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REVIEW ARTICLE

Emerging factors affecting peri-implant bone metabolism

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1 | INTRODUCTION

During the last few decades, dentists have observed an astonishing change in clinical implant dentistry. Currently, implant survival is predictable even when faced with various differences in bone quantity and quality, implant length or diameter, and even despite various surgical or prosthetic protocols.[1-11] The continuous development of implant designs, surfaces, and a deeper understanding of bone biology and metabolism have been achieved due to the amount of clinical and scientific research on this topic.[1]

Dental implant surfaces play an important role in the biological stability of implanted materials and are subjected to surface modifications to improve the host-to-implant tissue response, leading to better bone responses and the preservation of marginal bone.[1,12] This may explain the increases observed in the implant survival rate over the years and the predictability of dental implant treatments, including immediate placement and/or loading.[2,3] Nevertheless, even with improvements in implant surfaces, it has been reported that between 40%[13] and 83.4%[14] of all implant failures occur at early time points (less than 6 months after implantation), and a better understanding of such failures is needed. Specifically, the presence of low-density bone (i.e., in the posterior strophic maxilla) is a challenging situation that requires proper treatment planning and surgical protocols, in addition to a modified implant surface to diminish the risk of implant failure.[4,5] Implant surface modifications can be grouped into subtractive and additive processes.[15] Whereas the subtractive methods remove material from the implant surface, the additive methods add material onto the implant surface. These modifications are designed and applied to alter the roughness of the surface and/or oxide composition, including the incorporation of bioactive agents into the surface composition.[4] Some elements, such as calcium, magnesium, zinc, and strontium, have a relevant role in some molecular and biochemical processes during bone regeneration and have been investigated on implant surfaces.[4,16] Others such as copper, zinc, cobalt, and strontium, are known for their anabolic effects on bone metabolism.[17]

Thus, a continuous improvement in surface treatment technologies has optimized the performance and ability of implants to osseointegrate either better or even faster. Furthermore, different techniques have been proposed to introduce various exogenous metal ions onto the implant surface not only to improve osseointegration, but other beneficial factors include increased corrosion resistance as well as anti-inflammatory or antibacterial properties.[18] Due to the balance of biocompatibility, mechanical properties, resistance to corrosion, and capacity for osseointegration, titanium (Ti) has been the preferred material for biomedical applications over the past several decades.[19,20] However, this wide use of Ti in the medical field has also increased concerns, such as the effects of free Ti particles released within the human body and their long-term accumulation.[20]

It is critical to conceive aseptic bone loss as a risk factor for long-term biological complications. Early bone loss (6 months) may jeopardize bone stability and implant survival over the long term[21] and the role of early bone loss as a predictor for peri-implantitis was validated in a 10-year prospective cohort study.[22] More recently, it was demonstrated that interproximal thread exposure dictates the long-term bone stability of implants. It was concluded that even one thread exposed implied an 8× increase in risk for peri-implantitis,

and every further thread added an additional 4× of added risk.[23] For these reasons, preventing aseptic bone loss around implants is a key priority to achieve preferable long-term success. Nevertheless, many other contributing factors that affect bone metabolism have not yet been fully explored. As marginal bone loss and peri-implantitis can be considered conditions with a complex and multifactorial pathogenesis, the synergistic action of several of these factors (implant-, surgical-, prosthetic-, microbiological-, and host-related) may be necessary to exceed the individualized threshold of each patient for the pathology to appear.[24] Some authors proposed that the objective of the treatment should not only be the control of bacterial plaque but also to avoid or minimize a pro-inflammatory microenvironment surrounding the implant.[24] A paradigm shift should be made to avoid osteoclast differentiation and activation caused by the local or systemic release of proinflammatory cytokines and other molecules.[25-28] This overexpression of inflammatory mediators is generated not only with the colonization and activity of pathogenic bacteria[28,29] but also due to other factors such as the presence of Ti particles, corrosion, wear, abutment micromovement, occlusal overload, and the presence of cement remnants.[24] It is important to point out that only 28.8% of peri-implantitis cases were considered purely plaque-induced peri-implantitis, while 40.8% and 30.4% were considered surgically and prosthetically triggered cases.[30] Indeed, in some cases, several risk factors may act synergistically and make it difficult to find the initial triggering factor.

Therefore, the aim of this narrative review was to provide an update on the understanding of osseointegration and peri-implant bone remodeling and to illustrate situations where bone stability can be jeopardized due to reasons inherent to either the surgery, the implanted materials, the patient's current drug use, diet, and the host response to bone metabolism.

2 | IMPLANT-RELATED FACTORS ALTERING BONE METABOLISM

Immediately after implantation, the external metal surfaces are surrounded by extracellular fluid and proteins. Then, a dense passive oxide film is formed on a titanium surface at the Ti(IV) oxidation state.[31] After exposing Ti to oxygen, spontaneous passivation of the surface occurs, leading to the formation of amorphous or low-crystalline TiO_2 of thickness 4–6 nm.[32-34] This layer provides Ti with low toxicity, low reactivity with molecules, low solubility in water, corrosion resistance, and biocompatibility.[33] Interestingly, the composition of the adsorbed protein layer on the implant surface has a major relevance to the beginning and progress of the biological response after implantation.[4] For example, some coatings of dental implants like atmospheric plasma spraying, induce the formation of a thicker oxidated layer responsible for lower tissue adhesion and a slower osteogenesis process.[35] Thicker oxide layers around 100 nm would improve their corrosion resistance, but with worse biological properties.[36] The presence of this titanium oxide layer has been considered critical for the prevention of corrosion of the superficial and inner core of the implant and for osseointegration maintenance.[37] Nevertheless, this presence alone is not enough to avoid corrosion owing to the complex media contained in the oral cavity that impairs the stability of the dioxide titanium layer by chemical or mechanical mechanisms, including mechanical wear, fretting, stress, fatigue corrosion, and electrochemical processes (Figure 1).[31,33] In summary, once the protective oxide layer is damaged, changes in the chemical composition, surface topography, roughness, and mechanical properties can be expected.[32,33] At this point, damage to this layer induces Ti and metal particles' release; osseointegration may be impaired, bone resorption process may induce peri-implant bone loss; and even mucositis and peri-implantitis could be initiated.[37,38] Titanium has been perceived as biocompatible due to the presence of a stable oxide layer caused by its high affinity for oxygen.[37] But since titanium, also in different medical grades (II–IV) than an alloy (grade V), is highly reactive, the damage or disappearance of this external layer leads to the release of particles or ions.[38]

