

Avoiding Implant-Related Complications

In Medically Compromised Patients

With Or Without Unhealthy Lifestyle/Elevated Oxidative Stress

Gregorio Guabello MD, MSc¹ | Francesco Zuffetti MD, DDS² | Andrea Ravidà DDS, MS³ | Matteo Deflorian DDS² |
Giorgio Carta MD, PhD⁴ | Muhammad H.A. Saleh BDS, MS, MSD⁵ | Matteo Serroni DDS, MSc⁶ | Bernhard Pommer DDS,
PhD⁷ | Georg Watzek DDS, MD, PhD⁷ | Luca Francetti MD, DDS⁸ | Tiziano Testori MD, DDS, MSc, FICD^{9,10,11}

¹ Medical Doctor, Team member of the Endocrinology Unit, IRCCS Galeazzi Sant'Ambrogio Hospital, Milan, Italy

² Research Fellow, IRCCS Galeazzi Sant'Ambrogio Hospital, Dental Clinic, Section of Implant Dentistry and Oral Rehabilitation, Milan, Italy

³ Clinical Assistant Professor, Department of Periodontics and Preventive Dentistry, University of Pittsburgh School of Dental Medicine, Pittsburgh, PA, USA

⁴ Scientific Director Argo Academy International Research Bologna, Medical Expert in Functional Medicine and Osteometabolism, Senior Lecturer at Lake Como Institute.

⁵ Clinical Assistant Professor, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA

⁶ Research Fellow, Department of Innovative Technologies in Medicine & Dentistry, University 'G. D'Annunzio', Chieti-Pescara, Italy

⁷ Clinical Associate Professor, Academy for Oral Implantology, Vienna, Austria

⁸ Full professor, IRCCS Galeazzi -Sant'Ambrogio Hospital, Dental Clinic, Dean of the Dental Clinic Milan, Italy. Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, Milan, Italy.

⁹ Head of Section of Implant Dentistry and Oral Rehabilitation, Dental Clinic, IRCCS Galeazzi Sant'Ambrogio Hospital, Milan, Italy. Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, Milan, Italy.

¹⁰ Adjunct Clinical Associate Professor, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA

¹¹ Visiting Assistant Professor, Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, USA

Correspondence to:

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Tiziano Testori MD DDS MSc FICD

IRCCS Galeazzi Sant'Ambrogio Hospital, Dental Clinic, Section of Implant Dentistry and Oral Rehabilitation, Via Cristina Belgioioso 173, Milano, 20157 Milan MI, Italy

Email: tiziano.testori@unimi.it

Telephone: +39 0312759092 Fax: 031243027

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ABSTRACT

Increased human life expectancy broadens the alternatives for missing teeth and played a role in the widespread use of dental implants and related augmentation procedures for the aging population. Though, many of these patients may have one or more diseases. These systemic conditions may directly lead to surgical complications, compromise implant/bone healing, or influence the long-term peri-implant health and its response to biologic nuisances. Offering patients credible expectations regarding intra- and post-operative complications and therapeutic prognosis is an ethical and legal obligation. Clear identification of potential types of adverse effects, complications, or errors is important for decision-making processes as they may be related to different local, systemic, and technical aspects. Therefore, the present review structures the underlying biological mechanisms, clinical evidence, and clinical recommendations for the most common systemic risk factors for implant-related complications.

INTRODUCTION

Increased human life expectancy broadens the alternatives for missing teeth and played a role in the widespread use of dental implants and related augmentation procedures for the aging population. Though, many of these patients may have one or more diseases. These systemic conditions may directly lead to surgical complications, compromise implant/bone healing, or influence the long-term peri-implant health and its response to biologic nuisances¹. Similar risks may pertain to the medications taken by this population rather than the disease itself². Thus, understanding the biological events behind the each of these conditions is indispensable for the implant team.

Offering patients credible expectations regarding intra- and post-operative complications and therapeutic prognosis is an ethical and legal obligation. Complications must be explicitly communicated to the patient to render informed consent to every elective surgical intervention. For medically complex patients presenting with synergistic effects of different comorbidities, it is no clear

understanding for what preventive measures exactly must be taken ³. Precautions may involve perioperative antibiotic coverage, prolonged and/or submucosal implant healing times, and avoiding bone augmentation surgery ³. The bone and soft tissue response following endosseous implant placement is associated with a cascade of molecular events controlled by wound-healing mediators (cytokines, chemokines, and growth factors) as well as mineral metabolism (hormones and diet) potentially affecting initial osseointegration as well as long-term success ¹.

Clear identification of potential types of adverse effects, complications, or errors is important for decision-making processes as they may be related to different local, systemic, and technical aspects⁴. Likewise, these complications will influence the predictability of treatment. As a result, knowledge of the clinical evidence regarding adverse effects, errors, and complications is required and cannot be ignored. Therefore, the present review structures the underlying biological mechanisms, clinical evidence, and clinical recommendations for the most common systemic risk factors for implant-related complications.

1 | SMOKING

Biological mechanism: Although the biomolecular mechanisms are still not well understood, it seems that the local and systemic effects of nicotine and other tobacco components may compromise bone metabolism at the bone/implant interface and jeopardize the maintenance of a stable osseointegration. Several animal and in-vitro studies indicated that nicotine can inhibit the proliferation of fibroblasts and their production of fibronectin and collagen⁵⁻⁹. Other studies reported that tobacco products can modulate bone turnover by increasing the production of MMP-1,2,3 in osteoblasts and, consequently, favoring the bone resorption processes^{10,11}. Based on current experimental evidence, an amplification of oxidative stress in periodontal and peri-implant tissues, an increase in the production of IL-6, IL-8, PGE2 and AGEs by gingival fibroblasts and an impairment

of the function of polymorphonuclear neutrophils could justify the mechanisms underlying the onset of biological complications around implants¹².

Clinical evidence: The effects of smoking constantly seem to be dose-dependent. Conversely, they might not be influenced linearly by the exposure over time¹³. Indeed, two studies have showed that heavy smokers (>20 cigarettes/day) have a threefold higher risk than moderate or light smokers of experiencing implant loss, while for marginal bone loss greater effects (especially in the maxilla) have been reported for heavy smokers compared with non- or moderate smokers^{14,15}. A systematic review and meta-analysis by Manzano et al., in which factors that could jeopardize the establishment of an intimate bone-to-implant contact in the early stages of bone healing were evaluated, concluded that tobacco consumption is an important risk factor capable of significantly increase the risk of early implant failure from 1.3- to 2.3 fold¹⁶. Furthermore, in a review by Moraschini et al., after a follow-up ranging from 8 to 240 months, a statistically significant difference in marginal bone loss in favor of the non-smoking group (standardized mean difference = 0.49, $p < 0.00001$) was detected¹⁷. Similarly, Nazeer et al. found significantly higher marginal bone loss at 3-, 6- and 9-months after implant loading in the smoking patients compared to non-smokers¹⁸. At the same time, several authors have suggested that bone loss is greater in the maxilla than in the mandible^{17,19,20}.

When smokers were compared to non-smokers, the implant-related odds ratio (OR) for late failure rate of osseointegrated implants was significantly elevated, as demonstrated by Moraschini et al. (OR= 1.96), Strietzel et al. (OR= 2.25) and Hinode et al. (OR= 2.17)^{17,21,22}. Similarly, a more recent review reported a significantly greater relative risk (RR= 2.45) for implant failure in smokers of >20 cigarettes per day compared with non-smokers²³.

Finally, some authors have reported that tobacco consumption is able to negatively influence the survival rate of the implant after ridge augmentation procedures^{22,24,25}. Notably, a review by Chambrone et al. found a significantly higher risk of implant loss (RR= 1.87) after sinus lift in the

smoking group than in the control group²⁴. A retrospective study by Kan et. al over a mean follow-up period of 41.6 months, found a significantly different cumulative implant success rate ($p=0.027$) in grafted maxillary sinuses between non-smokers and smokers, with values respectively by 82.7% and 65.3%²⁵.

Unlike periodontitis, the correlation between smoking and peri-implantitis seems to be controversial. A multilevel cross-sectional study by Pimentel et al. conducted on 147 patients observed a three times higher probability of developing peri-implantitis (prevalence ratio= 3.49) in smokers compared to non-smokers²⁶. A study by Roos-Jansåker et al. carried out on 218 implant patients followed up for 9-14 years concluded that smoking was a variable significantly associated with the risk of peri-implantitis in both univariate and multivariate analyses²⁷. A recent cross-sectional study by Costa et al on 350 subjects reported an adjusted OR for the occurrence of peri-implantitis of 2.63 for current smokers compared with non-smokers²⁸.

A review by Sgolastra et al. revealed, with little evidence and a limited number of studies, that smoking was a significant risk factor for peri-implantitis when an implant-based meta-analysis was conducted (OR= 2.1), unlike the patient-based analysis which did not obtained the same significance (OR= 1.17)²⁹. A meta-analysis by Stacchi et al. found no evidence justifying the role of smoking in the pathogenesis of peri-implantitis, reporting no statistically significant differences for the rate of implant loss and peri-implantitis between smokers and non-smokers³⁰.

Finally, the 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions stated that the available evidence supporting tobacco consumption to be a risk factor/indicator for peri-implantitis is still inconsistent and inconclusive³¹.

