46]. Different antimicrobials, active molecules, compounds, and ions were incorporated into implant surface to stimulate bactericidal or/and bacteriostatic effect on surrounding tissue decreasing in this way bacterial adhesion on implant surface. Unfortunately, this strategy has a short-term effect since the remains of dead cells on the uncleaned surfaces may act as bridges for bacteria coaggregation and colonization [47] leading to possible peri-implantitis onset.

1.2 Other peri-implantitis risk factors

Other risk factors such as smoking, diabetes, medications used in the treatment of chronic diseases may influence bone metabolism supporting plaque accumulation and adversely impacting the periimplant-tissue response. Despite limited evidence, survival of implants in patients with diabetes could be disturbed by high blood glucose level, that affects the immune system impairing tissue repair and host defenses against dental plaque [48], therefore accelerating peri-implantitis development or progression. Special caution in the peri-implantitis treatment should be advised in patients with chronic disorders/ diseases.

2. Treatment of peri-implantitis

Peri-implantitis is a complex multi-microbial and multifactorial disease, thus, therapy continues to be a challenge. It has been suggested that peri-implantitis surgical therapy is superior to non-surgical one [49]. Implant surface decontamination is an important but at the same time difficult step in peri-implantitis treatment. The goal of implant surface decontamination is to completely remove all causative bacteria from the implant surface preparing the tissue for regeneration and re-osseointegration [12]. Considering the possible role of micro- and micro-design on peri-implantitis initiation, special care should be taken in the process of implant surface decontamination.

The removal of microbes from the implant surface may cause possible implant surface damage. As a result of surface damage, surface chemical oxide layer changes could lead to induced corrosion, acidic pH, changes in surface roughness, plaque accumulation, and osteoclast activation impairing implants biocompatibility [50]. Additionally, different methods of decontamination could generate mechanical or chemical processes on implant surfaces releasing titanium' ions and particles, and promoting the pathogenic biofilm growth on treated surfaces as well [45].

Although there is no standardized protocol for peri-implantitis treatment, many methods of implant surface decontamination have been proposed including mechanical methods, chemical methods, laser, photodynamic therapy, and implantoplasty, usually combined with systemic antibiotics administration [51–60]. Accordingly, this chapter aimed to determine which method of implant surface decontamination could be successfully performed assessing comparably if implant topography could have influenced the decontamination method choice in peri-implantitis treatment.

2.1 Mechanical and chemical methods of implant surface decontamination

The removal of biofilms and calculus is essential for long-term clinical success and bone regeneration [12]. Therefore, mechanical removal of granulation tissue and surface cleaning presents the first steps in peri-implantitis or periodontal therapy. Ideal mechanical methods should be capable of completely removing deposits and bacteria along with their products from the implant surface without altering or damaging implant surface integrity and biocompatibility, or affecting the implant-tissue interface. Due to implant surface macro- and micro-design as well as bacterial characteristics, it is difficult to achieve long-term results using a mechanical method alone. Therefore, this method is usually combined with chemical methods, photodynamic or laser therapy.

Several instruments such as curettes and brushes have been proposed for mechanical implant surface decontamination. Metal (stainless steel) curettes, burs and conventional sonic and ultrasonic scalers, have been shown to damage the smooth or rough (TPS and SLA) implant surface leaving behind the debris by removing the surface coating, threads and edges. Nevertheless, these instruments are only used when smooth surface of implant, implantoplasty, is required [61]. Titanium curettes were also advised to be used with caution due to their tendency to leave marks on the implant surface increasing the depth of the surface roughness and in this way causing an inability to effectively remove biofilm [62]. Plastic curettes did not leave any surface scratches on different implants surfaces. However, their limited flexibility and size resulted in incomplete plaque removal in screw-type implants [63]. Even when combined with chemical methods such as chlorhexidine gluconate (CHX), plastic curette was not effective in biofilm removal from Osseotite® or SLA titanium disks [64] thereby only being recommended for use during maintenance care [65].

Peri-implantitis treatment performing the Vector system improved oral hygiene, yet showing no improvement in clinical parameters compared to carbon curettes after six months of follow-ups [66]. According to systematic reviews, Vector systems with carbon tips efficiently removed biofilms from polished titanium and SLA surfaces. Hence, the potential to produce SLA and TPS surface damage was found to be a drawback, and could be possible explanation for poor clinical outcomes [61, 63, 67].

The market offers a variety of rotating titanium brushes that are successfully used in combination with other chemical agents or physical methods for implant surface decontamination (**Figure 1**). Rotating brushes effectively clean SLA, TiUnite, and OsseoSpeed surfaces without compromising their properties [67]. Contrary to this, *in vitro* study demonstrated that titanium brushes could create titanium surface craters with remaining titanium particles on SLA surface. The significance of this result must be interpreted carefully since this study was conducted under *in vitro* conditions, the coating surfaces were not contaminated, and the treatment was done on "sterile" surfaces [68]. In a recent randomized clinical trial (RCT), rotating titanium brushes combined with 3% H_2O_2 during regenerative surgical procedures of peri-implantitis significantly reduced both PPD and BOP after 12 months from the surgery [69]. The titanium brushes could be proposed for implant surface decontamination during the surgery.

Other mechanical methods of implant surface decontamination, air powder-water sprays, have not shown to be superior in terms of improvement in clinical parameters and possible re-osseointegration compared to other mechanical methods. Recent *in vitro* study revealed that air-power-water spray was not effective in removing biofilms from titanium surfaces, grades 4 and 5, acid-etched, sand-blasted, or functionally anodized surfaces compared to electrolytic methods that