2.1 | Toxicity of titanium and presence of metal particles

The extreme conditions of the oral cavity make even a stable and "noble" metal such as Ti undergo wear and corrosion, both from the external Ti coating and from the inner Ti core.[20] Although the main causes of implant failures or peri-implantitis are the presence of plaque or biofilm around dental implants, the toxicity of particles released from implants or the immune response to any of the metals present in the implants may also have a prominent role in bone loss (Figure 2).[20,39–43] Relatively high concentrations of Ti have been measured in periprosthetic tissues, body fluids, and distal organs such as lymph nodes, liver, and spleen.[44,45] The widely used cobalt–chromium alloy or Ti, may release cobalt, chromium, or Ti ions,[46] which can damage the surrounding tissues and affect the osseointegration of dental implants.[18] Ti ions can be defined as a particulate metal in an unstable atomic electric condition, whereas titanium particles are a particulate metal in a stable atomic electric condition,[47] both capable of impacting cellular activity. Changes in the oral cavity pH, the presence of a bacterial biofilm, the continual wearing of the implant-prosthesis connection, and electrolytic effects may lead metals such as cobalt–chromium or titanium to corrode and promote deleterious effects on osseointegration and the surrounding tissues. Corrosion is an electrochemical phenomenon, and the most common oral cavity types are galvanic corrosion, crevice corrosion, and pitting corrosion[41,48] even when other types can be found (like uniform, stress, fretting, or microbial corrosion). While pitting corrosion occurs at the connection between implant and abutment, crevice corrosion is provoked by a high concentration of chloride ions, low pH conditions, and a low exchange of oxygen. When the peri-implant area is under these acidic conditions, the Ti oxide layers may be dissolved, leaving the inner implant core more susceptible to further damage if the oxygen flow is not enough to passivate the corroded implant surface. In galvanic corrosion, there is an exchange

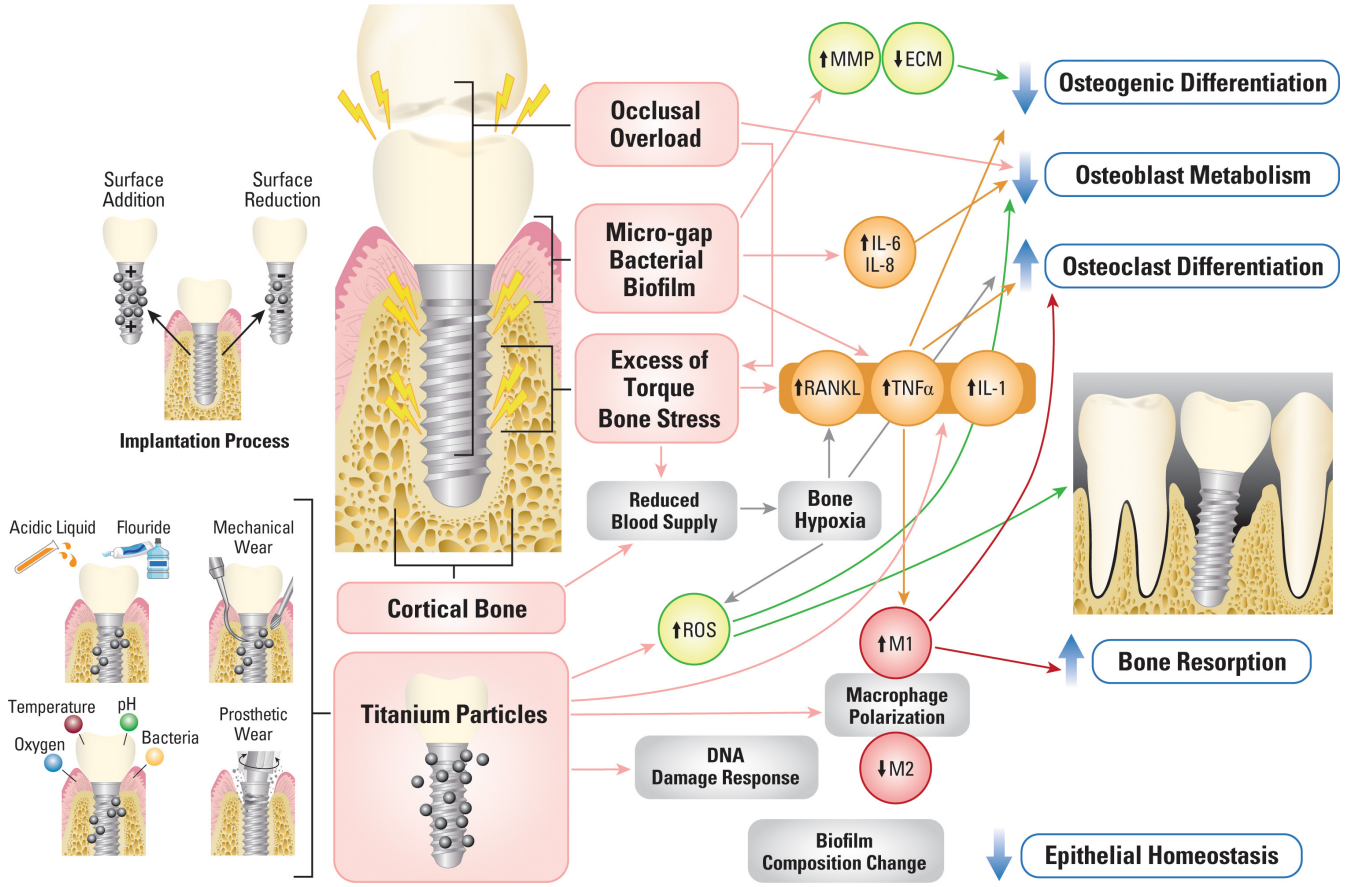

FIGURE 1 Implant-related factors altering bone metabolism.

of ions between implants and their prosthetic components.[41] This type of corrosion may be more frequent due to the increase of cost of gold superstructures and the consequent higher use of other alloys such as Cr-Co, Ag-Pd, or Ni-Cr. In detail, the combination of Ti implants with Cr-Co prosthetic parts showed corrosion effects frequently.[49] The difference in potential between dissimilar metals or alloys in contact with oral fluids creates an electric current flow called galvanic current. This galvanic current accelerates the corrosion rate of the lesser noble metal and the release of metal ions into the peri-implant tissues. In depth, the lesser noble metal becomes an anode and accumulates ions from the cathode formed by the noble metal (titanium implant). Implant surfaces may undergo oxidation, corrosion, and ion release. Moreover, the accumulation of bacteria on implant surfaces and micro-gaps tends to reduce pH and oxygen levels and create a favorable situation for corrosion. In detail, the areas with low oxygen concentrations act like an anode and suffer corrosion and metallic ion release. These metallic ions join the end yields of bacteria and chloride in saliva to form corrosive products that stimulate later corrosion.[41]