Clinical recommendations: Although there are no contraindications to implant placement in smoking patients, the clinician should take the above observations into consideration. There are currently no clear guidelines indicating the daily cut-off of cigarettes that the implant patient can smoke. However,

patients should be informed that the hazardous effects of tobacco maybe directly proportional to the dose and frequency of smoking habit and therefore it should be recommended that they quit before any implant procedure. The most common reasons given to support patient obedience with perioperative smoking cessation are the potential high costs of implant failure and understanding that implants are “an investment worth of smoking cessation”. Besides, smoking patients who are candidates for implant therapy should be advised to follow cessation programs that incorporate multidisciplinary approaches, both medical and psychological.

Some of the deleterious effects of smoking on periodontal tissues are reversible after cessation and therefore the possibility of quitting smoking can represent, a prerequisite for maintaining and preserving the long-term implant health ³².

2 | DIABETES

Biological mechanism: Diabetes represents a group of metabolic disorders characterized by hyperglycemia and caused by partial or total insulin deficiency or resistance. Epidemiological studies have predicted an increase in the worldwide prevalence of diabetes from 2.8% in the 2000s to 4.4% in 2030 ³³. The increasing prevalence of this disorder and its potential biological implications underline the importance of making some considerations before and during implant therapy for this type of patient. Several Histomorphometric and animal studies have highlighted some mechanisms that would justify an alteration of surgical wound healing and osseointegration. First, studies in pigs with streptozocin-induced diabetes reported a significant delay in wound re-epithelialization associated with a significant decrease in wound fluids of concentration of growth factors such as IGF-1 and TGF- β ³⁴. Secondly, studies in diabetic mice have found overexpression of MMP-9 metalloproteinases in the wound microenvironment impairing granulation tissue formation and producing the inactivation of various growth factors ³⁵. In fact, the increased amount of MMP-9 would favor a shift towards a

pro-degradative activity of the fibroblasts determining the production of a lesser and texture-altered extracellular collagen matrix³⁶. The hyperglycemia-induced chronic inflammatory state could also have unfavorable repercussions on osseointegration. In fact, the production of AGEs (Advanced glycation end-products) and the increase in the levels of reactive oxygen species would seem to be the basis of the mechanisms that could justify the increase in bone resorption and a decrease in its formation. First, the interaction of AGEs with their RAGE receptors (Receptor for advanced glycation end products) would lead to the release of proinflammatory cytokines and the inactivation of osteoblasts. Second, systemically produced ROS (Reactive oxygen species) would induce apoptosis of bone marrow stromal cells, osteocytes and osteoblasts altering their differentiation processes and their ability to modulate mineralization³⁷. Finally, immunohistochemical studies on rats injected with AGEs found less bone-to-implant contact and a slower rate of osseointegration, which would lead to compromised implant stability³⁸.

Clinical evidence: Similar to smoking, findings on the implant failure and the onset of peri-implantitis rate in diabetic and non-diabetic patients appear to be controversial and not as strong as in periodontitis where diabetes is considered as a grade modifier. The biological mechanisms could explain the results of some studies that reported an increase in the failure rate and peri-implantitis in diabetic subjects.

A retrospective study by Fiorellini et al. conducted on 40 (well-controlled) diabetic patients with 215 implants followed for an average follow-up of 8.9 ± 14.3 years, revealed a lower cumulative success rate (85.7%) than the criteria established in the literature. Notably, 24 of the 31 total implants lost in the study were found to have occurred between the first 6 and 18 months, resulting in a first year cumulative success rate of 88.9%³⁹. Similarly, a review by Annibali et al., while not finding a statistically significant difference for the overall implant survival rate between diabetic and non-diabetic patients, a higher tendency for implant failure was observed in diabetic patients during the

period of osseointegration and the first year after loading reporting an implant loss rate of $4\% \pm 1\%$ and $3\% \pm 1\%$, respectively. After the first year, these values remained constant throughout the 6 years of follow-up⁴⁰.

Finally, an analysis of the implant survival rate did not allow to show a statistically significant difference between diabetic (type 1 and 2) and non-diabetic patients in a review by Moraschini et al (RR= 1.43, p= 0.47; RR= 3.65, p=0.29) ⁴¹. A difference in the implant failure rate was also not appreciated in a comparison between patients with type 1 and type 2 diabetes (RR=1.56, p=0.34). Also a review by Chrcanovic et al., including 14 publications, demonstrated that diabetes is unable to significantly influence the implant failure rate with a risk ratio of 1.07⁴². Finally, by evaluating the implant failure rate over a longer time frame, a 21-year retrospective cohort study was able to conclude that a diabetic condition is significantly correlated with an increased risk of implant loss (OR= 2.75) ⁴³. A review by Al Ansari, including 89 studies with a mean follow-up of 3.2 ± 2.9 years, also found a slightly higher but statistically significant relative risk of implant failure when diabetic patients were compared with healthy subjects (OR=1.777, p< 0.001). In addition, patients with type 1 diabetes experienced failure more frequently than type 2 diabetics (OR = 4.477, p = 0.03) ⁴⁴.

Conversely, some authors have not observed a significant effect of diabetes on early implant failure. An observational study by Eskow et al. demonstrated that diabetic patients with poor glycemic control ($8.0\% \leq \text{HbA1c} \leq 12.0\%$) had a very high 1-year survival rates (98.6%), without the onset of any complications ⁴⁵. Another review reported a significant association between diabetes with poor glycemic control and implant failure, with a 50% higher probability for implant failure compared to healthy patients (OR = 1.89, p <0.001) ⁴⁶.

Last but not least, the healing time is another consideration that should be kept in mind when placing implants in diabetic patients. A study by Oates et al., evaluated the effects of controlled glycemic levels on implant stability quality (ISQ) over a 1-year time. Although delayed implant integration was

observed in the group with HbA1c > 8.1% compared with the group with well- or moderately controlled glucose levels, no association between ISQ and HbA1c was appreciated in the one-year post-loading period⁴⁷.

Concerning the mean difference (MD) of marginal bone loss (MBL) around implants, a review by Al Ansari et al. reported a significant difference (MD=0.776 mm, p= 0.027) between diabetic and non-diabetic patients in favor of the latter⁴⁴. A meta-analysis by Chrcanovic et al. detected an MD (0.20 mm, p<0.001) for MBL which, although significantly greater in the diabetic group, was almost clinically irrelevant⁴². Also in a review by Moraschini et al., in which 5 included studies reported outcomes for MBL, they found a minimal but statistically significant MD (0.18, p<0.00001) favoring the non-diabetic group⁴¹.

Regarding the incidence of peri-implantitis, a review by Dreyer et al., noted that patients with type 2 diabetes mellitus have more than double the risk than non-diabetic patients for developing peri-implant disease (OR= 2.5) ⁴⁸. However, most of the studies included in that review were cross-sectional compromising the quality of the evidence which was rated as medium level⁴⁸. Conversely, several studies have failed to find a correlation with diabetes. In a retrospective study by Alberti et al. conducted on 204 patients followed up for 5.7 ± 3.82 years after loading, found an adjusted OR (0.47) for diabetes as a nonsignificant risk factor for peri-implantitis ⁴⁹. A retrospective analysis by Renvert et. al performed on 240 patients also failed to demonstrate a correlation between type 2 diabetes and the development of peri-implantitis⁵⁰. Finally, the 2017 World Workshop also stated that it is not yet possible to establish with conclusiveness and consistency whether diabetes represents an effective risk factor for the onset of peri-implantitis³¹.

Clinical recommendations: Diabetes is not an absolute contraindication to implant therapy. Generally, it can be concluded that the survival rate for implants in diabetic patients maybe slightly lower than that of healthy patients, and failure is appreciable especially in the long term ⁵¹. Though, the literature

regarding survival rates and the need for glycemic control is quite inconsistent due to a lack of standardization of collected data and results, it is desirable and recommended to have well-controlled glycemic control in patients undergoing implant therapy. According to the American diabetes Association (2005) diabetes is defined as 'well-controlled' when HbA1C values are <7%. In addition to this parameter, which evaluates the glycemic levels in the previous 2-3 months, a measurement of the pre-prandial glucose levels and the post-prandial peak could also give us a broader view of the current state³. A good peri-operative glycemic control would guarantee a better and faster osseointegration of the implants and a better healing of the surgical wound. Conversely, poor metabolic control ($\geq 8.1\%$) associated with diabetic microangiopathy would cause an alteration of the immune response, an impairment of the flap vascularization and would favor the onset of infectious complications. Based on the same rationale, prophylactic antibiotic therapy is also recommendable in diabetic patients⁵². Amoxicillin is the antibiotic of choice to prevent any infections caused by streptococci, gram-negative and gram-positive anaerobes. The use of topical antiseptics (chlorhexidine digluconate 0.12%) have also proved to be useful in reducing the risk of implant failure³.

3 | OSTEOPOROSIS

Biological mechanism: Osteoporosis is a skeletal disease characterized by a qualitative and quantitative decrease in bone mass. According to WHO, osteoporosis is defined as a condition in which bone mineral density (BMD) is 2.5 standard deviations or more below the average of healthy young women⁵³. The microstructural alterations of the bone tissue, such as increased cortical bone porosity and thinning of the medullary trabeculae, causes bone deterioration and consequently an increase in the risk of fractures.