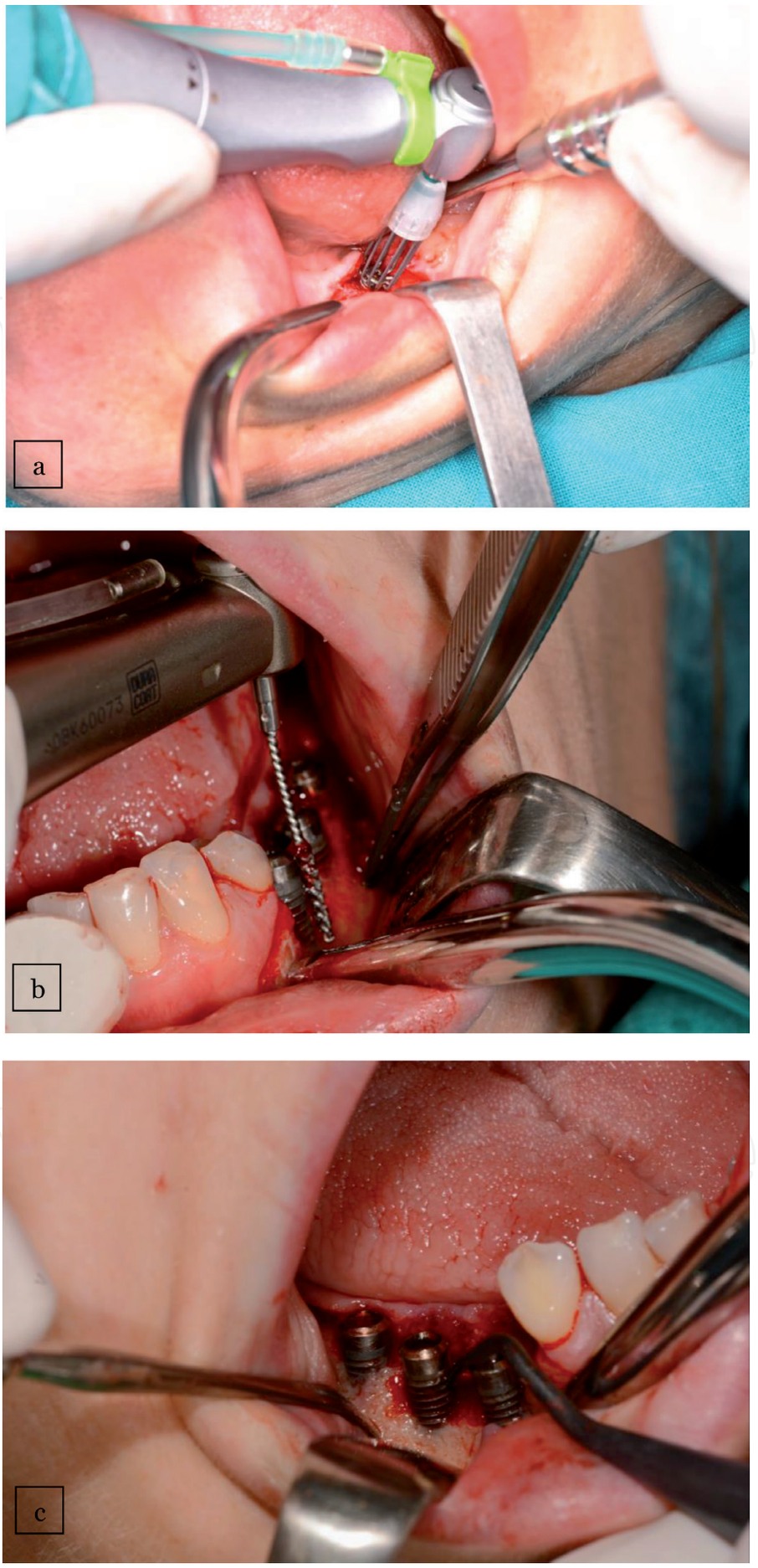

Figure 1.
Mechanical methods of implant surface decontamination by performing two different titanium brushes (a, b,) and graphite curette (c).

completely eradicate biofilms from treated surfaces [70]. Furthermore, air-powder system properties such as water flow, powder medium, air pressure, and exposure time seemed to influence biofilm removal and implant surface changes. There was a significant difference in the effectiveness of the medium for hydroxyapatite/tricalcium phosphate and hydroxyapatite, while the cleaning effect was less pronounced on titanium dioxide and phosphoric acid. In addition, amino acid glycine powder effectively removed microbes from implants without altering implant surface as compared to classical sodium bicarbonate powder. It was found that the sodium bicarbonate powder left craters and abrasive residue on the surface. As a result of this, the immune system may be impaired causing an inflammatory response of the tissue [67].

Implantoplasty is another mechanical method of implant surface decontamination that is usually used during surgical peri-implantitis therapy to smoothen the supracrestal exposed implant surface (**Figure 2**). Whenever there is a persistent supracrestal bone defect (Class II bone defect, classified by Schwarz [71]), implantoplasty appears to be the most effective treatment. Among the benefits of implantoplasty there is a very low bacteria adhesion and recolonization rate.

Due to the implant surface roughness, it could not be possible to remove bacteria and their waste products completely. Therefore, it is recommended to be combined with antiseptics and antibiotics. Various chemical agents such as chlorhexidine gluconate (CHX), hydrogen peroxide (H_2O_2), citric acid, and phosphoric acid have been proposed as means to decontaminate titanium implant surfaces in both non-surgical and surgical therapies.

The CHX is a commonly used antiseptic agent that is considered a 'gold standard' in various treatment procedures. It is a time-dependent chemical agent which exhibits both bactericidal and bacteriostatic effects. With increasing CHX concertation, in both pure titanium discs and titanium-zirconium alloy discs there was a decrease in the mean number of colony-forming units indicating antibacterial dose–response and biofilm control [72]. Even so, the clinical and microbiological outcomes in one of RCTs had not shown statistical differences when two CHX concentrations (2% vs. 0.12% CHX + 0.5% CPC) were used for the decontamination of commercially available implant surfaces during peri-implantitis resective surgery [73]. These results were consistent with our prior published study in which implant surface decontamination was performed by applying 1% gel of CHX followed by saline solution irrigation during regenerative surgery. Our study concluded that this chemical procedure had insufficient effectiveness in clinical and microbiological results [57]. Under *in vitro* conditions, CHX can remain on implant surfaces gradually releasing and acting within 24 hours against bacteria without harming the surface. Nevertheless, a special caution needs to be taken during implant surface decontamination due to CHX cytotoxic effects on osteoblastic, endothelium, and fibroblastic cells [74]. Irrigation by saline solution for approximately a minute could alleviate the negative effect of CHX; however, it should be noted that this irrigation might reduce CHX-substantivity. Furthermore, because of CHX's low cleaning capacity, gauze soaked in saline solution should be taken after CHX application to mechanically remove debris and death cells that might act as a substrate for recolonization, and consequently, disease reappearance.