There is growing literature correlating an impairment in the health of peri-implant soft and hard tissues and failures in osseointegration with the accumulation of Ti ions in peri-implant tissues.[41,47,50,51,52] These hypotheses have been postulated in the orthopedic field for several years, and some authors believe that titanium ions released from orthopedic implants may reach levels of approximately 1 micromol in serum and play a negative role in aseptic loosening of implants.[31,44,53,54,55]

Release of Ti particles starts from the very insertion of the implant[56] and high levels of these Ti particles have negative influences on osteoblast formation and promote the activity of osteoclasts and inflammatory cells.[18] An in vitro study in rat calvaria analyzed the influence of Ti particles on osteoblast function and bone mineralization.[57] Concentrations of 10 ppm Ti inhibited osteoblast proliferation, whereas concentrations of 5 ppm or less Ti had no effect but prevented the stimulation of cell proliferation.[57] Ti ion concentrations of 11 ppm were found to produce cytotoxic effects on bone and epithelial cells,[50] even with the induction of necrosis.[58] Below this cytotoxic threshold, 5 ppm titanium ions increased the levels of CCL2 mRNA expression in gingival epithelial cells exposed to bacterial LPS in a synergistic manner, and 9 ppm Ti ions significantly increased the mRNA expression of TLR-4 and ICAM-1 versus controls.[58] In summary, relatively low levels of Ti ions are cytotoxic toward epithelial cells, and under that value, epithelial cells become more sensitive to pathogens, which is related to increased monocyte infiltration and to an increased inflammation of tissues surrounding dental implants.[58]

Other in vitro studies have correlated strong inflammatory responses with the release of TNF-α, IL-1β, and IL-6 after exposure

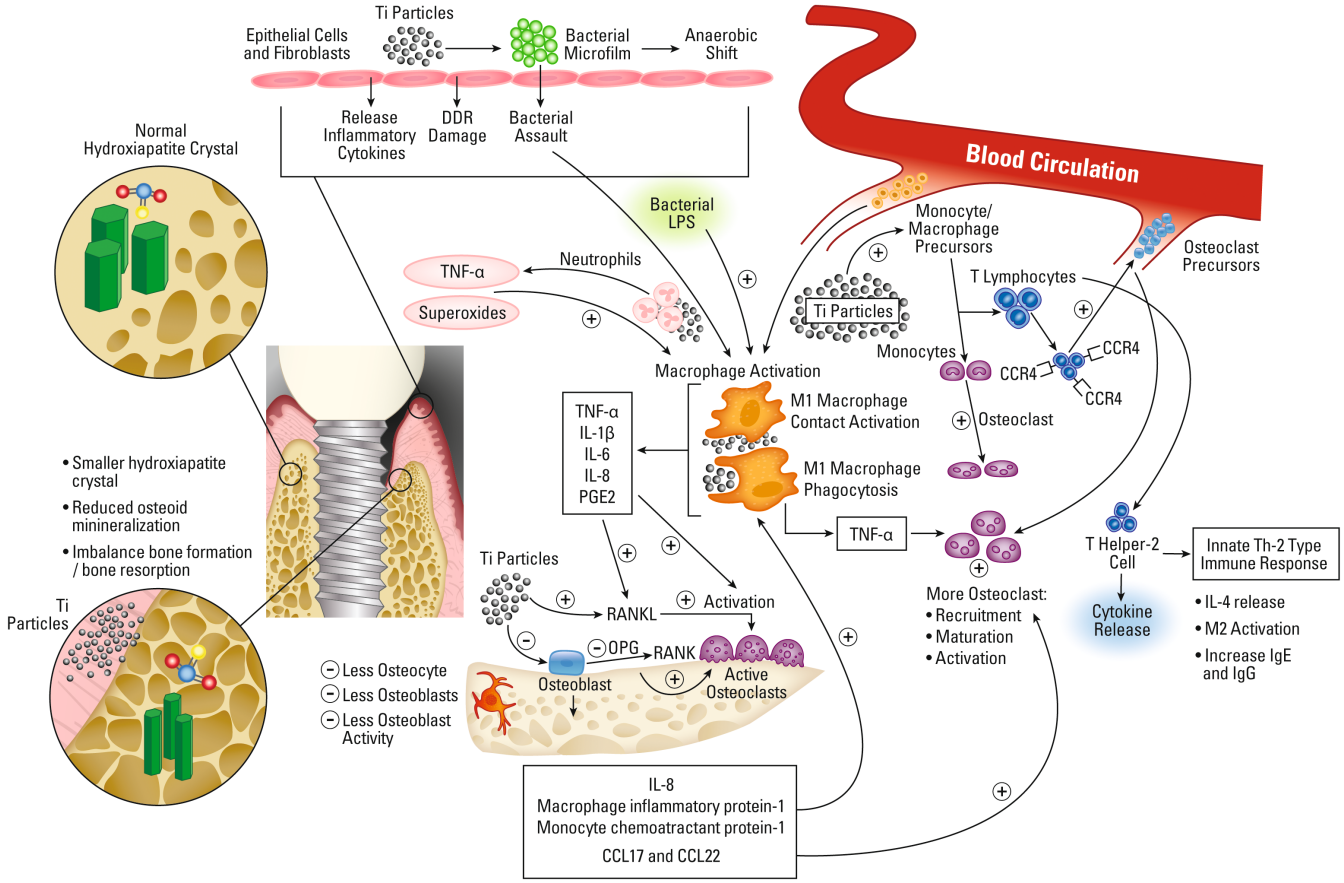

FIGURE 2 Potential effects of metal particles on bone metabolism.

of human macrophages to Ti micro- and nanoparticles (50 ng/mL).[59] This enhanced inflammatory response has been associated with osteolysis and bone resorption.[50,60] The synergistic stimulation between Ti ions and bacterial LPS, with the consequent increase in the RANKL/OPG ratio and the higher expression of CCL2 in gingival and bone tissues, have a key additional role in inflammation and bone loss.[50] A study in rats measured the release of titanium ions equivalent to 15–50 ppm after exposure of a pure titanium mini-implant to fluoride (F) for 30 min. Therefore, concentrations between 9 and 50 ppm can stimulate a strong release of proinflammatory cytokines in the presence of LPS in vivo.[50] Considering that some studies have reported that the concentration of titanium particles released during implant insertion reaches values of 11.66–37.52 ppm,[56] well above the cytotoxic thresholds described above, it can be inferred that titanium ions or particles may be involved in peri-implant pathologies and bone loss.[50] Additionally, a reduction in the mineral deposition of osteoid nodules is evidenced when Ti concentrations reach 5 ppm. Moreover, at this concentration of titanium particles, the expression of osteonectin (OSN) and osteopontin (OPN) is dramatically reduced, inhibiting osteoblast differentiation.[18,57] Similarly, titanium ion values above 100 ppm promote the formation and maturation of osteoclasts, leading to an increase in bone resorption.[61]