In 80% of cases this condition is diagnosed in women, as postmenopausal estrogen decline causes an acceleration of bone resorption. At the same time, the chronic use of some medications (such as glucocorticoids, antiepileptics, immunosuppressive drugs, proton pump inhibitors, Selective Serotonin Reuptake Inhibitors (SSRI) and some systemic conditions (diabetes mellitus, severe hyperthyroidism, Cushing's syndrome, severe hepatic disease, multiple myeloma, leukemia, lymphoma, hemophilia, rheumatoid arthritis) may be associated with the development of osteoporosis⁵⁴.

The success of implant therapy and osseointegration are strictly conditioned by bone quality of the jaws and it is for this reason that osteoporosis could represent a condition of important clinical relevance. Type IV bone with poorly represented cortical and trabecular bone was shown to be more frequently associated with implant failure; due to difficulty obtaining primary stability⁵⁵. However, the relationship between skeletal and mandibular or maxillary bone density is limited and inconsistent^{56,57}. Indeed, some authors have found a weak evidence to establish that regional bone density could be a useful parameter in predicting primary implant stability and at the same time a useful indicator of skeletal BMD^{56,58}.

Clinical evidence: In response to these issues, Merheb et al., in fact, evaluated the quality of implant stability (ISQ) at the time of implant and abutment placement using a resonance frequency analysis in osteoporotic and non-osteoporotic patients. Although a statistically significant difference in quality scores at abutment placement was found between osteoporotic patients (66.4 ± 9.5 ISQ) and healthy patients (72.2 ± 7.2 ISQ), in favor of the latter, an overall survival rate of 100% was reported⁵⁹.

On the other hand, a retrospective analysis by Alsaadi et al., using multivariate logistic regression, found a significant association between early implant failure and osteoporosis (OR=2.88, $p < 0.001$); however, a causal relationship could not be established⁶⁰. Interestingly, the same research group in another study using a Fischer test assessment and a GEE statistical method was unable to identify

poor bone quality as a factor influencing osseointegration and early implant failure rate⁶¹. Therefore, despite the micro and macroscopic anatomical modifications linked to osteoporosis which could undermine the primary stability of the implant, the literature, albeit very lacking, does not seem to place emphasis on this issue and does not outline osteoporotic conditions as a contraindication to implant therapy.

Regarding marginal bone loss, some studies reported a significantly greater increase in osteoporotic patients than in healthy ones⁶²⁻⁶⁴. Notably, De Medeiros et al. found a statistically significant difference in marginal bone loss around implants between patients with and without osteoporosis (0.18 mm, 95% CI 0.05-0.30, P = 0.005)⁶². The prospective cohort study by Tabrizi et al. observed a mean MBL of 1.20 ± 0.29 mm in the osteoporosis group and 0.87 ± 0.15 in the control group, with a significant difference between the two groups ($p=0.001$)⁶³. While such significance was reported by the groups mentioned above, the slightest appreciated difference hardly demonstrates any clinical relevance. Finally, a prospective controlled multicenter study by Temmerman et al., which analyzed 148 implants in 48 women over an observation period of 5 years, concluded that no statistically significant differences in MBL values were obtained between the osteoporosis group and the group of healthy women at both patient level ($p=0.54$) and implant level ($p=0.31$)⁶⁵.

Regarding the incidence of peri-implantitis, a 2017 World Seminar on the Classification of Periodontal and Peri-Implant Diseases and Conditions, although with limited data available, did not observe a correlation with osteoporosis³¹. A cross-sectional study by Dvorak of 203 women with 967 implants failed to identify an association between systemic bone loss and peri-implantitis (OR=2.1, $p=0.6$)⁶⁶. A systematic review by Dreyer et al., who reviewed 3 studies that provided data on osteoporosis concluded that there is little evidence indicating that osteoporosis is a risk factor for peri-implantitis

Lastly, analyzing the available data for late implant failure, several systematic reviews and meta-analyses did not report a significant correlation between osteoporosis and implant failure^{62,67,68}. In particular, De Medeiros et al., considering 15 publications involving 8859 patients and 29,798 implants, found no differences in the implant survival rate between patients with and without osteoporosis, nor at the implant level (RR 1.39, p= 0.11) nor at the patient level (RR 0.98, p=0.94)⁶². Similarly, a meta-analysis by Lu et al. and Chen et al. could not demonstrate a significant detrimental effect of osteoporosis on implant survival (RR= 1.19, p=0.067; RR= 1.09, p= 0.14, respectively)^{67,68}.

Clinical recommendations: There are no reported contraindication for implant placement in patients with osteoporosis. However, the healing process of bone tissue might take longer and the low quality of bone could affect primary stability and consequently osseointegration⁶⁹. There are no studies that provide indications on the exact healing time in these cases, but generally a 50% increase in the standard waiting times should be sufficient. Choosing to under-prepare the implant site or using a wider implant than in an ordinary situation may be beneficial⁷⁰. In many respects, this condition would not seem to represent a limitation *per se* for implant therapy, but rather the necessary therapy usually made up of bone resorption inhibitors could expose the patient to serious post-surgical complications.

4 | ANTIRESORPTIVE AND ANTIANGIOGENICS MEDICATIONS Fig. 1a, b, c, d

Biological mechanism: Bisphosphonates (BPs) are antiresorptive medications, consisting of inorganic pyrophosphate analogs. They are used for the prevention of osteoporosis-related fractures in patients with osteoporosis or osteopenia or in the management of cancer-related fractures in patients with bone metastases associated with multiple myeloma or solid tumors (such as lung, prostate, and breast cancers). They have also been shown to be effective in the treatment of Paget's disease and osteogenesis imperfecta⁷¹. BPs act by suppressing bone turnover processes through

inhibition of osteoclastic activity. They exhibit strong binding capacity to hydroxyapatite crystals and reach higher concentrations in areas of bone tissue subject to processes of neo-apposition and resorption. Because of these properties, they can persist incorporated into bone tissue for up to 10 years, increasing bone mass and mineral density and reducing the risk of fractures ⁷². The route of administration can be oral, intramuscular, or intravenous.

Denosumab (DNB) is the active substance of a newer antiresorptive medication, which finds indication generally in the same clinical scenarios as BFs. It is able, by mimicking the effects of osteoprotegerin, to bind the receptor activator of the nuclear factor-kappa B ligand (RANKL) blocking its interaction with the RANK receptor and consequently neutralizing the function and differentiation of osteoclasts and their progenitor cells ⁷³. In particular, DNB is able to interact with the precursors of osteoclasts in the marrow bone tissue, interrupting their maturation and altering the activity and survival of the already differentiated osteoclasts ⁷⁴. The use of antiangiogenic agents in combination with antiresorptive drugs is known to increase the risk of MRONJ development; however, little is known regarding the incidence and prevalence of antiangiogenic-related MRONJ in antiresorptive drugs-naïve individuals. Antiangiogenic inhibitors have been increasingly used in the management of a range of malignancies including ovarian cancer, metastatic renal cell cancer, breast cancer, colorectal cancer, non-small-cell lung cancer (NSCLC), and glioblastoma multiforme . Antiangiogenic inhibitors can be categorised into three major groups based on their mechanism of action: anti-VEGF monoclonal antibody (e.g., bevacizumab), VEGF decoy receptors or VEGF-Trap (e.g., aflibercept), and small molecule tyrosine kinase inhibitors (TKI) that block the VEGF receptors downstream signaling pathways (e.g., sunitinib, cabozantinib, and sorafenib) . Additionally, the mammalian target of rapamycin (mTOR) inhibitors also seems to have antiangiogenic effects by inhibiting the production of VEGF and platelet-derived growth factors (PDGF).

Clinical evidence: Implant failure in patients treated with BFs and DNS needs to be investigated from several angles. Firstly, the loss of the implant could be strictly correlated with the pharmacodynamic mechanisms of antiresorptive medications which significantly reduce bone turnover, putting at risk all processes related to implant osseointegration. Second, concerns about an increased risk of implant failure in bisphosphonate users should also be seen considering MRONJ.

Regarding non-MRONJ-related implant failure, a retrospective study by Memon et al., in which 153 implants placed on 100 women treated with oral BFs were analyzed, a greater early implant failure (6.5%) was observed in women treated with antiresorptive drugs, even if not statistically different from the control group⁷⁵. Similarly, a retrospective cohort study by Yajima et al. of 25 patients with 53 total implants failed to identify a significant association between implant loss and use of BFs. However, in the test group, 3 implants (7.7%) in 3 patients (17.6%) did not achieve osseointegration and were lost within the first year before functional loading. In contrast, a 100% survival rate was observed in the control group⁷⁶.

A retrospective radiographic study by Zahid et al. reviewed the treatment records of 362 patients undergoing implant therapy. Using a generalized estimating equation analysis the authors failed to report a significant association between use of BFs and implant failure; however, a statistically significant correlation was noted between antiresorptive therapy and implant thread exposure (OR= 3.25, $p < 0.001$)⁷⁷. Finally, a meta-analysis by Chrcanovic et al., including 18 publications, detected an OR for late implant failure of 1.73 ($P = 0.003$) when patients treated with BFs were compared with patients without BFs. At the same time, antiresorptive therapy did not appear to negatively affect MBL outcomes. However, the author advises that these results should be taken with caution due to the limited number of studies included, their low specificity and the lack of controls⁷⁸.