The use of adjuvant systemic or local antibiotic therapy could also be affected by implant surface topography in peri-implantitis therapy. A successful treatment outcome was documented in only 45% of treated implants by Carcuac et al. In this study, 79% of implants with non-modified surface features and 34% of implants with modified surfaces had successful treatment after peri-implant surgery [75]. In the Heitz-Mayfield et al. study, a significant improvement of clinical parameters was achieved within 12 months after an open-flap surgical procedure of moderate and advance

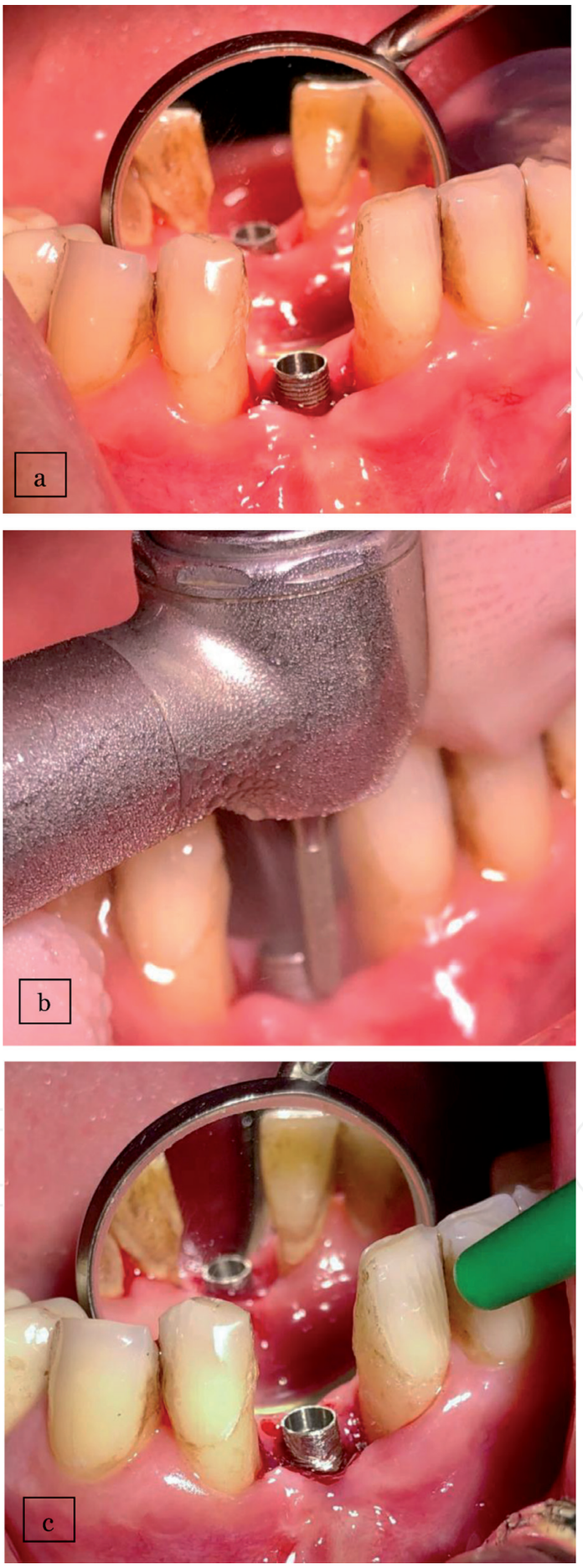

Figure 2.
Implantoplasty as a mechanical method for implant surface decontamination: Exposed implant surface (a), implantoplasty procedure (b), smooth implant surface (c).

peri-implantitis followed by adjuvant systemic antibiotics administration (amoxicillin and metronidazole) and antiseptic solution (0.12% CHX). Approximately 47% of implants with various surface topographies completely resolved inflammation postoperatively. However, within 12 months of implant surgery, bone continues to lose on implants with porous anodized, titanium plasma-sprayed, and machine surfaces [54]. Systemic antibiotics had limited penetration into the biofilm attached to the titanium implant surface. These findings would support the recommendation that implant surface should be carefully evaluated prior to adjuvant systemic antibiotics administration. Apart from this, broad-spectrum antibiotics' excessive use, their side effects, and allergic reactions have led to bacterial-resistance development, thus additional care should be taken in their administration.

In order to overcome these drawbacks of chemical and mechanical methods, novel methods such as laser or photodynamic therapy were introduced to improve implant surface decontamination.

2.2 Application of laser and photodynamic therapy in peri-implantitis treatment

2.2.1 Laser use in peri-implantitis therapy

In the late 1980's, a laser system was introduced in dentistry [76] increasing laser popularity in dental implantology considerably. Due to the laser's capacity to achieve satisfactory cutting, induce good coagulation, and antibacterial effect, the laser is widely used in dental implantology for the safe second stage surgery of submerging implants, peri-implant soft tissue plastic surgery, and implant surface decontamination. Lasers have been described to possess ability to facilitate implant site preparation enhancing bone healing and osseointegration [56, 77, 78].

The lasers' use in non-surgical and surgical peri-implantitis therapy was widely examined, especially its effects on implant surface decontamination and re-osseointegration. Titanium implant surfaces have greater absorption characteristics resulting in the surface overheating and alteration, so special consideration should be given when they are exposed to the laser. A literature review has recommended a few types of lasers for decontaminating implant surfaces [56].

Er: YAG laser is suggested for successful implant surface decontamination with a tendency to achieve re-osseointegration (**Figure 3**). Safe irradiation settings for this laser should be above 300 mJ/10 Hz for 10s achieving efficiently a bactericide effect, and not increasing implant temperature or altering the surface of polished or

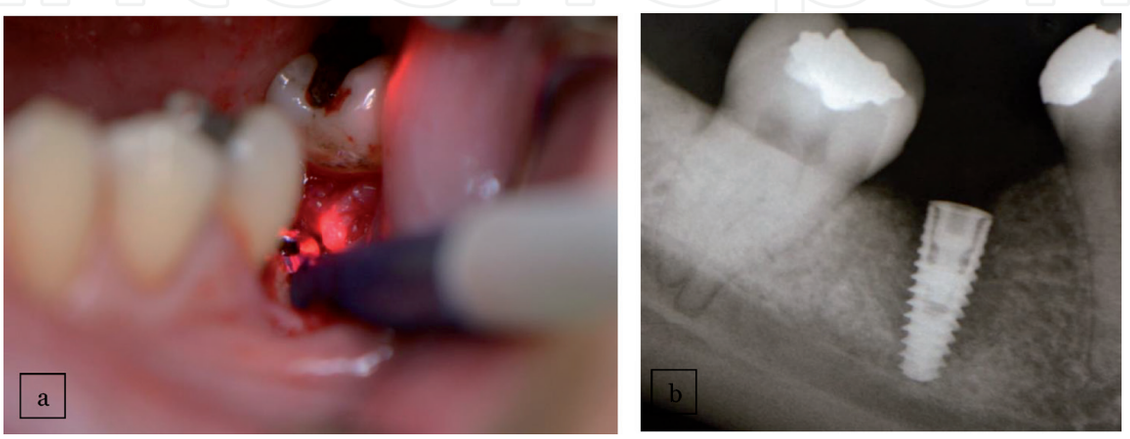

Figure 3.
Implant surface decontamination by performing laser therapy in the treatment of early peri-implantitis stage (LightWalker, Fotona, Slovenia) (a) implant radiography before laser therapy (b).