Other authors have concluded that Ti ions could also affect osteoclastogenesis and differentiation even at lower concentrations by changing the sensitivity of the epithelium to microorganisms.[50] For example, exposing epithelial cells to 9 ppm titanium ions increases their mRNA of Toll-like receptor 4 (TLR-4) in a dose-dependent manner to Ti concentration and enhances the sensitivity of these bacterial endotoxin receptors. Moreover, direct binding between titanium dioxide nanoparticles and the TLR4 receptor without the LPS protein complex (LPS binding protein (LBP) and CD14) allows metal particles to activate the complex in a similar way as LPS does, but without the need for the previous binding between LPS, LBP, and CD14.[62,63] Further activation of TLRs initiates nuclear factor kappa B (NF-κB) and promotes host inflammation-related target genes and inflammatory responses.[62] Based on these data, Ti particle recognition is mediated by the activation of TLRs and NF-κB, which are clearly linked to inflammation and tissue damage.[50,63,64]

Stimulation by LPS or by engulfment of titanium particles has different forms of action; however, both pathways share a common activation of NF-κB, and both increase the production of inflammatory cytokines independently yet act synergistically.[64] The authors also noted that the expression and discharge of IL-1β can be activated both by pathogen-associated molecular pattern molecules (PAMPs) and damage-associated molecular pattern molecules (DAMPs).[64,65] While bacterial LPS activates PAMPs, submicron titanium particles can be associated with DAMPs and promote a higher proinflammatory signal.[64,65]

One in vitro study assessed the influence of Ti ions on bone marrow stromal cell differentiation. These ions inhibited normal

cell differentiation, reduced calcium deposition on the cell matrix, and contributed to in vivo implant failure by hindering normal bone deposition.[66] Moreover, these particles led to a reduction in hydroxyapatite formation by binding to the crystal surface of hydroxyapatite and preventing crystal growth. All these processes can affect the normal mineralization of the osteoid and hinder the capacity of the bone-implant interface to repair itself.[18] This reduction in the levels of calcium salt deposition weakens the osteogenic ability of the already lowered number of osteoblasts to mature due to the presence of titanium particles.[18]

Moreover, an excessive amount of titanium particles also activates inflammatory cells and increases the production of proinflammatory cytokines related to bone resorption, including TNF-α, IL-6, IL-1α, and IL-1β.[31,44,67–69] This inflammatory status and the imbalance between bone formation and bone resorption can further lead to a higher rate of titanium corrosion, the release of more titanium particles, and the activation of a negative feedback loop that rapidly causes increased pathology.[18] An animal study found that the presence of titanium debris promoted deleterious effects on peri-implant tissue caused by activation of M1 macrophages and consequent release of inflammatory cytokines (mean bone loss in the test and control groups: 0.44 ± 0.15 mm vs. 0.13 ± 0.04 mm, respectively).[69] Based on this data, the authors concluded that Ti particles released into peri-implant tissues might induce a local aseptic inflammatory response with marginal bone loss around osseointegrated implants.[69]

Cytotoxicity is dependent on the size, chemical composition, and metallic content of the particles.[67,70,71] For example, the presence of bacterial LPS may inhibit the release of titanium particles when the peri-implant tissues are under low pH values (pH = 2) but could induce titanium particle release under neutral pH levels.[72] Albumin and H_2O_2 together enhance the corrosion of Ti-6Al-4V more than the presence of either element alone at physiological pH and temperature.[73] These findings may be relevant because albumin is the most abundant protein in blood plasma and extracellular tissue fluid[74] and because reactive oxygen species (ROS) such as H_2O_2 are present in tissue as a reaction to infection or inflammation. Furthermore, H_2O_2 may reach high concentrations within the bacterial biofilm and at the biofilm substrate interface.[74] This synergistic increase in the corrosion rate is due to the enhanced anodic reaction by H_2O_2 complexation of titanium and by the suppression of the cathodic reaction by albumin adsorption, which shifts OCP to the active region of titanium alloys.[73] This inflammatory condition, the consequent acidification of the medium, and the high concentration of ROS may even further induce higher implant corrosion, activation of the innate and adaptive response with pro-inflammatory cytokine discharge, bone resorption, or even implant loosening.[74] Thus, TiO_2 nanoparticles in tissues can adsorb inflammatory cytokines such as CXCL8 and IFN-gamma, causing disruption of neutrophil chemotaxis, modification in the amounts of inflammatory mediators in the tissues, and amplification of the inflammatory response.[20,75,76]

The presence of aluminum or vanadium has also been observed in the bone marrow of patients who received artificial iliac joints.[20,77] Whereas Co-Cr caused a more intense toxic effect, Ti alloy promoted inflammation by increasing the amount of interleukin 1 and 6, prostaglandin E2, and TNF.[20,78] The presence of vanadium (Ti-Al-V) was associated with a larger amount of inflammatory mediators released by monocytes than niobium (Ti-Al-Nb) and a higher risk of bone loss.[79] Similarly, metal particles from Cr-Co-Mo or Ti-6Al-4V alloys can react and bind to protein complexes of high molecular weight, leading to more intense inflammatory reactions.[80] Cr-Co-Mo, Ti alloy, and zirconium induce an inflammatory reaction in human osteoblasts, fibroblasts, and macrophages with the release of interleukin IL-1β, IL-6, tumor necrosis factor (TNF), and IL-8, which have all been shown to produce bone loss around orthopedic implants.[81,82] In summary, while all metal particles promote the high release of macrophage inflammatory mediators, Cr-Co-Mo, and titanium alloys lead to a higher inflammatory status. Macrophages in contact with Cr-Co-Mo release 100 times more IL-8 than controls, and fibroblasts and osteoblasts secrete 30 times more IL-6 and 15 times more TNF-α than controls.[81] In another study, both Co-alloy particles and Ti-alloy particles were found to increase IL-6, TNF-α, and IL-8 compared to Zr-based particles.[83] Other studies reported that Ti particles from implants were able to stimulate macrophages more strongly than other materials used in implant restorations, like polyethylene, CoCr, ZrO_2, and aluminum particles[84,85] or had a synergistic effect mixed with polyethylene.[86]