On the other hand, with regard to the MRONJ-related complications and risk of implant loss, a recent meta-analysis reported that there is moderate overall quality of evidence to conclude that in patients

treated with BFs (either oral bisphosphonates for osteoporosis or intravenous bisphosphonates for malignancy) or DNS, the risk of developing an “implant surgery-triggered” medication-related ONJ (MRONJ) is significantly higher than in patients without antiresorptive therapy. And, furthermore, it makes sense to assert that the risk of implant failure might increase when in association with concomitant MRONJ⁷⁹. Sher et al., analyzing 830 patients (2841 implants) treated with both oral and intravenous bisphosphonates, recorded 102 cases of MRONJ with an incidence of 12.3%. However, many authors do not consider the surgical procedure of implant placement to be the trigger for MRONJ^{80,81}, as most of the peri-implant osteonecrosis lesions are found as delayed complications on previously osteointegrated and prosthetically loaded implants^{80,82}.

An estimate of the risk of developing ONJ in patients on antiresorptive therapy requires a comprehensive assessment of the patient’s general and dental history. Indeed, several systemic and local risk factors could predispose to the development of MRONJ. First, the type of drug, the route of administration and the duration of the therapy over time would seem to influence its onset. Indeed, some authors have suggested that the risk of MRONJ is significantly lower in patients treated with oral BPs than in those treated with intravenous BPs⁸³, with an incidence of spontaneous osteonecrosis of 0.01-0.04% and 0.8-12%, respectively⁸⁴. Then, some studies concluded that the duration of treatment with antiresorptive drugs has a significant influence on the onset of ONJ, as a consequence of a cumulative dose load⁸⁰. Even cancer patients, usually treated with intravenous BFs (i.e. pamidronate or zoledronic acid) would seem to be at higher risk of developing ONJ than patients with benign bone diseases⁸³. Secondly, incongruous prostheses, the presence of periodontitis or peri-implantitis, the concomitant intake of other drugs or local anatomical factors could influence the onset of ONJ. In particular, the presence of an inflammatory and infectious condition, such as periodontitis or peri-implantitis, in association with osteoclastic-mediated bone turnover alterations, could lead to an increased risk of MRONJ. In fact, a study by Pichardo et al. demonstrated that dental

implants already placed and osseointegrated at the start of BFs therapy have an increased risk of developing MRONJ in the presence of concomitant peri-implantitis ⁸⁵. Corticosteroids, taken concomitantly with antiresorptive therapy, also increase the risk of ONJ. Finally, in term of localization, although both jaws may be affected by this drug-related condition, the mandible (75%) is more frequently involved than the maxilla (25%), for reasons not yet well understood ⁷¹.

Clinical recommendations:

It is advisable to follow the latest guidelines of AAOMS 2022 for the prevention of the Medication-Related Osteonecrosis of the jaws⁷¹ (Table 1).

Table 1. MRONJ PREVENTION STRATEGIES (Ruggiero et al. AAOMS' Position Paper on MRONJ—2022 Update. J Oral Maxillofac Surg 2022)

Pretherapy (Nonmalignant disease)	<ul style="list-style-type: none"> ▪ Educate patient about the potential risks associated with long-term Antiresorptive therapies (ART). ▪ Optimization of dental health can occur concurrent with ART.
Pretherapy (malignant disease)	<ul style="list-style-type: none"> ▪ Educate patients about the higher risk of MRONJ and the importance of regimented dental care. ▪ Optimization of the dental health prior to the initiation of ART if systemic conditions permit (extraction of nonrestorable teeth or teeth with a poor prognosis).
During antiresorptive therapy (nonmalignant disease)	<ul style="list-style-type: none"> ▪ No alteration of operative plan for most patients. ▪ Considerations include drug schedule, duration of therapy, comorbidities, other medications (especially chemotherapy, steroids, or antiangiogenics), degree of underlying infection/inflammation, and extent of surgery to be performed. Drug holidays are controversial. ▪ Bone turnover markers (BTM) are not a useful tool to assess MRONJ risk.
During antiresorptive therapy/ targeted therapies (malignant disease)	<ul style="list-style-type: none"> ▪ Educate patients about the higher MRONJ risk in the setting of malignant disease. ▪ Educate the patient about the importance of regimented dental care and prevention. ▪ Avoid dentoalveolar surgery if possible. ▪ Consider root retention techniques to avoid extractions. ▪ Dental implants are contraindicated. ▪ Drug holidays are controversial.

A special concern should be considered for suspending RANKL inhibitors in osteoporosis patients. Several studies have demonstrated a rebound increase in bone resorption following the discontinuation of DNS, resulting in an increased risk of multilevel vertebral fractures. If DNS is to be suspended, the timing and duration of the holiday should be optimized in order to minimize this risk. The planned dentoalveolar surgery can be completed 3-4 months following the last dose of DNS when the level of osteoclast inhibition is waning. It can then be reinstated 6-8 weeks postsurgery. This management strategy minimizes the length of the drug holiday while maintaining a favorable environment for bone healing.

However according to a recent consensus conference any planned dentoalveolar surgeries can theoretically take place without restrictions utilizing the following drug holiday with a “delayed dosing window” that lasts about 2 months, starts ideally 5 months after the last dose of denosumab and ends at the beginning of the 7th month ⁸⁶.

Finally, other measures brought to light by the AAOMS in 2022 suggest the use of prophylactic antibiotic therapy ⁸⁷⁻⁸⁹, the use of rinses with antiseptics, the closure of surgical wounds by first intention and the maintenance of good oral hygiene ⁷¹. A meta-analysis by Ata-Ali et al. demonstrated that antibiotic prophylaxis reduces the implant failure rate by 66.9% ⁹⁰. In addition to controlling any infectious or inflammatory foci in the oral cavity, smoking cessation and good glycemic control in diabetic patients would also be recommended as a preventive strategy for MRONJ. Furthermore, in patients undergoing implant therapy, careful monitoring and clinical and radiographic surveillance should be ensured throughout the healing phase and in the following years. Antiangiogenic inhibitors have the potential to increase the risk of MRONJ development and should be carefully assessed and their suspension should be considered according to oncologist recommendation in order to slow down the progression of the MRONJ⁹¹.

5 | RADIATION THERAPY

Biological mechanism: Implant therapy can significantly improve the quality of life in patients undergoing treatment for head and neck cancer. These patients usually undergo combined procedures involving ablative surgery and radiation therapy. Consequently, these treatment modalities, being able to involve the extraction of dental elements and determining residual bone defects of the jaws, could determine functional and aesthetic compromises of the maxillofacial mass⁹². Furthermore, the sometimes-necessary radiotherapy could make subsequent reconstructive and prosthetic procedures even more complex. In fact, radiotherapy represents a clear risk factor for dental implants and bone augmentation procedures⁹³ and at the same time the xerostomia-induced in these patients could make prosthetic rehabilitations with mucosal support less functional and comfortable⁹⁴.

Various radiation-induced alterations of soft and hard tissue could endanger implant therapy and should be taken into consideration by the clinician. In the affected tissues, exposure to radiation induces an acute inflammatory reaction characterized by the release of various proinflammatory cytokines (e.g. IL-1alpha and beta, TNF-alpha, IL-6, VEGF etc...) with a consequent increase in vascular permeability, thrombosis and endothelial cell depletion⁹⁵. Most of the radiation dose (30-40%) is absorbed by bone tissue due to its high calcium concentration⁹⁵. The earliest effects involve an alteration of the remodeling mechanisms, with an increase of the osteoclastic activity and a reduction of the osteoblastic activity. The result is a substantial qualitative and quantitative alteration of the bone tissue in general and of the architecture of the marrow microenvironment characterized by a thinning of the bone trabeculae and an increase in infiltration by the adipose cell population⁹⁶.

There is also a depletion and inhibition in the differentiation of hematopoietic cells and skeletal stem cells. These imbalances in bone metabolism can predispose the patient to develop fractures and osteoradionecrosis of the jaws^{97,98}.

Even soft tissues are compromised due to the high level of mucosal cell turnover, which amplifies the cytotoxic effect of radiation causing low resistance to them. The death of the basal cells of the oral mucosa leads to the onset of mucositis and ulcerations, with pain and possible bacterial superinfection⁹⁹.

Finally, radiation therapy can determine fibrosis of the major salivary glands, acinar atrophy, and fatty degeneration. As a result, salivary flow is impaired and the patient might develop xerostomia¹⁰⁰.

Clinical evidence: Impaired bone tissue remodeling and vascular alterations characterized by endarteritis and tissue hypoxia could plausibly put implant osteointegration at risk in patients undergoing radiation therapy. Regarding the early implant failure that could result, the data in the available literature are lacking and controversial. A retrospective study by Chrcanovic et al., using univariate binary logistic regression to assess implant failure up to abutment placement at patient level, failed to identify a potential correlation between early implant loss and radiation therapy (OR= 1.07, p=0.92). On the contrary, a review by Colella et al., while finding in the final follow-up an equal implant survival rate in irradiated and non-irradiated patients, recorded most implant losses in the first 36 months, and between 1 and the 12th month after placement. In agreement, a retrospective study by Granstrom et al., conducted on 631 irradiated cancer patients followed for an observational period of 25 years, reported a higher number of implant failures after the first surgical phase and before prosthetic loading or in the long term after irradiation.