SLA implants [79]. Favorable long-term outcomes following treatment of peri-implantitis with Er: YAG lasers were observed in a few clinical studies [80, 81]. A case report study on zirconium implants found that Er: YAG led to improvements in clinical parameters (PPD and BOP) six months after peri-implantitis surgery [82].

CO2 (carbon dioxide laser) and gallium-aluminum-arsenide lasers (one of the diode lasers) are introduced as safe methods for implant decontamination with antibacterial effects. Depending on implant surface topography, special attention should be taken considering the time of laser exposure, power, and irradiation mode (continues, CW, or pulse, PW, mode). *In vitro* study had shown that CO2 and diode laser with lower settings and at 810 nm wavelength could effectively destroy *P. gingivalis* on zirconium and titanium surfaces, whereas a higher setting of diode laser is required in order to eliminate *S. sanguis* and *P. gingivalis* adhered to zirconium surface [83]. Furthermore, diode laser of 810 nm and 4 W power showed a slight alteration on moderate roughness sandblasting implant surface compared to 3 W power laser settings [68]. On the polished and SLA implant surfaces, CO2 laser set in CW mode, up to 4 W, and diode laser set at 810 nm, CW mode, and 1 W–3 W showed no alteration [79], and thereby could be recommended as safe implant surface decontamination method in peri-implantitis treatment. To determine the influence of these recommended parameters on implant surface decontamination methods for different peri-implantitis stages and implant topographies, further experiments and clinical studies are required.

On the other hand, Nd: YAG lasers could induce surface alteration by causing surface melt and increasing its roughness. This type of laser is contraindicated for any dental implant surgical interventions. Application of diode lasers with other wavelengths or fiber systems should be used with special care as the laser light directly contacting the bone may cause thermal damage.

2.2.2 Photodynamic therapy assessment in peri-implantitis therapy

A novel antimicrobial treatment modality, photodynamic therapy (PDT) was introduced for the various oral infection treatments. The PDT mechanism is based on a suitable wavelength low-energy single-frequency diode laser activating a photoactive material (photosensitiser) that binds a target cell. In this mechanism, the photochemical oxygen-dependent reaction is induced producing very reactive superoxide radicals, such as single oxygen that causes photogenic species death.

Studies demonstrated the PDT efficiency in treating peri-implantitis with a particular emphasis on implant surfaces decontamination using the procedure (**Figure 4**). A few *in vitro* studies have demonstrated a reduction and elimination of bacteria from implant surfaces performing PDT [58, 60, 84, 85]. Haas et al. achieved a significant reduction in number of periodontopathogen bacteria (*P. gingivalis, P. intermedia* and *A. actinomycetemcomitans*) from machined, plasma-flame-sprayed, etched, and hydroxyapatite-coated implant surfaces [85]. Other *in vitro* studies also showed a significant reduction in the total number of bacteria on titanium implants (Bredent, Sedan, Germany) [58], zirconium implants [84], and anodized rough implant surface (TiUnite, Nobel) without any implant surface changes. Considering implant topography on zirconium surfaces, PDT has revealed greater efficiency in eliminating a total number of bacteria compared to titanium surfaces [86].

In our previous clinical study, the positive effects of PDT on microbiological reduction and clinical outcomes improvement after peri-implantitis surgery were assessed three months postoperatively [57]. PDT proved to be a very effective decontamination method for various titanium implant surfaces according to the research. Additionally, the further follow-up observation aimed to show the maintenance results achieved by performing PDT, six and 12 months postoperatively.

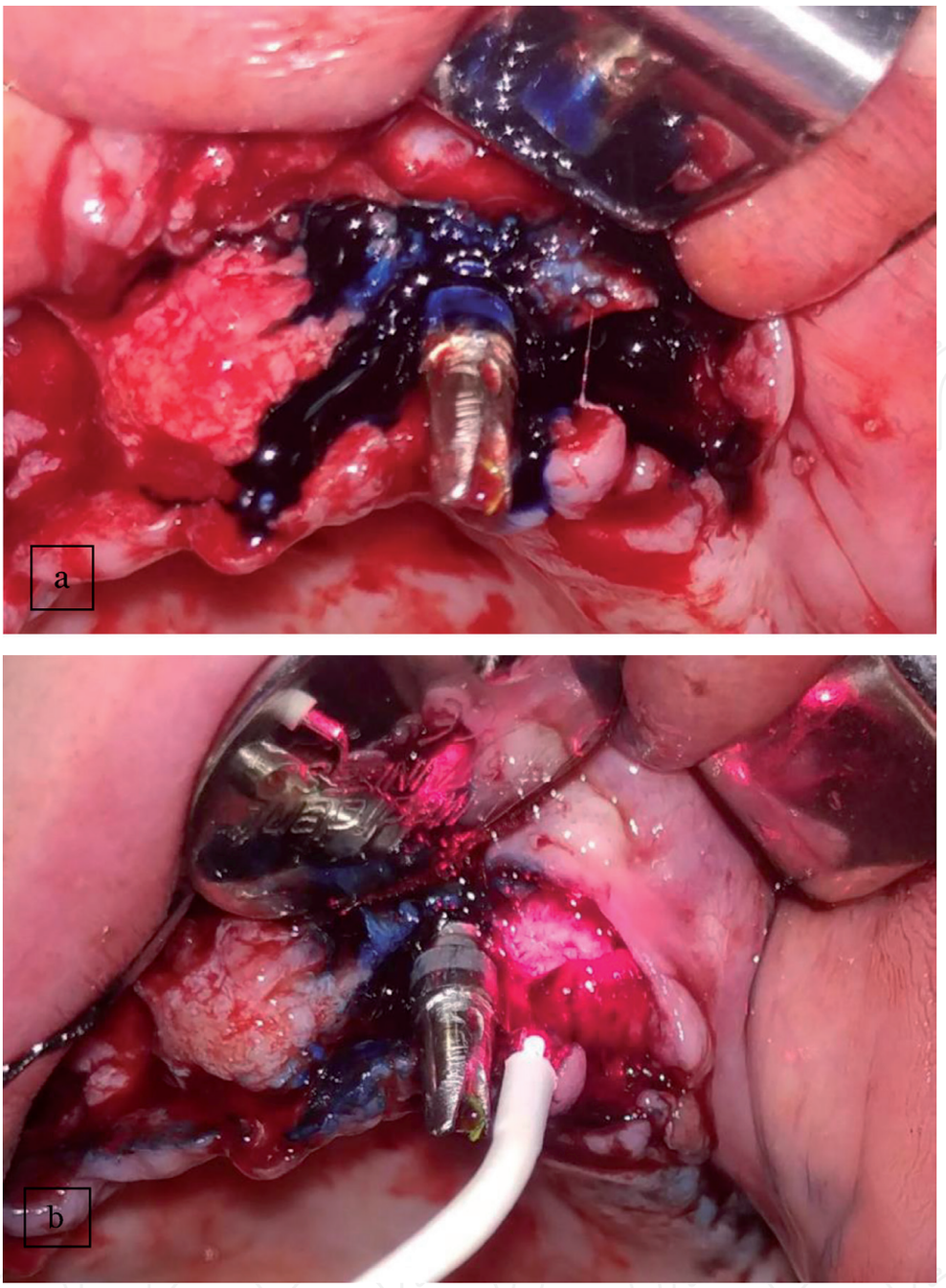

Figure 4.
Photodynamic therapy (HELBO, photodynamic systems GmbH, Bredent medical GmbH & Co KG) performed for implant surface decontamination during peri-implantitis surgery: Photosensitizer- phenothiazine chloride application (HELBO® blue photosensitizer) on implant surface and surrounding tissue (a) followed by diode laser irradiation with 2D fiber optic probe (b).