On the contrary, a study in vitro reported that Co particles can neutralize the inflammatory effect of IL-1B release caused by Ti particles coagreggated with serum particles.[87] While Co is considered toxic in most studies, the authors did not find impaired cell viability by Co nor with Cr addition compared with Ti alone. Indeed, Co enhanced the activation of M2 phenotype macrophages from resting cells in absence of exogenous cytokines.[88]

The RANKL/OPG ratio is relevant for the balance of bone formation and bone resorption by osteoclasts. While RANKL is an activator of NF-kB signaling and can increase the inflammatory response, OPG is a competitive ligand of the RANKL receptor.[82] Titanium particles increases the RANKL/OPG balance in a dose-dependent manner by increasing the expression of RANKL and diminishing the expression of OPG.[89–91] CoCrMo particles have an even stronger effect on the RANKL/OPG ratio than Ti particles.[82] The larger intensity of proinflammatory mediators caused by Co-Cr-Mo particles can be explained by their more intense cellular response, whereas titanium particles induce a chronic inflammatory reaction with macrophage activation, proinflammatory cytokine release, and osteoclast differentiation and activation.[82] These Co-Cr-Mo particles can induce monocyte/macrophage activation and secretion of proinflammatory cytokines via upregulation of the transcription factor NF-κB; however, these particles not only activate macrophages but also stimulate T cells of the immune system and activate the inflammasome danger signaling pathway in human macrophages.[82,83,92,93] This local and systemic inflammation may lead to both a reduction in osteoblast function and higher osteoclast metabolism.[83] Higher expression of TRAP, Ctr, and Nfatc1 and an increased RANKL/OPG

ratio have also been reported for Co-Cr-Mo particles compared with titanium particles in a mouse model.[82]

2.1.1 | Influence of size and form of the particles

Macrophages and monocytes are the cells that react against metal particles wear after local immune activation. Neutrophils first react in response to foreign materials, and then macrophages follow.[70] Neutrophils are proportionally the largest leucocyte type (between 54% and 65%), and their function is to initially react in a nonspecific manner to foreign objects, releasing cytokines and other signals to further activate and communicate with macrophages. These cells have a more complex function and reaction against foreign particles.[70] Depending on the size of the particles, different cells may tend to engulf them[94]; particles smaller than 1 μm can be taken up by nonphagocytic eukaryotic cells via endocytosis, while particles larger than 0.75 μm can be collected by macrophages, monocytes, or neutrophils through phagocytosis or by micropinocytosis (>1 μm) by all cell types.[95]

The response of macrophages and their effect on periprosthetic osteolysis seem to depend on the dose, size, form/shape, and composition of the implant debris.[82,83] Elongated particles might be more proinflammatory than round particles, and metal particles seem to induce more inflammation than polymer particles.[83] Some articles have reported that small and submicron particles between 0.1 and 1 μm might be more biologically reactive and induce a stronger inflammatory response, macrophage activation, and cytokine release.[81,96] Other authors have demonstrated that only particles of less than 10 μm can induce an inflammatory response.[82,97] In contrast, another study found no relationship between particle-induced osteoclast formation and related bone loss with particle shape or electrical charge but with contact between cells and wear particles.[98] In another study, particles between 0.24 and 1.7 μm increased the levels of cytokine secretion, whereas larger particles up to 7.6 and 88 μm resulted in considerably less cytokine release; consequently, size and volume were critical factors in an inflammatory reaction and macrophage activation.[97] Sabokbar et al.[98] considered that there was no need for particle phagocytosis and that the inflammatory reaction and the consequent periprosthetic osteolysis might be induced only by particle contact. Another study reached the same conclusion, stating that macrophages exposed to Ti particles stimulated the production of TNF-α by 40 times and IL-6 by 7 times, but the inhibition of the phagocytosis process did not reduce the production or release of inflammatory cytokines.[99]

A relevant production of ROS was observed under 5.0 and 10 μg/mL concentrations of TiO_2 nanoparticles; these data may indicate that one of the most relevant mechanisms of damage to cellular membranes and biological molecules induced by nanoparticles is caused by oxidative stress.[100] The same group reported that DNA damage at 20 μg/mL and under 10 μg/mL nanoparticles can regulate the levels of antioxidant enzymes and damage the cell reparative DNA system.[100]

Other studies found that the release of nitric oxide, PGE_2, and other cytokines from macrophages is dependent on particle size after exposure to Ti and Ti-6Al-4V particles.[71,101] Increased inflammation was reported when particles were smaller than the cell size.[71,101] Interestingly, titanium alloy particles induce the most inflammation, followed by commercially pure titanium. The authors also noted that nitric oxide may play a role in osteolysis by inhibiting DNA synthesis and cell proliferation and stimulating PGE_2 release, but their mechanisms are not totally clear.[101] Increased release of PGE_2 and IL-6 was reported after exposing osteoblasts to titanium debris.[102] These increased levels of PGE_2 were associated with a reduced level of OPG and consequently with enhanced osteoclast differentiation and activation.[102]

An in vitro study found that human neutrophils phagocytized titanium particles only when the particle size ranged between 1 and 3 μm (smaller than the neutrophile's size of approximately 5 μm).[70] After engulfing the particles, neutrophils produced and released superoxide anions and TNF-α.[101] These superoxide anions might alter the biocompatible surface layer of titanium implants and promote more particle release, and the combined effects induce a strong long-term inflammatory status.[101] Particles of less than 10 μm can also induce cytotoxicity and an inflammatory response in neutrophils, but cells are not able to engulf them.[70] In vivo tests performed in rats found that larger particles between 40 and 150 μm elicited an inflammatory response, but they were mainly surrounded by soft tissue, presupposing that larger particles are more biocompatible than smaller particles.[101] In conclusion, titanium particles less than 10 μm trigger an inflammatory response in neutrophils around titanium implants.[101] Moreover, macrophages stimulated with titanium particles less than 2 μm increase in vitro bone resorption by 125%.[71] Indeed, the presence of particles leads to macrophage release of IL-1 and PGE_2, as well as inhibition of DNA synthesis, cell damage, or apoptosis.[71]

Macrophage response to particulate biomaterials is also size dependent. Macrophages can phagocytize 10 μm diameter particles[103] but never larger than 25 μm[104]; these cells try to digest, degrade, and internalize particles in their phagosomes.[103] If particle size is larger and beyond the capacity of a single macrophage, several cells will fuse into multinucleated giant cells (MNGCs)[105] in an attempt to engulf the debris.[103] When MNGCs are not capable of internalizing the object, they will try to digest it with the help of additional macrophages by releasing extracellular degradation enzymes or lowering the pH.[103] It is believed that these cells can stay at the biomaterial–tissue interface for the lifetime of an implanted device (Table 1).[103,106]

2.1.2 | Influence of implant design on particle release

Factors such as the implant surface, implant and abutment composition, or type of connection may be relevant to the number of particles released. Stability and sealing of the implant-abutment connection are out of the scope of this review, but these characteristics are crucial in the generation of wear and further scattering of debris

TABLE 1 Effect of metal particles on human bone, epithelial, and inflammatory cells.