Regarding long-term implant survival, there is currently good homogeneity in the literature among the studies that have demonstrated a significantly increased risk of implant loss in patients undergoing radiation therapy¹⁰¹. Although the current research reports good 5-year implant survival rates (84.3-92.9%) in patients with irradiated sites, several reviews demonstrate a significantly higher implant failure rate than in patients without radiation therapy. Gupta et al. found a strongly significant correlation between implant failure rate and irradiated sites in a follow-up between 6 and

120 months, with an OR of 2.95 ($p < 0.00001$)⁹³. At the same time, the authors reported a comparable cumulative survival rate between the two groups at 7-10 years. Doll et al., including 157 patients (830 implants) followed up to 20 years, demonstrated a 1.9-fold increased risk of implant loss in patients treated with radio chemotherapy compared to patients undergoing only ablative surgery¹⁰². In a recent meta-analysis, Lu et al. established an obvious correlation between radiotherapy and implant failure, identifying a RR of 2.09¹⁰³. Ihde et al. concluded that, considering only studies reporting a statistically significant difference, implants placed in irradiated bone have a 2-3 times higher risk of failure than untreated sites⁹⁵.

Several factors can then influence the efficacy and survival rates of dental implants in patients' candidates for radiation therapy. First, the anatomical location of the implants would appear to be an important risk factor. Studies report a double risk of failure for implants placed in the maxilla rather than in the mandible^{95,104}. In particular, Ilhe et al. comparing maxillary and mandibular implants revealed an adjusted RR of 1.79 in favor of mandibular ones⁹⁵. Chambrone et al. and Javed et al. reported a significantly increased probability of implant loss at maxillary sites, with a 496% (Risk ratio: 5.96, $p < 0.0001$) and 300% higher failure risk compared to the mandible. In fact, the greater primary stability achieved following implant placement in the mandible could justify the results, if an early failure is considered^{24,105}. Conversely, better long-term results could be expected in the maxilla, as better secondary stability and a higher percentage of vascularized marrow could mitigate the adverse delayed vascular effects of radiation¹⁰⁶. Some authors (Shugaa-Addin 2016, Nooh 2013) have also identified a significant reduction for implant survival rate in irradiated grafted sites compared to irradiated native bone, due to lower vascularity and density of regenerated bone^{107,108}. Second, the radiation dose affecting the bone tissue appears to be another risk factor that may affect the success of implant therapy and a radiation dose-response relationship appears to exist with the rate of loss. Animal studies have demonstrated a decrease in implant survival as the average

administered dose increases ¹⁰⁹, but, however, there is no univocal and precise cut-off that outlines the presence or absence of the risk of implant failure. In a recent review, the authors report no implant loss when the surgical site is irradiated with a mean dose < 38Gy ¹¹⁰. Similarly Schoen et al. showed a higher risk with doses > 40 Gy ¹¹¹. Ihde et al. and Esposito et al., however, associated a higher failure rate with doses > 50Gy and > 55Gy, respectively ^{95,112}. Sammartino et al., in a 36-month longitudinal and multicenter study, also obtained a survival rate of 78.6% and 93.6%, for implants placed in sites irradiated with doses >50Gy and <50 Gy, respectively ¹⁰⁴. In contrast, Visch et al. reported a lower survival rate for implants placed in bone with a history of less than 50Gy compared to those with a dosage >50Gy ¹¹³.

Furthermore, the amount of radiation also appears to influence the risk of Osteoradionecrosis (ORN) associated with implant therapy. Lee et al. established as a cut-off not to be exceeded in order not to run into the ORN risk of 61.5 Gy ¹¹⁰; other authors, however, reported values of 50-55 Gy ^{113,114}.

Thirdly, the timing of implant placement from radiation therapy seems to influence the quality of implant therapy, even if the results in the literature are still quite controversial. Chrcanovic et al. found no difference in the survival rate of implants placed before or 12 months after RT. Similarly, Ihde et al. did not find any correlation between implant survival rate and fixture placement time. Other studies have suggested not to wait less than 12 months otherwise adequate osseointegration may not be achieved ^{104,115,116}. Other studies recommend waiting a period of at least 6 months after RT, since a restoration of osteogenesis and vascularization takes place after 3-6 months ^{117,118}. Other authors have concluded to wait at least 24 months from the last irradiation, while others, on the contrary, have demonstrated a lower implant survival after 2 years due to the delayed effects of RT on the vessels of the irradiated area ^{119,120}.

Clinical recommendations: Implant therapy should only be considered a relative contraindication in patients undergoing radiotherapy. A careful overall assessment of all the factors that could influence

the treatment should be carried out in advance, to reduce the related risks and avoid the onset of complications. A thorough interview and informed consent should be guaranteed to the patient, to illustrate both the benefits obtainable from an improvement in quality of life and the greater risk of implant failure and development of ONR related to irradiated bone sites compared to non-irradiated ones. In general, the implementation of implant therapy is not recommended during RT. Some considerations must be kept in mind regarding the implant placement before (primary placement) or after (secondary placement) RT¹²¹.

The use of implantology is advised and considered safer if implemented at least 14 days before RT. However, primary placement may have some disadvantages, related to possible implant failure due to cancer recurrence or the risk of backscatter which can weaken the radiation therapy and increase the concentration of the dosage in the tissues immediately surrounding the implant ¹²².

Conversely, secondary placement could be related to all the complications, such as failure and ORN. If implant therapy is not feasible before RT, it is advisable to wait for a period of 6-18 months before implant placement. During this time, the acute effects of RT have worn off, normal healing mechanisms have resumed, and delayed side effects have yet to occur. Due to compromised bone remodeling and osseointegration processes, it is advisable to wait an additional time of 3 months compared to the normal times before proceeding with the second surgical uncovering phase ¹²¹.

Another factor that the clinician must take into consideration is the dosage of exposure. Anderson et al.'s guidelines for:

- <50Gy: indicate a low risk of implant failure and recommend the adoption of standard precautions.
- 50-65 Gy associate moderate risk and recommend caution.
- 65-74 Gy indicate a relatively high risk and advise against the placement of implants unless hyperbaric oxygen therapy is also used.
- 75-120 Gy implant therapy is not recommended due to the high associated risks ¹²¹.

However, no unique and definitive protocol can be outlined due to the inconsistency which still characterizes some aspects of the available literature.

6 | IMMUNODEPRESSED PATIENTS AND HIV

General considerations: A cross-sectional analysis in the North American population reported a 2.8% prevalence of temporary or chronic immunosuppressive conditions ¹²³.

A state of immunosuppression can be associated with a wide variety of circumstances, ranging from pathological conditions to physiological states (i.e., pregnancy). Most cases of short-term or long-term non-HIV-related changes in the immune system that the oral or maxillofacial surgeon may face in the treatment of implant patients could derive from the intake of drugs ¹²⁴.

Steroid derivatives (i.e., corticosteroids) are medications used for a wide range of pathologies, including asthma and especially autoimmune diseases (i.e., rheumatoid arthritis, pemphigus vulgaris, lupus erythematosus, Sjogren's syndrome, polymyalgia rheumatica). Obviously, immunomodulatory drugs are also used in patients with transplanted organs, for whom in addition to the use of corticosteroids (CS), other drugs such as cyclosporine, tacrolimus, sirolimus and mycophenolate are also used ¹²⁴.

One of the side effects mainly related to the prolonged use of corticosteroids is an alteration of bone metabolism, so much so that it represents one of the three leading causes of osteoporosis. In fact, CSs induce apoptosis of most osteoblastic cells and osteocytes and inhibit the differentiation of stem cells into osteoblasts and prolong the lifespan of osteoclasts ¹²⁵. CSs also cause a reduction in the production of insulin-like growth factor (IGF-I) by the osteoblastic cell population, compromising its anabolic and proliferative activity and the formation of new bone. At the same time it causes an increased release of RANK ligand from osteoblastic cells, which in turn has a potentiating action on osteoclastic activity ¹²⁶. The result is an imbalance between the osteoblastic-mediated activity of bone

neo-apposition and that of osteoclastic-mediated resorption, in favor of the latter, causing a reduction in the volume and density of the bone tissue.

The same effect was found among the side events of cyclosporine, as observed in a rat Histomorphometric study by Shen et al.¹²⁷ Another animal study demonstrated that cyclosporin, thanks to its ability to induce the production of TGF-beta, is able to determine a suppression of MMP 2 and -9 in rats. As a consequence, there is an impairment of the processes of angiogenesis and bone remodeling and healing¹²⁸.