Patients' inclusion criteria, follow-up parameters and surgical treatment procedures have previously been reported in detail [57]. In brief, the surgical regenerative treatment procedure was performed on each patient with early or moderate peri-implantitis. During the surgery, after careful mucoperiosteal flap elevation, granulation tissue removal, patients were randomly divided into two groups. In one group (21 systemically healthy patients), PDT (HELBO, Photodynamic Systems GmbH, Wels, Austria) was performed for implant surface decontamination, while in another group (19 systemically healthy patients), CHX was used as a chemical decontamination method. Clinical and microbiological outcomes were used to assess treatment success. Microbiological samples were taken both from the pockets around the implant prior to any procedure and during follow-ups, and during

surgical procedures before and immediately after surface decontamination. Samples were cultured and biochemically analyzed using standard procedures for anaerobic bacteria diagnosis. Detailed microbiological sample collecting and analyses were explained in the previous study [57]. The results were examined using SPSS 20.0.

Different pathogenic bacteria (**Table 1**) were isolated either from various examined implant surfaces (**Table 2**) during the surgical therapy or from the peri-implant pockets prior to any treatment. The presence of *S. aureus* on implant surfaces confirmed the earlier statements of bacteria affinity to colonize the titanium implant surface [41, 42]. This could emphasize the possible influence of *S. aureus* on the onset and progression of peri-implantitis. Furthermore, *C. albicans* was isolated from peri-implant pockets indicating a possible role of *Candida species* in peri-implantitis onset. This observation reported that mechanical implant surface decontamination followed by PDT along with regenerative surgical therapy successfully reduced pathogenic bacteria (**Table 1**) and improved clinical parameters in terms of PPD and BOP reduction three, six and 12 months postoperatively (**Table 3**). Similar clinical parameters' improvements and pathogen reduction in peri-implantitis treatment were recorded in other clinical and experimental studies [87–89]. Performing either PDT or titanium brushes combined with PDT for implant surface decontamination in *in vitro* study, *S. aureus* was successfully reduced from polished, SLA, and SLAactive implant surfaces [41].

	T_0	S_1	S_2	T_1	T_2	T_3
P.g.	4 (14)	8 (29)	0 (0)¥	0 (0)¥	0 (0)	0 (0)
P.i.	5 (17.9)	6 (21.4)	0 (0)¥	0 (0)¥	0 (0)	0 (0)
P.s.	5 (17.9)	3 (10.7)	0 (0)¥	0 (0)¥	0 (0)¥	2 (7.1)
F.n.	1 (3.6)	4 (14.3)	0 (0)¥	0 (0)	0 (0)	0 (0)
A.n.	2 (7.1)	8 (29)	0 (0)¥	3 (10.7)	2 (10.7)	3 (10.7)
V.	9 (32.1)	9 (32.1)	2 (7.1)¥	2 (7.1) ¥	5 (17.9)	7 (28)
S.a.	0 (0)	3 (10.7)	0 (0)	0 (0)	0 (0)	0 (0)
A.o.	1 (3.6)	0 (0)	0 (0)	3 (10.7)	3 (10.7)	2 (7.1)

¥Statistically significant change from baseline, three, six and 12 months after therapy, and also before and after implant surface decontamination during surgical procedure by Cochran Test, $p < 0.05$;
T_0 – isolated bacteria form peri-implant pocket before any treatment; T_1, T2, T3- isolated bacteria form peri-implant pocket three, six and 12 months postoperatively; S_1 and S_2– isolated bacteria from implant surface decontamination before and immediately after decontamination followed by PDT during surgical therapy;
P.g. - Porphyromonas gingivalis; P.i.- Prevotella intermedia; P.s. - Peptostreptococcus spp.; F.n.- Fusobacterium nucleatum; A.n.- A. naeslundii; V.- Veillonella spp.; S.a.- Staphylococcus aureus; A.o.- A. odontolyticus.

Table 1.
Number (n) of culture-positive implants at baseline and culture-negative after selected bacteria decontamination with photodynamic therapy.

Implant surface	Number (N)
Acid washed surface, MTX	10%
Titanium-oxide layer, TiUnit	47%
Osseospeed surface	16%
Machined polished surface	27%

Table 2.
Percentage of various implant topographies decontaminated by photodynamic therapy.

Parameter	Baseline	3 months	6 months	12 months	p-value
PPD (mm)	5.74 ± 1.55	3.26 ± 0.79	2.52 ± 0.92	2.52 ± 0.54	<0.001*
BOP	86 ± 19.5	0.67 ± 3.3	0.3 ± 1.1	0.67 ± 3.1	<0.001*

**Significant statistical difference measured before and after surgical therapy by T test;*

Table 3.
Mean pocket probing depth (PPD) ± SD, and mean bleeding on probing (BOP) for each implant at baseline and three, six and 12 months later.

One of the goals in peri-implantitis therapy is the total elimination of pathogens allowing the tissue to regenerate. As a final result, re-osseointegration is considered to be an essential outcome of peri-implantitis treatment that may be affected by different implant surface decontamination protocols. Experimental outcomes demonstrated partial peri-implant defect reconstruction and re-osseointegration after performing PDT for SLA implant surface decontamination combined with or without guide bone regeneration (GBR) and collagen membrane [90]. One of the earliest experimental studies evaluated the ability of PDT to re-osseointegrate peri-implantitis defects around a variety of implant surfaces utilizing GBR and polytetrafluoroethylene membrane [91]. Study results indicated that the TPS surface showed a greater re-osseointegration rate than HA implant surface. Based on these findings, PDT may have potential effects in peri-implantitis treatment with a potential to lead to re-osseointegration. Different bone grafts application in filling peri-implant defects might contribute to clinical outcomes improvement that may be an explanation for earlier interpreted clinical results.