Type of cells	Function	Evidence
Bone cells	Reduction in the differentiation of bone marrow stromal cells	Thompson et al. (1996)[66]
	Reduced calcium apposition on the extracellular matrix during healing Lowered levels of calcium in the osteoid reduces the proliferation, maturation, and final number of osteoblasts	Chen et al. (2021)[18]
	Reduced normal bone deposition	Thompson (1996)[66]
	Impaired hydroxyapatite formation by binding to the surface and preventing crystal to growth	Chen et al. (2021)[18]
	Reduction in osteoid mineralization	Chen et al. (2021)[18]
	Reduction in the capacity of the bone-implant interface to heal	Chen et al. (2021)[18]
	Increment of osteoclast recruitment, differentiation, and activation Faster osteoclast maturation	Meng et al. (2010), Li et al. (2018)[61,82]
	Reduction of osteoblast recruitment and differentiation. Reduced dose-dependent metabolism or apoptosis	Chen et al. (2021), Wachi et al. (2015), Liao et al. (1999), Makihira et al. (2010) [18,50,57,58]
	Increased release of PGE_2 and IL-6 by osteoblasts	Vallés et al. (2008)[102]
	Increased osteoclast precursor recruitment by CCL17/TARC, CCL22/MDC, and other pro-inflammatory cytokines	Cadosch et al. (2010)[158]
	Longer survival of osteoclasts in the metal-tissue interface area	Cadosch et al. (2009), Cadosch et al. (2009), Greenfield (2002)[31,44,168]
	Promotion of monocyte differentiation into mature and functional osteoclasts	Cadosch (2009)[31]
	Newly differentiated osteoclasts disconnected from physiological osteoblastic control (RANK-L and M-CSF)	Cadosch et al. (2010)[158]
	Local inflammation ➔ indirect reduction in osteoblast formation and increased osteoclast activity	Chen et al. (2021), Wachi et al. (2015), Liao et al. (1999), Souza et al. (2013)[18,50,57,60]
	Alteration of the RANKL/OPG quotient Increase in RANKL. Reduction in OPG	Li et al. (2018), Fernandes and Gomes (2016), Alrabeah et al. (2017), Berryman et al. (2020), Geng et al. (2010)[82,89,90,91,176]
Epithelial cells	Activation of the DNA damage response in epithelial cells	Suarez-Lopez (2017)[128]
	Dose-dependent reduction in fibroblast cell viability or apoptosis	Bressan et al. (2019)[188]
	Damage to collagen fibers by the induced secretion of metalloproteinase	Bressan et al. (2019)[188]
	Production of inflammatory cytokines by fibroblasts	Dalal et al. (2012), Li et al. (2018)[81,82]
Inflammatory cells	Increased production of pro-inflammatory mediators related to bone resorption: TNF-α, IL-1β IL-6, IL-8, and PGE2	Kim et al. (2019), Cadosch et al. (2009), Messous et al. (2021), Stea (2000), Wang et al. (2019), Haynes et al. (1993), Hallab et al. (2009), Eger et al. (2018), Wu et al. (2022), Berryman et al. (2020), Shi et al. (2013)[20,44,67,68,69,76,78,83,149,151,176]
	Chronic inflammatory status and disbalance between bone formation and bone resorption ➔ positive feedback with higher rates of titanium corrosion and release of more titanium particles	Chen et al. (2021)[18]
	Activation of NLRP3 inflammasomes and increased IL-1 β release are directly induced by Ti particles	Dodo et al. (2017)[59]
	Activation of NLRP3 inflammasomes and synergistic increase in IL-1 β release induced by LPS and Ti particles	Taira et al. (2010), Pettersson et al. (2017), Jämsen (2020)[64,181,204]
	Activation of NLRP3 inflammasomes and increased IL-1 β release induced by Ti particles + TNF-α	Jämsen (2020)[204]
	Activation of NLRP3 inflammasomes and increased IL-1 β release induced by excess ROS promoted by Ti particles	Yazdi et al. (2010), Moon et al. (2010), Armand et al. (2013), Mariathasan et al. (2006)[201,203]
	Activation of TLR4 and further NF-κB directly and synergistically with LPS	Chen et al. (2011), Wachi et al. (2015), Mano et al. (2013), Chen et al. (2011), Taira et al. (2010)[18,50,62,63,64]
	Increased neutrophil and monocyte/macrophage chemotaxis Increased production of inflammatory mediators by macrophages	Kim et al. (2019), Batt et al. (2018), Shi et al. (2013), Dalal et al. (2012), Hallab et al. (2009)[20,75,76,81,83]
	Neutrophil release of superoxide anions and TNF-α after phagocytosis	Shanbhag et al. (1998)[101]
	Stimulation of immune T cells, consequent cytokine release, inflammation, and tissue damage. Increased osteoclast activity due to cytotoxic T lymphocyte-associated protein 4 (CTLA-4)	Li et al. (2018), Hallab (2009), Pearson et al. (2015), Caicedo et al. (2009), Ma et al. (2019)[82,83,92,93,229]

(Continues)

TABLE 1 (Continued)

Type of cells	Function	Evidence
Other effects	Induction of changes in the composition of oral biofilms and progression to microbial dysbiosis	Souza et al. (2020)[189]
	Increment in the levels of anaerobic periodontal pathogens by a reduction in the oxygen availability in bacterial biofilms	Souza et al. (2020)[189]

into the peri-implant tissues.[107,108] Several processes can induce deformation or wear of the implant connection, leading to an increased microgap, enhanced bacterial leakage, and dissemination of particles: repeated abutment connection and disconnection, reduced thickness of implant walls, overload, excess torque, narrow implant diameters, or nonpassive adjustment of the restoration, among others, are all critical factors.[107–110]