Clinical evidence: Although the mechanisms described above justify the intentions of some studies to investigate the plausible correlation between the administration of these drugs and implant failure, the scarce literature available to date seems to have failed to outline a correlation. In a study by Fujimoto et al. In rabbits with dexamethasone-induced osteoporosis, impaired osseointegration and primary stability was found in implants placed in extraoral bones (tibia and femur) compared to control rabbits without dexamethasone-induced osteoporosis. However, the authors concluded that osseointegration might be more at risk in skeletal bones than in the mandible¹²⁹. A review by Duttenhoefer et al., in which 19 studies (11 case reports, 6 retrospective and 3 prospective) were included, investigated the influence of autoimmune diseases and their treatment with steroid derivatives on implant loss over a period ranging from 6- to 156 months of follow-up. In none of the studies did the comorbidity associated with these conditions influence implant failure, reporting a survival rate of 88.8%¹²⁴. A retrospective study by Petsinis et al., in which 31 patients (105 implants) receiving glucocorticoid therapy for various systemic diseases were followed up for 3 years, observed an implant survival rate of 99% and did not find any signs clinically or radiographically relevant evidence of impaired osseointegration¹³⁰.

Similarly, in the review by Duttenhoefer et al., in which 6 studies of patients with organ transplants and immunosuppressive therapy were included (2 prospective and 4 case reports), an implant

survival rate of 100% was reported at a mean follow-up of 58 months and no clinically appreciable effect on osseointegration was found. A recent systematic review and meta-analysis by Burtscher et al., however including only case-control studies and case series/case reports, found a 100% implant survival rate in transplant patients receiving various drugs for immunosuppressive therapy at an average follow-up of 60 months. At the same time, no studies described early implant loss and no statistically significant differences were reported for marginal bone loss between transplant recipients and healthy control patients.

Clinical recommendations: Although the quality of the available evidence is very low, above all due to the prevalent presence of non-controlled and non-randomized studies, the results we have available today seem to find no contraindication to implant therapy in patients with drug-induced immunosuppression and organ transplants¹²⁴. New investigations are certainly necessary to increase the data at our disposal and to highlight the aspects of such a vast and articulated research field.

Generally, to avoid peri-operative complications in patients on prolonged corticosteroid therapy, some considerations must be made. Indeed, steroid-derived drugs could cause some level of suppression of the hypothalamic-pituitary-adrenal axis, rendering the patient unable to produce cortisol in stressful occasions such as surgical procedures. This could trigger an adrenocortical crisis manifesting in hypotension and collapse¹³¹. To prevent this event, an administration of a supplemental dose of corticosteroids to the patient 30 minutes before surgery has been suggested. However, the available evidence has shown that the risk of adrenocortical crisis is very low in patients on prolonged steroid therapy undergoing minor surgery and, therefore, supplemental steroid therapy is unnecessary¹³².

Finally, since immune-suppressed patients are a category to be considered at high risk for postoperative infections, prophylactic antibiotic therapy should always be contemplated. A 5-6 day protocol depending on the type of drug (first choice amoxicillin+clavulanic acid or clindamycin or

moxifloxacin in case of allergy), to be started 12-24 hours before implant placement, is considered adequate ¹³³.

New investigations are certainly necessary to increase the data at our disposal and to highlight the aspects of such a vast and articulated research field.

HIV

Biological mechanism: HIV is the pathogen of an infectious condition which in its final stages can lead to AIDS. CD4+ T helper lymphocytes represent the cell population that expresses the greatest number of surface receptors for HIV. Their depletion, which typically occurs in AIDS, occurs through a direct cytolytic effect of the virus and through an immune attack on virus-infected cells ¹³⁴. The virus is also capable of invading macrophages and dendritic cells, causing a progressive collapse of the immune system. The reduction in the lymphocyte count results in an increased susceptibility of the patient to develop opportunistic infections and malignancies. Furthermore, the lack of inhibition of viral replication can predispose to the development of cardiovascular, hepatic, renal, neurological and tumoral diseases, significantly compromising the life expectancy of the HIV+ patient ¹³⁵.

With the introduction of highly active antiretroviral therapy (HAART) and combined antiretroviral therapy (cART), mortality from AIDS has drastically reduced, allowing a stabilization of the patient's immune status and an improvement in quality of life. Several mechanisms in the HIV+ patient may explain an increased risk of implant therapy failure. In addition to immunodeficiency which may predispose to infectious conditions in the oral cavity, chronic inflammation, immune dysregulation and antiretroviral therapy itself may impair bone tissue metabolism ¹³⁶. In vitro studies have demonstrated that several HIV-associated viral proteins are able to promote osteoclastic activity and the release of proinflammatory cytokines (i.e. IL-6, TNF- α) which induce osteoclastogenesis and bone resorption ^{137,138}. Furthermore, the viral RNA load is correlated to an increase of plasmatic

concentration of RANKL capable of stimulating osteoclastic activity and altering bone turnover^{139,140}. In addition, several drugs that are part of HAART, including protease inhibitors (PIs), can also affect bone mineral density (BMD) resulting in osteopenia and osteoporosis.

Clinical evidence: Several studies have highlighted that the CD4+ T cell count and the implementation of antiretroviral therapy are two very important factors capable of influencing implant therapy in HIV+ patients. May et al., in a prospective study that monitored AIDS-only patients with CD4+ T cell count <200 cells/ μ L for 5 years, reported a slightly higher implant failure rate (10%) for HIV+ patients compared to healthy patients (5-7%)¹⁴¹. Other authors have reported a higher incidence of postoperative complications in patients with severe immunodeficiency (CD4+ T cell count < 200 cells/ μ L) who underwent oral surgical procedures in general^{142,143}. Neumeier et al., at 3 years, in HIV+ patients with a controlled CD4 count (mean CD4+ T cell count: 603 cells/ μ L), cART therapy, antibiotic prophylaxis, well-designed prosthetic restorations, and regular 6-month maintenance found rates of implant survival and marginal bone loss comparable to those of healthy patients¹⁴⁴. Similarly, Vidal et al., in HIV+ patients with CD4+ T cells > 350/mm³ showed an eventless implant healing, an implant survival rate of 100% and the same incidence of peri-implant disease (mucositis/peri-implantitis) of healthy patients¹⁴⁵. Sivakumar et al., also reported a good implant survival rate (95%) in AIDS patients in the short term (2.8 years)¹⁴⁶. A systematic review by Ata-Ali et al., in which 7/9 of the included studies evaluated HIV+ patients with CD4+ T cells >350/mm³, reported good and similar prognostic values for implant therapy between AIDS patients and healthy ones¹³⁵. A review by Lemos et al., in which 5/6 included studies evaluated patients with CD4+ T cells >400/mm³, reported survival rate values for HIV+ patients (95%) in line with those of the healthy population¹⁴⁷.

As far as peri-implant diseases are concerned, Casula et al. found a peri-implantitis prevalence of 34% in HIV+ patients who underwent single crown/bridge implant rehabilitations; it was possible to

correlate the variable relating to the immunological profile (CD4+ and CD8+ counts) of the patient exclusively with peri-mucositis disease, but not with peri-implantitis. Only 'age' has been identified as the main risk factor for implant loss ¹⁴⁸.

Other authors, however, have highlighted that the risk of peri-implantitis and implant failure could be correlated with other factors not related to immunodeficiency. Gay-Escoda et al., in fact, although only patients with CD4+ T cells $>250/\text{mm}^3$ were analyzed, recorded a high prevalence of peri-implantitis (45%) diagnosed above all in non-compliant patients and with a history of advanced periodontitis ¹⁴⁹. Sabbah et al, in another 5-year retrospective analysis, found similar implant failure (HR=1.4, p=0.34) between HIV+ and HIV- patients. However, an adjusted analysis demonstrated a significant correlation in HIV+ patients between implant loss and various risk factors, such as CD4+ T cells $<20\%$ (HR= 2.72, p=0.04), smoking (HR= 2.61, p =0.05), PI administration (HR=2.74, p=0.04) and implant placement in the anterior maxilla (HR= 5.82, p<0.001). The concomitant presence of these 4 risk factors determines a drop in the implant survival rate to 58.3% ¹⁵⁰.

Finally, a recent study with 12 years of follow-up, evaluated the possible side effects of cART influencing the failure of implant therapy. In fact, due to mechanisms that are not yet well understood, antiretroviral therapy can favor the onset of osteopenia, osteoporosis, and a lowering of BMD. In particular, the risk of developing osteopenia appears to be 2 times greater in patients treated with PIs than in patients who do not use them ¹⁵¹. However, Oliveira et al, reported mean MBL values after a 7-year follow-up of 2.43 (1.48) mm, which are consistent with physiological peri-implant bone remodeling processes and are similar to those recorded in a healthy population in a 10-year follow-up ^{151,152}.

Clinical recommendations: although the available evidence is lacking and sometimes inconsistent in defining clear guidelines for clinicians in the treatment of HIV+ patients undergoing implant therapy, the use of dental implants is generally not contraindicated in patients with AIDS. Long-term

maintenance of CD4+ T lymphocyte levels > 250 cells/mm³ appears to be an important factor that can mitigate the risk of impaired osseointegration and implant failure rates in these patients^{151,153}.

Furthermore, studies, albeit with controversial results, seem to establish that an ideal control of major risk factors such as smoking habits (>10 cigarettes/day), uncontrolled periodontitis, poor compliance in maintaining hygiene can guarantee the success of implant therapy even in HIV+ patients. Antiretroviral therapy is not a contraindication to oral rehabilitation treatments^{150,151}.