Nevertheless, decontamination of implant surfaces aims to recreate the conditions that existed before infection or after the implant was placed and integrated. Hence, in order to achieve re-integration, and considering implant topography as well, both micro- and macro-design need to be almost identical to what existed before the implant was placed enhancing osteoblast stimulation and creating re-novel BIC. Accordingly, peri-implantitis requires special consideration in determining the appropriate decontamination methods since there are no standard treatment protocols. Consequently, more clinical trials are required to determine the efficacy of proposed decontamination methods for implant surfaces, with or without regenerative and resective methods.

3. Conclusion

Implant micro- and macro-design could be possible risk factors in peri-implantits onset or progression. Various implant surfaces may lead to peri-implantitis. In addition, choosing the right decontamination method could be influenced by the very implant surface. Mechanical methods coupled with PDT or a chemical method such as CHX and H_2O_2 may be effective in peri-implantitis treatment. Antibiotics administration in peri-implant treatment, on the other hand, must be taken with caution. Laser decontamination of implant surfaces is indicated provided that all parameters necessary for successful treatment are respected.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Albrektsson, T., et al., *Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man.* Acta Orthop Scand, 1981. **52**(2): p. 155-70.

[2] Ryu, H.S., et al., *The influence of thread geometry on implant osseointegration under immediate loading: a literature review.* J Adv Prosthodont, 2014. **6**(6): p. 547-54.

[3] Albrektsson, T. and A. Wennerberg, *Oral implant surfaces: Part 1--review focusing on topographic and chemical properties of different surfaces and in vivo responses to them.* Int J Prosthodont, 2004. **17**(5): p. 536-43.

[4] Javed, F., et al., *Role of primary stability for successful osseointegration of dental implants: Factors of influence and evaluation.* Interv Med Appl Sci, 2013. **5**(4): p. 162-7.

[5] Wennerberg, A. and T. Albrektsson, *Effects of titanium surface topography on bone integration: a systematic review.* Clin Oral Implants Res, 2009. **20 Suppl 4**: p. 172-84.

[6] Novaes, A.B., Jr., et al., *Influence of implant surfaces on osseointegration.* Braz Dent J, 2010. **21**(6): p. 471-81.

[7] Schwarz, F., G. Iglhaut, and J. Becker, *Quality assessment of reporting of animal studies on pathogenesis and treatment of peri-implant mucositis and peri-implantitis. A systematic review using the ARRIVE guidelines.* J Clin Periodontol, 2012. **39 Suppl 12**: p. 63-72.

[8] Schwarz, F., et al., *Peri-implantitis.* J Periodontol, 2018. **89 Suppl 1**: p. S267-s290.

[9] Misch, C.E., M.W. Bidez, and M. Sharawy, *A bioengineered implant for a predetermined bone cellular response to loading forces. A literature review and case report.* J Periodontol, 2001. **72**(9): p. 1276-86.

[10] Berglundh, T., et al., *Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.* J Clin Periodontol, 2018. **45 Suppl 20**: p. S286-s291.

[11] Lang, N.P., T.G. Wilson, and E.F. Corbet, *Biological complications with dental implants: their prevention, diagnosis and treatment.* Clin Oral Implants Res, 2000. **11 Suppl 1**: p. 146-55.

[12] Mombelli, A., *Microbiology and antimicrobial therapy of peri-implantitis.* Periodontol 2000, 2002. **28**: p. 177-89.

[13] Heitz-Mayfield, L.J. and N.P. Lang, *Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis.* Periodontol 2000, 2010. **53**: p. 167-81.

[14] Dalago, H.R., et al., *Risk indicators for Peri-implantitis. A cross-sectional study with 916 implants.* Clin Oral Implants Res, 2017. **28**(2): p. 144-150.

[15] Heitz-Mayfield, L.J., et al., *Group 4 ITI Consensus Report: Risks and biologic complications associated with implant dentistry.* Clin Oral Implants Res, 2018. **29 Suppl 16**: p. 351-358.

[16] Heitz-Mayfield, L.J.A., F. Heitz, and N.P. Lang, *Implant Disease Risk Assessment IDRA-a tool for preventing peri-implant disease.* Clin Oral Implants Res, 2020. **31**(4): p. 397-403.

[17] Mombelli, A., N. Muller, and N. Cionca, *The epidemiology of peri-implantitis.* Clin Oral Implants Res, 2012. **23 Suppl 6**: p. 67-76.

[18] Zandim-Barcelos, D.L., et al., *Implant-based factor as possible risk for*

peri-implantitis. Braz Oral Res, 2019. **33**(suppl 1): p. e067.

[19] Abuhussein, H., et al., *The effect of thread pattern upon implant osseointegration.* Clin Oral Implants Res, 2010. **21**(2): p. 129-36.

[20] Misch and S. C.E., T. & Bidez, M.W., *Scientifific rationale for dental implant design*, in *Contemporary Implant Dentistry*, Misch and C.E., Editors. 2008: St Louis: Mosby. p. 200-229.

[21] Hansson, S. and M. Werke, *The implant thread as a retention element in cortical bone: the effect of thread size and thread profile: a finite element study.* J Biomech, 2003. **36**(9): p. 1247-58.

[22] Albrektsson, T., et al., *Statements from the Estepona consensus meeting on peri-implantitis, February 2-4, 2012.* Clin Implant Dent Relat Res, 2012. **14**(6): p. 781-2.

[23] Aguirre-Zorzano, L.A., et al., *Prevalence of peri-implant inflammatory disease in patients with a history of periodontal disease who receive supportive periodontal therapy.* Clin Oral Implants Res, 2014.

[24] Serino, G. and A. Turri, *Extent and location of bone loss at dental implants in patients with peri-implantitis.* J Biomech, 2011. **44**(2): p. 267-71.

[25] Dvorak, G., et al., *Peri-implantitis and late implant failures in postmenopausal women: a cross-sectional study.* J Clin Periodontol, 2011. **38**(10): p. 950-5.

[26] Korsch, M., U. Obst, and W. Walther, *Cement-associated peri-implantitis: a retrospective clinical observational study of fixed implant-supported restorations using a methacrylate cement.* Clin Oral Implants Res, 2014. **25**(7): p. 797-802.

[27] Linkevicius, T., et al., *Does residual cement around implant-supported restorations cause peri-implant disease? A retrospective case analysis.* Clin Oral Implants Res, 2013. **24**(11): p. 1179-84.

[28] Quesada-García, M.P., et al., *Dental Implant Stability Is Influenced by Implant Diameter and Localization and by the Use of Plasma Rich in Growth Factors.* Journal of Oral and Maxillofacial Surgery, 2012. **70**(12): p. 2761-2767.

[29] De Bruyn, H., et al., *Implant surface roughness and patient factors on long-term peri-implant bone loss.* Periodontology 2000, 2017. **73**(1): p. 218-227.