An interesting paper demonstrated that narrow-diameter implants with internal connections presented with surface damage and Ti particle release after insertion in type II artificial bone.[109] One implant underwent reduction of the inner walls after insertion of 186.21 μm (initial 655.89 μm ± 4.21 μm; final 469.68 μm ± 27.6 μm).[109] These major deformations in the walls and scratches in the connection just after implant insertion reveal one of the main sources of particle release. Another study testing Morse-taper implants reported less wall deformation and suggested inserting the implants with carriers engaging at the implant platform instead of at the implant-abutment connection to avoid friction-induced damage.[111] Morse-tapered connections can avoid wear under loading if the antirotational features are not incorporated within the implant body.[111] This fact might not be feasible to implement due to the intrinsic characteristics of conical connections. Pure conical connections had the highest magnitude of micromotion compared with three other connection designs[112]; in general terms, while butt joint connections tend to wear, conical connections tend to rotate[107,112] and friction occurs vertically with axial displacement into the implant.[113] A study analyzed the behavior of a pure conical versus a conical with an antirotational index.[114] The authors reported failures of pure conical abutments under lateral cyclic loading with torsional moment and stated that there is no antirotational capacity in a purely conical connection.[114] When an octagonal index was added to the abutments, the bending strength was reduced, and wear, plastic deformation, and fractures were found under SEM.[113,114] Furthermore, marked fritting wear was reported around the edges of the antirotational index.[113,114] In summary, no perfect implant shoulder geometry is able to avoid some micromotion at the implant-abutment level. In another study, 30-degree angle cyclic load micromovements between 1.52 and 94.00 μm were measured depending on the connection.[115] In detail, some Morse taper connections showed micromovements of approximately 20–40 μm during loading.[115] Moreover, no implant-connection design (even Morse taper connection) is free of the presence of microgaps during implant fixation or during cyclic loading.[116–120] For these reasons, it is expected that the occlusal load of the implant prosthesis will promote wear between the parts of the connection, and once fatigue appears and promotes gap opening, metal particles are expected to be released and scattered throughout the neighboring tissues and inner parts of the implants colonized by bacteria.

Platform switching has been associated with a reduction in biocorrosion and lower particle release that may minimize adverse tissue reactions.[121] In a comparative study, all platform-switched groups released fewer metal ions than platform-matched groups, with the highest metal ion release found in implants with platform-matched cobalt–chrome abutments (218 ppb), whereas the lowest measurements were in platform-switched implants with titanium abutments (11 ppb).[121] These metal ions boosted the osteoblast expression of inflammatory cytokines (IL-6, IL-8, RANKL, and COX-2) in a dose-dependent manner after exposure.[91]

One study measured particle generation from the implant–abutment connection of titanium and zirconia implants and abutments during cyclic loading of 240 000 cycles.[122] The authors found evident wear signs in all samples and low levels of ions generated by corrosion. While smaller particles (0.253–1.7 μm) were found in the container liquid, larger particles remained inside the implant connections (size range from 3.25 to 95.3 μm). Moreover, alloys of titanium-zirconia implants generated larger particles than titanium implants,[122] indicating that the size of particles may be affected by the implant and abutment material. Similarly, titanium implants exhibited more wear in their implant-abutment interface when zirconia abutments were used compared to titanium abutments after 1 200 000 cycles of loading.[123] The mean wear at the implant shoulder calculated by software was 0.7 μm caused by titanium abutments and 10.2 μm for groups that used zirconia abutments. In the same way, another study found that the mean wear area after 250 000 cycles of loading was 8 times larger for the group using zirconia abutments than for the group using titanium abutments ($131.8 \pm 14.5 \times 10^3\,mm^2$ vs. $15.8 \pm 3.3 \times 10^3\,mm^2$).[124] Based on these data, cautious use of zirconia abutments on titanium abutments should be considered to avoid an excessive release of metal particles. A recent study found that macrophage reactivity was lower for zirconia particles than for dioxide titanium particles. In detail, TiO_2 particles raised the cytokine expression up to 3.5 times more than ZrO_2 particles did.[125]

A study found that wider implant diameters released more metal debris than narrow ones and that Ti alloys (Ti-6Al-4V) scattered significantly more particles than grade 4 commercially pure titanium implants and titanium-zirconium alloys. Indeed, fewer particles were detected around tapered implants than around cylindrical implants.[126] Particles from all the samples were internalized by human fibroblasts and macrophages in vitro, suggesting their potential cytotoxicity, especially Ti-6Al-4V.[126] Furthermore, bone density and implant macrogeometry are related to the amount of Ti debris released.[56] While bone types I–II promote less release of

Ti particles, bone types III–IV induce more surface changes and scatter more metal particles.[56] Ti cylindrical alloy fixation releases less titanium than CP Ti-tapered alloy fixation (11.66 ± 28.55 ppm vs. 37.52 ± 25.03 ppm, respectively). Surface modifications to increase roughness, such as hydrophilicity, make the surface more prone to damage, to greater roughness reductions, and to higher particle release during insertion than normal implants.[127] Rough surfaces have a higher coefficient of friction and enhanced wear during implant insertion.[67] Anatomically, particles were detected along the entire length of the drilled bone, and especially in the cervical area with hydrophilic implants.[127] In that study, Ti alloy implants released fewer particles than hydrophilic grade 4 pure Ti implants.

A similar correlation between higher release of Ti and higher surface roughness was reported.[51,128] Comparing the two types of rough implants, machined implants showed significantly less release of Ti ($p < 0.001$). The Ti content ranged from a mean of 2.80 ± 0.85 μg for the Nobel Branemark System MkIV with an anodized TiUnite surface and an S_a value of 1.1 μm to 0.91 ± 0.36 μg with a machined surface and an S_a value of 0.9 μm.[51] According to these data, the implant surface can modify the release of Ti particles during implant fixation, and the presence of Ti debris may enhance the inflammatory process in the peri-implant tissues.[51]

Another interesting study concluded that more surface damage and a greater reduction in volume were present on surfaces with higher height parameters and peaks (Ssk > 0).[129] In detail, the volume reduction at the crest of the threads after insertion was 8723 μm^3 and equivalent to 0.06 mg of released titanium for the anodized turned surface (Nobel Biocare), 13 320 μm^3 and 0.14 mg of Ti for the grit-blasted and acid-etched implant (Osseospeed, Astra Tech), and 31 431 μm^3 and 0.54 mg of Ti for the grit-blasting and acid-etched implant (SLActive, Straumann).[129] Loose, larger particles (10–20 μm) were also located in implantation sites, mainly in the cortical layer and especially around implant microthreads. Strong evidence of damage was visualized, and anodized implants presented with chipping of the porous structures along the surface associated with cracks on the base of the anodized layer and even with exposure of the bulk titanium core.[129] The release of titanium particles ranged from 0.06 to 0.54 mg.[129] Some studies in the traumatological field stated that the presence of metal particles in concentrations between 0.2 and 3.0 mg was able to induce aseptic osteolysis.[130,131] Mints et al. under SEM showed that while turned implants did not change much after insertion, the acid-etched group exhibited a reduction in peak height and flat roughness. The anodized group presented with extensive damage after fixation; in some implants, the entire porous oxide layer was removed both at the apical aspect and on the crests of the threads, even with exposure of the underlying Ti core and a clear reduction in roughness.[132]