There is no strong evidence demonstrating an increased susceptibility of HIV+ patients to local post-surgical infections¹⁵⁴. In fact, usually, the implementation of HAART guarantees a potentiation and an increase of circulating hematopoietic lineages. Antibiotic prophylaxis is indicated only when the CD4+ T lymphocyte count and polymorphonuclear granulocyte count are <200 cells/ μ L and <500 cells/ μ L, respectively. According to the guidelines of the American Heart Association (AHA), the use of antibiotics is also indicated in HIV+ patients who use intravenous drugs, due to their greater susceptibility to developing bacterial endocarditis. The use of mouth rinses with antiseptics may also be recommended in these cases¹⁵⁴.

Because of the immune thrombocytopenia that can affect patients with AIDS, an evaluation of hemostatic function would be advised in patients who will undergo extensive surgical procedures. A platelet count $<60,000$ /mm³ or hemoglobin levels <7 g/dl should lead to surgery postponement^{154,155}.

7 | CVD AND ANTICOAGULANT THERAPY

General mechanisms: The term cardiovascular disease (CVD) indicates a broad spectrum of diseases affecting the heart and blood vessels of the entire body and represents the main cause of death in the USA, Europe, and Asia. Among the main CVDs we can include ischemic heart disease, angina pectoris, heart failure, aortic aneurysm, and cerebrovascular diseases, including ischemic and hemorrhagic stroke. CVDs include sex, age, and family history among non-modifiable risk factors.

Among the modifiable risk factors, we mainly include hypertension, atherosclerosis, hypercholesterolemia/dyslipidemia, diabetes, obesity/sedentary lifestyle, and smoking habits. In most of its forms, CVDs occur following an obstruction, a reduction of the lumen or a rupture of medium and large arterial vessel, consequently compromising the perfusion of downstream tissues which go against necrosis from hypoxia and lack of nutrients¹⁵⁶. Hypoxia manifests itself with an alteration of the homeostatic mechanisms of tissue oxygenation which results in an impairment of the healing processes, with a reduction in fibroblast proliferation, collagen synthesis, capillary growth and macrophage activity¹⁵⁷. Due to the nature of these mechanisms, it has been hypothesized that CVD may alter bone healing mechanisms around implants. Therefore, it was considered plausible to investigate a possible correlation between CVD and impaired osseointegration.

Clinical evidence: Several retrospective studies with follow-up from 7.3 up to 21 years, didn't found a significant increase in the implant failure rate in cardiovascular patients^{43,60,157-159}. No influence ($p=0.359$) of coexisting cardiovascular disease was appreciated on the implant survival rate of diabetic patients in a retrospective study by Araujo Nobre¹⁶⁰.

Surprisingly, a review by Wu et al. reported the positive effect of antihypertensive drugs on implant survival. An analysis of survival adjusted for confounders obtained favorable results in favor of users of antihypertensive drugs ($HR=0.12$, $p=0.01$). Beta-blockers, thiazine diuretics and ACE inhibitors, in fact, would seem to positively influence bone metabolism, stimulating its formation and reducing its reabsorption¹⁶¹. Conversely, a review by Schimmel et al. and several retrospective studies unanimously demonstrated that there is no evidence regarding hypertension as a risk factor for implant failure¹⁶²⁻¹⁶⁵.

Regarding the incidence of peri-implantitis, a retrospective study by Renvert et al. found a history of CVD in 27.3% of patients with peri-implantitis and only 3% of patients in the healthy implant/mucositis group reporting an OR (adjusted for age, gender, and smoking) of 8.7⁵⁰. Saabi et

al. through a retrospective assessment found the presence of CVD in 26% of patients with peri-implantitis. Conversely, Neves et al. failed to establish a significant correlation between cardiac disease and peri-implantitis (OR=1.14, p=0.61)¹⁵⁸. Froum et al, in a systematic review of the literature concluded that an inconsistency of data in the literature and a heterogeneity of the evaluated populations make further investigations necessary to establish the existence of a link between CVD and peri-implant disease¹⁶⁶. Similarly, there is currently no evidence demonstrating that CVD was or not an actual risk factor for implant loss.

Clinical recommendations: However, the clinician should take into consideration a few other issues before undertaking any surgical treatment in this category of patients. In fact, an increased risk of bleeding, a rise in blood pressure and the appearance of ischemic attacks during surgery could occur. Comprehensive informed consent, in which the aforementioned risks are explained, continuous monitoring during surgery and periodic updating of the medications taken by these patients are highly recommended¹⁶⁷.

First, there is an absolute contraindication to proceeding with implant placement in patients with recent myocardial infarction or cardiovascular attack up to 6 months after preliminary care; in fact, it is very probable that harmful complications can occur in this time window. Similarly, patients undergoing heart valve replacement surgery should not undertake implant therapy before 6 months³. In any case, adequate antibiotic prophylaxis must be performed to prevent the development of endocarditis.

Another aspect to carefully evaluate is the possible intake of anticoagulant or antiplatelet drugs.

When we are going to treat patients treated with vitamin K or direct oral anticoagulants (DAOs), an assessment of the INR is always recommended. INR values necessarily established between 2-4 do not contraindicate implant placement associated with minor surgical procedures¹⁶⁸. Obviously, a weighing of the type of surgery that is planned is always necessary, considering that less invasive

procedures are associated with a lower risk of bleeding while more complex interventions such as the insertion of bimaxillary or zygomatic implants and the use of bone grafts correlate at a higher risk. In patients on antiplatelet therapy (AT) (i.e., acetylsalicylic acid, clopidogrel, ticlopidine, prasugrel and ticagrelor) an adequate evaluation of hemorrhagic risk should be done by assessment of platelet count and hematocrit. Platelet counts $<50,000$ cells/mm³ are associated with a higher risk of postoperative bleeding, while values $<20,000$ cells/mm³ also predispose to spontaneous mucosal bleeding. On the other hand, hematocrit levels $<60\%$ of normal values should be carefully evaluated¹⁶⁹.

Several systematic reviews do not recommend discontinuing DAO or AT therapy before undertaking oral surgical procedures. Kämmerer et al. concluded that in patients with INR <4 treated with vitamin K antagonists dental surgery procedures can be performed safely without suspending therapy, implementing local hemostatic measures¹⁷⁰. Similarly recent reviews found a clinically insignificant risk of peri- and post-operative bleeding in patients who have not stopped anticoagulant therapy^{171,172}. Analogous results have been achieved in studies of patients on antiplatelet therapy¹⁷³. Iwabuchi et al., in a cross-sectional multicenter observational study carried out on 2817 patients, reported a low absolute incidence of bleeding events in the anticoagulated group, but slightly higher than in untreated patients. In particular, age <65 years, high INR values and presence of acute inflammation before extraction surgery could significantly increase the risk of bleeding¹⁷⁴. Furthermore, some authors also report a greater risk of thromboembolic events or myocardial infarction which may derive from the interruption of therapy with DAO or with antiplatelets, respectively^{175,176}. At the same time, other studies showed that the implementation of bridging therapies (i.e. heparin) can increase bleeding events compared to patients who continued the canonical anticoagulant therapy; no differences, however, have been delineated for thromboembolic risk in this case^{177,178}.

Finally, among the local measures to ensure hemostasis in these patients, the use of compressive sutures, the application of hemostatic dressings (collagen, absorbable sponges, oxidized cellulose, bone wax, L-PRF) or topical tranexamic acid (5%, 3-4 times/day) can reduce peri- and post-operative bleeding complications and make the procedure safer^{104,179}.

8 | CHRONIC ALCOHOLISM

Biological mechanisms: Chronic alcoholism is defined as a voluntary excessive ingestion of ethyl alcohol. It is a primary chronic disease related to genetic, environmental and lifestyle factors, implying serious consequences from both a health and psychosocial point of view¹⁸⁰. A national survey on drug use and health estimated the alcoholism rate in the population of North America at 10%¹⁸¹.

The parameter that allows quantifying the alcohol content in a certain volume of alcoholic beverage is the so-called alcoholic unit (UA). One unit corresponds to 12 grams of ethanol, which is equivalent to the amount contained in a medium-alcoholic glass of wine (125 ml), a medium-sized can of beer (330 ml) or a shot of liqueur (40 ml). The guidelines for a healthy diet of the National Research Institute for Food and Nutrition, in accordance with the indications of the World Health Organization, defines as moderate a daily amount of alcohol equivalent to no more than 2-3 units of alcohol for a man, no more than 1-2 units of alcohol for a woman and no more than 1 unit of alcohol for the elderly¹⁸².

Various investigations have highlighted the negative effects of alcohol on various human tissues and organs, including the liver, marrow, brain, heart, and musculoskeletal system.

In particular, animal studies observed a significant reduction in trabecular bone volume, bone mineralization and bone matrix synthesis in rats chronically exposed to alcohol^{183,184}. Friday & Howard, evaluating the effects of alcohol on cultured normal human osteoblastic cells, reported a dose-dependent reduction in protein and DNA synthesis. A reduction in the mitogenic effect of

sodium fluoride and insulin-like growth factor type II was also found on these cell cultures ¹⁸⁵; moreover, some substances contained in alcoholic beverages, such as nitrosamines and ethanol, can promote bone resorption and inhibit the stimulation of bone formation ¹⁸⁶. A rabbit study by Koo et al. found that an alcoholic diet caused a significant reduction in bone formation, bone density and bone-to-implant contact ¹⁸⁷.