[30] Li, D., et al., *Biomechanical comparison of the sandblasted and acid-etched and the machined and acid-etched titanium surface for dental implants.* J Biomed Mater Res, 2002. **60**(2): p. 325-32.

[31] Zitzmann, N.U. and T. Berglundh, *Definition and prevalence of peri-implant diseases.* J Clin Periodontol, 2008. **35** (8 Suppl): p. 286-91.

[32] Polizzi, G., F. Gualini, and B. Friberg, *A two-center retrospective analysis of long-term clinical and radiologic data of TiUnite and turned implants placed in the same mouth*. Int J Prosthodont, 2013. **26**(4): p. 350-8.

[33] Albouy, J.P., et al., *Spontaneous progression of peri-implantitis at different types of implants. An experimental study in dogs. I: clinical and radiographic observations.* Clin Oral Implants Res, 2008. **19**(10): p. 997-1002.

[34] Albouy, J.P., et al., *Implant surface characteristics influence the outcome of treatment of peri-implantitis: an experimental study in dogs.* J Clin Periodontol, 2011. **38**(1): p. 58-64.

[35] Fickl, S., et al., *Experimental Peri-Implantitis around Different Types of Implants - A Clinical and Radiographic Study in Dogs.* Clin Implant Dent Relat Res, 2015. **17 Suppl 2**: p. e661-9.

[36] Susin, C., et al., *Safety and efficacy of a novel, gradually anodized dental implant surface: A study in Yucatan mini pigs.* Clinical Implant Dentistry and Related Research, 2019. **21**(S1): p. 44-54.

[37] Teughels, W., et al., *Effect of material characteristics and/or surface topography on biofilm development.* Clin Oral Implants Res, 2006. **17 Suppl 2**: p. 68-81.

[38] Weerkamp, A.H., et al., *The Role of Surface Free Energy in the Early In vivo Formation of Dental Plaque on Human Enamel and Polymeric Substrata.* Microbial Ecology in Health and Disease, 1989. **2**(1): p. 11-18.

[39] Conserva, E., et al., *Plaque accumulation on titanium disks with different surface treatments: an in vivo investigation.* Odontology, 2018. **106**(2): p. 145-153.

[40] Meza-Siccha, A.S., et al., *In Vitro Evaluation of Bacterial Adhesion and Bacterial Viability of Streptococcus mutans, Streptococcus sanguinis, and Porphyromonas gingivalis on the Abutment Surface of Titanium and Zirconium Dental Implants.* Int J Dent, 2019. **2019**: p. 4292976.

[41] Widodo, A., et al., *An in vitro study on disinfection of titanium surfaces.* Clinical Oral Implants Research, 2016. **27**(10): p. 1227-1232.

[42] Salvi, G.E., et al., *One-year bacterial colonization patterns of Staphylococcus aureus and other bacteria at implants and adjacent teeth.* Clin Oral Implants Res, 2008. **19**(3): p. 242-8.

[43] Leonhardt, A., S. Renvert, and G. Dahlen, *Microbial findings at failing implants.* Clin Oral Implants Res, 1999. **10**(5): p. 339-45.

[44] Souza, J.G.S., et al., *Biofilm Interactions of Candida albicans and Mitis Group Streptococci in a Titanium-Mucosal Interface Model.* Appl Environ Microbiol, 2020. **86**(9).

[45] Souza, J.G.S., et al., *Targeting implant-associated infections: titanium surface loaded with antimicrobial.* iScience, 2021. **24**(1): p. 102008.

[46] Ferraris, S. and S. Spriano, *Antibacterial titanium surfaces for medical implants.* Mater Sci Eng C Mater Biol Appl, 2016. **61**: p. 965-78.

[47] Koo, H., et al., *Targeting microbial biofilms: current and prospective therapeutic strategies.* Nat Rev Microbiol, 2017. **15**(12): p. 740-755.

[48] *Academy Report: Peri-Implant Mucositis and Peri-Implantitis: A Current Understanding of Their Diagnoses and Clinical Implications.* Journal of Periodontology, 2013. **84**(4): p. 436-443.

[49] Schwarz, F., et al., *Influence of different treatment approaches on non-submerged and submerged healing of ligature induced peri-implantitis lesions: an experimental study in dogs.* J Clin Periodontol, 2006. **33**(8): p. 584-95.

[50] Louropoulou, A., D.E. Slot, and F.A. Van der Weijden, *Titanium surface alterations following the use of different mechanical instruments: a systematic review.*

[51] Levin, L., et al., *Water jet with adjunct chlorhexidine gel for nonsurgical treatment of peri-implantitis.* Quintessence Int, 2014.

[52] Schwarz, F., et al., *Impact of the method of surface debridement and decontamination on the clinical outcome following combined surgical therapy of peri-implantitis: a randomized controlled clinical study.* J Clin Periodontol, 2011. **38**(3): p. 276-84.

[53] Carcuac, O., et al., *The effect of the local use of chlorhexidine in surgical treatment of experimental*

peri-implantitis in dogs. J Clin Periodontol, 2014.

[54] Heitz-Mayfield, L.J., et al., *Anti-infective surgical therapy of peri-implantitis. A 12-month prospective clinical study.* Clin Oral Implants Res, 2012. **23**(2): p. 205-10.

[55] Valderrama, P. and T.G. Wilson, Jr., *Detoxification of implant surfaces affected by peri-implant disease: an overview of surgical methods.* Int J Dent, 2013. **2013**: p. 740680.

[56] Romanos, G.E., et al., *Lasers use in dental implantology.* Implant Dent, 2013. **22**(3): p. 282-8.

[57] Rakašević, D., et al., *Efficiency of photodynamic therapy in the treatment of peri-implantitis – A three-month randomized controlled clinical trial.* Srp Arh Celok Lek, 2016. **144**(9-10): p. 478-84.

[58] Azizi, B., et al., *Antimicrobial Efficacy of Photodynamic Therapy and Light-Activated Disinfection Against Bacterial Species on Titanium Dental Implants.* Int J Oral Maxillofac Implants, 2018. **33**(4): p. 831-837.

[59] de Waal, Y.C., et al., *Implant decontamination during surgical peri-implantitis treatment: a randomized, double-blind, placebo-controlled trial.* J Clin Periodontol, 2013. **40**(2): p. 186-95.

[60] Marotti, J., et al., *Decontamination of dental implant surfaces by means of photodynamic therapy.* Lasers Med Sci, 2013. **28**(1): p. 303-9.

[61] Louropoulou, A., D.E. Slot, and F. Van der Weijden, *The effects of mechanical instruments on contaminated titanium dental implant surfaces: a systematic review.* Clin Oral Implants Res, 2014. **25**(10): p. 1149-60.