Biochemical and Histomorphometric evaluations revealed a significant impairment caused by habitual alcohol exposure on primarily osteoblastic cell function and proliferation, while osteoclastic activity would be unaffected ¹⁸⁸. Thus, alcohol-induced bone disease results in a reduction of apposition processes in favor of resorption processes. The decoupling of these two physiological mechanisms results in defective remodeling and reduction of skeletal tissue mass, increasing the risk of fractures. These mechanisms justify the link between habitual alcohol consumption and osteopenia.

In vivo and in vitro studies also showed an alcohol-induced weakening of the immune system. In particular, it has been observed that ethanol is able to inhibit the key functions of polymorphonuclear neutrophils, determining through a time- and dose-dependent mechanism a reduction of IL-8 production and mRNA synthesis ¹⁸⁹.

Finally, excessive chronic alcohol consumption can indirectly lead to coagulation defects due to secondary liver cirrhosis. In addition to a reduction in the production of all factors necessary for hemostasis, cirrhosis can also lead to impaired platelet distribution and result in hypersplenism and folate deficiency ¹⁹⁰.

Clinical evidence: Several clinical studies, therefore, have deemed it appropriate to investigate the possible correlation between alcohol consumption and peri-implant bone resorption. In a prospective clinical study by Galindo-Moreno et al., through a multivariate linear regression analysis, alcohol use, implant surface area and gingival index were identified as variables significantly

associated with peri-implant bone loss. In addition, the mean marginal bone loss adjusted for implant surface and gingival index was significantly greater in alcohol users (1.49mm) than in non-users (1.23mm)⁹⁰.

Block et al. in a retrospective case-control study used backward variable selection to predict whether an implant failed within 1 year, 1 to 4 years, or after 4 years in 3 multivariable logistic regressions. In addition to other factors, alcohol was also associated with an increased likelihood of implant loss within 1 or more periods¹⁹¹. A matched case-control analysis by Alissa & Oliver found a higher incidence of implant failure in patients who consumed >5 units/day of alcohol compared with non-drinkers or consumers of less than 5 units/day¹⁹².

Clinical recommendations: Currently available evidence is not sufficient to state that alcoholism is a contraindication to implant therapy. However, patients who undergo this therapy could face a series of complications relating to altered bone metabolism, bleeding problems deriving from liver pathologies and an increased susceptibility to infection due to compromised immune system.

9 | OXIDATIVE STRESS

Biological mechanism: Many oral problems are related to an imbalance of antioxidants and reactive oxygen species (ROS) in the body. Recently, free radicals have been found to be related to the occurrence and development of dental diseases, and antioxidants have also been used in dental treatment¹⁹³.

Oxidative stress is an imbalance in the production of free radicals and in the antioxidant system (2), so it could be measured monitoring some useful parameters: Reactive Oxygen Species (ROS), Malondialdehyde (MDA), Superoxide Dismutase and Total Antioxidant Capacity (TAC)¹⁹³⁻¹⁹⁵. All these parameters are present also in in peri-implant crevicular fluid (PICF)¹⁹⁵.

On one side, ROS are required for cell signaling and normal metabolism. On the other hand, excessive

oxidative stress, may lead to damage on DNA, ribonucleic acid (RNA), and proteins¹⁹⁶. Short-term oxidative stress may occur in tissue loss such as trauma, heat damage and infection. In these damaged tissues, the production of enzymes (rich of free radicals) is increased by phagocytic cells with release of free metal ions, epoxidation and production of excessive ROS^{197,198}.

When ROS production increases or antioxidant capacity decreases there's oxidative damage of cellular components as in proteins, lipids, and nucleic acids¹⁹⁹.

It has already been proven that oxidative stress is related to many diseases, including cardiovascular disease, diabetes, rheumatoid arthritis, cancer and various kinds of inflammation²⁰⁰.

Oxidative stress and oxidative damage are in the context of dental procedures and it has been shown that periodontal inflammation is a direct result of increased ROS and oxidative damage products in the oral cavity²⁰¹.

Alcohol consumption and nicotine exposure can increase ROS and are related to periodontal disease.

A lot of dental procedures such as implants, bleaching, and fillings are related to oxidative stress²⁰²⁻²⁰⁴.

Clinical evidence: The process of dental implant implantation inevitably generates ROS. Tsarik et al. reported that the oxide layer generated on the surface of titanium alloy implant may reduce the potential corrosion²⁰⁵. Friction during implantation would lead to the metal surface rupture and the titanium dioxide layer corrosion and an electrochemical reaction with free radicals and hydrogen peroxide were generated as intermediate products. When titanium dioxide is corroded, hydrogen peroxide generated by electrochemical reaction will continue to react with titanium dioxide to form hydroxyl radicals²⁰⁶.

Bressan et al. analyzed the effects of titanium (Ti) particles on mesenchymal stem cells (MSCs) and fibroblasts (FU); they evaluate cell proliferation and generation of ROS and it was found that titanium

particles reduced the survival time of the cells and increased the generation of ROS. Concomitant with oxidative stress, bone regeneration imbalance was induced²⁰⁷.

The implant placement process may lead Ti particles to enter the tissue and cause inflammation. Therefore, tetracycline, doxycycline, chlorhexidine, hydrogen peroxide, and citric acid can be used to remove excess Ti particles, among which hydrogen peroxide, citric acid, and chlorhexidine are more effective²⁰⁸.

Also, Abdulhameed et al. reported that titanium dioxide nanoparticles (TiO₂NPs) can induce oxidative stress, reduce osteogenesis, and damage the antioxidant defense system²⁰⁹.

After a dental implant placement, friction and twisting could damage the oxide layer on the surface, leading to an increase of ROS and an inflammatory, such as peri-implantitis (PI)^{210,211}.

Antioxidants are choices for treatment. PI and periodontal disease are manifested by soft tissue and bone damage, in which ROS play an important role in cell transmission, maintenance, and proliferation²¹².

A certain amount of ROS is already present before the dental implant is implanted²¹³ and the administration of antioxidants have a protective effect on periodontal tissue and can neutralize ROS to prevent tissue damage²¹⁴. A lot of antioxidants can be obtained from diets and supplements, and supplements can be taken in addition to a diet rich in berries and vegetables¹⁹³. Some useful antioxidants are tannic acids macromolecules consisting of a central glucose molecule linked to 10 surrounding gallic acid units²¹⁵⁻²¹⁸. Green tea and quercetin have both anti-inflammatory and antioxidant properties²¹⁹⁻²²². Polyphenols are natural compounds with antioxidant and antimicrobial properties^{223,224}. The antioxidant activity of polyphenols cleans free radicals by supplying hydrogen atoms from hydroxyl groups in the phenolic ring²²⁴, and chelating iron and other metal ions, thereby preventing the catalytic oxidation of hydrogen peroxide and superoxide to hydroxyl radicals²²⁵.

Curcumin, a polyphenolic compound can also lead to an increase in the level of the antioxidant enzyme glutathione peroxidase, which reduces the ROS level in cells²²². Vitamin E is a common antioxidant with the highest concentration in human mitochondria. The main of action of vitamin E is to interact with superoxide in mitochondria, limiting its formation, stabilizing mitochondrial membrane, and removing antioxidants that have been generated²²⁶. A study indicated that adding low concentrations of vitamin E (less than 0.1%) did not affect the physical and mechanical properties and can prevent oxidation for up to 24 months post-implantation ²²⁷.

At present, antioxidants in the treatment of local inflammatory reactions, such as periodontitis, and PI usually quickly disappear with ROS and other free radicals. Some studies reported the effects of new materials in which hydrogels can reduce the presence of ROS, inhibit hydrogen peroxide and lipid peroxidation^{195,228}.

Clinical recommendations: There are no reported contraindication for implant placement in patients with elevated oxidative stress. However, there's evidence that lowering the level of ROS could help the healing process of peri-implant bone tissue^{195,229}.

Studies that evaluate peri-implantitis found significant correlations between probing pocket depth, level of Malondialdehyde (MDA) and total antioxidant capacity (TAC)¹⁹⁵.

Moreover, level of oxidative stress markers (MDA, SOD and TAC) in peri-implant crevicular fluid (PICF) does not significantly change in peri-implantitis compared to healthy implants^{195,212}.

Therefore, the prevention of possible peri-implantitis could be supported by antioxidants supplementation and delivery by new gel encapsulation that is worth of studying^{209,229}.

While the clinical relevance of the Oxidative Stress is growing, we need to focus attention to how it affects the possible outcome of patient with dental implants²³⁰. Like inflammation, it is likely to play a major role in both healing and harm. As diagnostic biomarker techniques become more, reliable and sophisticated, we need to interlace this information into new protocols of peri-operative

evaluation in dentistry. The pre-operative and postoperative evaluation of oxidative stress its used in other surgical fields like colon-rectal oncology, a desirable outcome would be the application in dental implant surgery^{231–234}.

CONCLUSIONS

Systemic conditions and/or an unhealthy lifestyle may directly lead to surgical complications, compromise implant/bone healing, or influence the long-term peri-implant health and its response to biologic nuisances. Similar risks may pertain to the medications taken by implant patients rather than the disease itself.

The present review shows that there are very few absolute contraindications and a full evaluation of each individual patient is of the utmost importance to avoid implant-related complications in medically compromised patients with or without unhealthy lifestyle/elevated oxidative stress.

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