[62] Mengel, R., et al., *An in vitro study of the treatment of implant surfaces with different instruments.* Int J Oral Maxillofac Implants, 1998. **13**(1): p. 91-6.

[63] Louropoulou, A., D.E. Slot, and F.A. Van der Weijden, *Titanium surface alterations following the use of different mechanical instruments: a systematic review.* Clin Oral Implants Res, 2012. **23**(6): p. 643-658.

[64] Schwarz, F., et al., *Influence of plaque biofilm removal on reestablishment of the biocompatibility of contaminated titanium surfaces.* J Biomed Mater Res A, 2006. **77**(3): p. 437-44.

[65] Fox, S.C., J.D. Moriarty, and R.P. Kusy, *The effects of scaling a titanium implant surface with metal and plastic instruments: an in vitro study.* J Periodontol, 1990. **61**(8): p. 485-90.

[66] Karring, E.S., et al., *Treatment of peri-implantitis by the Vector system.* Clin Oral Implants Res, 2005. **16**(3): p. 288-93.

[67] Louropoulou, A., D.E. Slot, and F. Van der Weijden, *Influence of mechanical instruments on the biocompatibility of titanium dental implants surfaces: a systematic review.* Clin Oral Implants Res, 2015. **26**(7): p. 841-50.

[68] Lollobrigida, M., et al., *The Prevention of Implant Surface Alterations in the Treatment of Peri-Implantitis: Comparison of Three Different Mechanical and Physical Treatments.* Int J Environ Res Public Health, 2020. **17**(8).

[69] de Tapia, B., et al., *The adjunctive effect of a titanium brush in implant surface decontamination at peri-implantitis surgical regenerative interventions: A randomized controlled clinical trial.* J Clin Periodontol, 2019. **46**(5): p. 586-596.

[70] Ratka, C., et al., *The Effect of In Vitro Electrolytic Cleaning on*

Biofilm-Contaminated Implant Surfaces. J Clin Med, 2019. **8**(9).

[71] Schwarz, F., et al., *Surgical therapy of advanced ligature-induced peri-implantitis defects: cone-beam computed tomographic and histological analysis.* J Clin Periodontol, 2011. **38**(10): p. 939-49.

[72] Souza, J.G.S., et al., *Dose-response effect of chlorhexidine on a multispecies oral biofilm formed on pure titanium and on a titanium-zirconium alloy.* Biofouling, 2018. **34**(10): p. 1175-1184.

[73] de Waal, Y.C., et al., *Implant decontamination with 2% chlorhexidine during surgical peri-implantitis treatment: a randomized, double-blind, controlled trial.* Clin Oral Implants Res, 2014.

[74] Giannelli, M., et al., *Effect of chlorhexidine digluconate on different cell types: a molecular and ultrastructural investigation.* Toxicol In Vitro, 2008. **22**(2): p. 308-17.

[75] Carcuac, O., et al., *Adjunctive Systemic and Local Antimicrobial Therapy in the Surgical Treatment of Peri-implantitis: A Randomized Controlled Clinical Trial.* J Dent Res, 2016. **95**(1): p. 50-7.

[76] Myers, T.D., W.D. Myers, and R.M. Stone, *First soft tissue study utilizing a pulsed Nd:YAG dental laser.* Northwest Dent, 1989. **68**(2): p. 14-7.

[77] Schwarz, F., et al., *Influence of different treatment approaches on the removal of early plaque biofilms and the viability of SAOS2 osteoblasts grown on titanium implants.* Clin Oral Investig, 2005. **9**(2): p. 111-7.

[78] Schwarz, F., et al., *Influence of implant bed preparation using an Er:YAG laser on the osseointegration of titanium implants: a histomorphometrical study in dogs.* J Oral Rehabil, 2007. **34**(4): p. 273-81.

[79] Stubinger, S., et al., *Surface alterations of polished and sandblasted and acid-etched titanium implants after Er:YAG, carbon dioxide, and diode laser irradiation.* Int J Oral Maxillofac Implants, 2010. **25**(1): p. 104-11.

[80] Schwarz, F., et al., *Four-year follow-up of combined surgical therapy of advanced peri-implantitis evaluating two methods of surface decontamination.* J Clin Periodontol, 2013. **40**(10): p. 962-7.

[81] Schwarz, F., et al., *Combined surgical therapy of advanced peri-implantitis evaluating two methods of surface decontamination: a 7-year follow-up observation.* J Clin Periodontol, 2017. **44**(3): p. 337-342.

[82] Schwarz, F., et al., *Non-surgical treatment of peri-implant mucositis and peri-implantitis at zirconia implants: a prospective case series.* J Clin Periodontol, 2015. **42**(8): p. 783-788.

[83] Hauser-Gerspach, I., S. Stübinger, and J. Meyer, *Bactericidal effects of different laser systems on bacteria adhered to dental implant surfaces: an in vitro study comparing zirconia with titanium.* Clinical Oral Implants Research, 2010. **21**(3): p. 277-283.

[84] Azizi, B., et al., *Antimicrobial efficacy of photodynamic therapy and light-activated disinfection on contaminated zirconia implants: An in vitro study.* Photodiagnosis Photodyn Ther, 2018. **21**: p. 328-333.

[85] Haas, R., et al., *Elimination of bacteria on different implant surfaces through photosensitization and soft laser. An in vitro study.* Clin Oral Implants Res, 1997. **8**(4): p. 249-54.

[86] Gabrić, D., et al., *Evaluation of the Antimicrobial Efficacy of Different Types of Photodynamic Therapy on the Main Pathogenic Bacteria of Peri-Implantitis*. 2020.

[87] Dortbudak, O., et al., *Lethal photosensitization for decontamination of implant surfaces in the treatment of peri-implantitis.* Clin Oral Implants Res, 2001. **12**(2): p. 104-8.

[88] Wang, H., et al., *Adjunctive photodynamic therapy improves the outcomes of peri-implantitis: a randomized controlled trial.* Aust Dent J, 2019. **64**(3): p. 256-262.

[89] Hayek, R.R., et al., *Comparative study between the effects of photodynamic therapy and conventional therapy on microbial reduction in ligature-induced peri-implantitis in dogs.* J Periodontol, 2005. **76**(8): p. 1275-81.

[90] Ramos, U.D., et al., *Comparison between two antimicrobial protocols with or without guided bone regeneration in the treatment of peri-implantitis. A histomorphometric study in dogs.* Clin Oral Implants Res, 2017. **28**(11): p. 1388-1395.

[91] Shibli, J.A., et al., *Treatment of ligature-induced peri-implantitis by lethal photosensitization and guided bone regeneration: a preliminary histologic study in dogs.* J Periodontol, 2003. **74**(3): p. 338-45.