Measurement of Ti particles present in epithelial cells was performed by analyzing different implant surfaces after implant fixation.[128] Surfaces such as fluoride-modified, phosphate-enriched Ti oxide and grit-blasted revealed increased positivity and more DDR damage in cells. Surfaces with increased roughness are associated with a higher risk of Ti particle release, thereby triggering inflammatory signals.[128]

2.1.3 | Fluoride and titanium corrosion

Corrosion of the superficial titanium dioxide seems to be more relevant in low pH conditions or with high levels of fluoride (F).[133–136] An acceleration of the corrosion of this layer in the presence of other substances (Figure 3), such as lactic acid, hydrogen peroxide, citric acid, or artificial saliva, was reported.[67,137,138] Interestingly, the presence of F ions increases Ti particle release by up to 10 000 times more than without contact with sodium fluoride (NaF).[133] Ti surfaces do not withstand certain acidic F prophylactic agents, and it is recommended to use neutral NaF solutions to avoid damage to the implant surfaces.[133] Könönen et al. found that topical F solutions were able to cause stress corrosion cracking to CP Ti. The Ti surfaces of 5-day exposed specimens presented with narrow corrosion cracks associated with branching.[139]

Moreover, F can bind strongly to the Ti surfaces and change their structure.[140] Any oxidative agent can enhance the stability and resistance to corrosion of the Ti surface by thickening and condensing the superficial titanium dioxide layer, but reductive molecules such as F have the opposite effect and jeopardize this layer,[135,140] lowering Ti resistance to corrosion.[141] F ions seem to increase corrosion and ion leakage by reducing the polarization resistance and increasing the anodic current on Ti surfaces.[33] Both NaF solution (3800 ppm) and gel (12 500 ppm) were found to strongly corrode the polished surface ((Ra) = 0.2 μm) and increase the surface roughness of ASTM grade 4 titanium discs by 10 times.[141] This increase was explained by the formation of hydrofluoric acid (HF) in an aqueous solution under acidic pH. Only 30 ppm HF is needed to locally corrode Ti surfaces.[137] Under high concentrations of F(−), an association between fluoride and H(+) can form HF, which is highly corrosive for Ti.[142] Additionally, human epithelial cell attachment to the implant surface was significantly increased by using gel versus mouthwash or NaF solution.[141] These adverse results should be taken into consideration when high F(−) and low pH prophylactic gel/mouthwash are used in patients with dental implants or other Ti devices.[141,143]

Wachi et al. reported that titanium ion release ranged between 15 and 50 ppm in the gingiva around pure Ti mini-implants placed on rats after exposing them to NaF 1000 ppm, pH 4.2 for 30 min. The authors noted the amount of Ti extracted from the implant despite the in vivo salivary buffer capacity.[50] Moreover, they reported a threshold of corrosion in pure Ti of 200–9000 ppm at pH 3.5–7.0[144] and explained that Ti resistance to corrosion is weaker when low dissolved-oxygen conditions are present, for example, in the oral cavity in the presence of F.[50,144]

Commercially pure (CP) Ti was less resistant to corrosion than Ti alloy and presented with pitting corrosion, whereas the titanium alloy degraded with general corrosion and microcracks on its surface.[137] In contrast, CP titanium was found to be significantly more

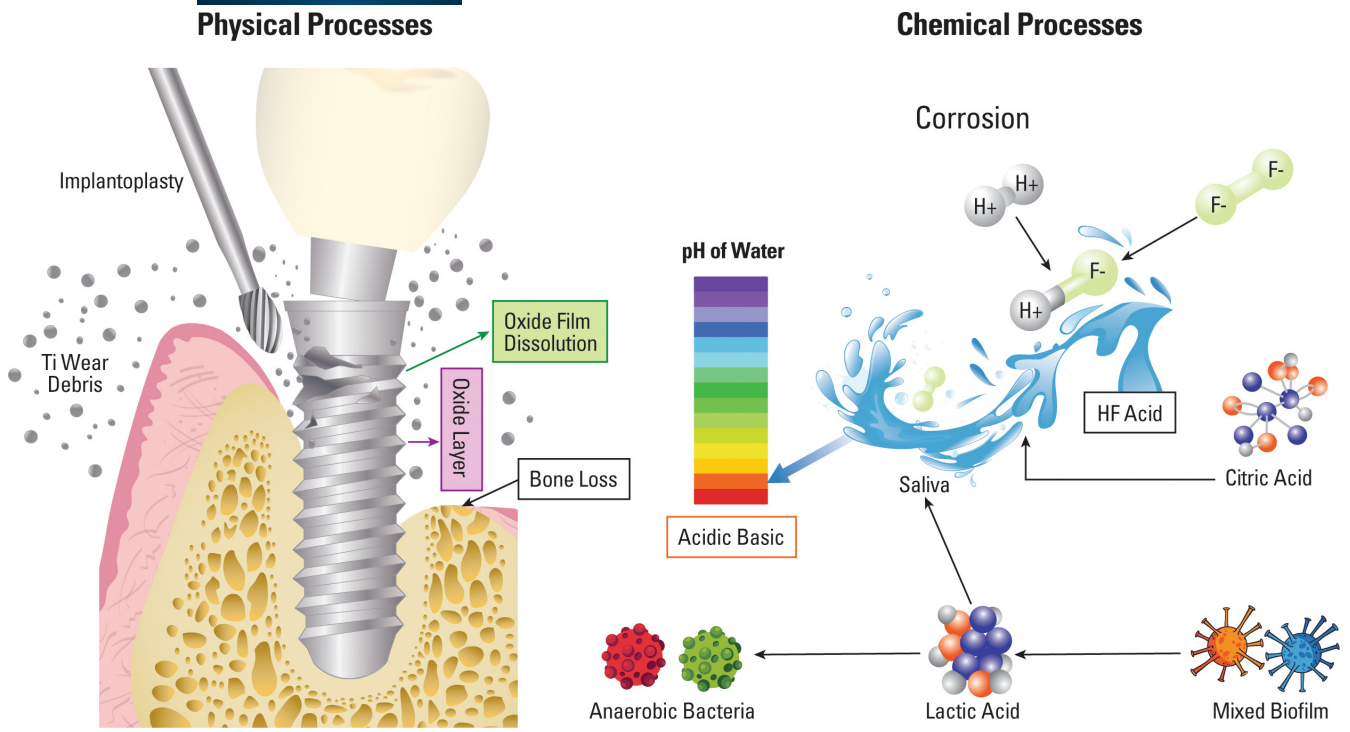

FIGURE 3 Physical and chemical processes altering implant surfaces.

resistant to corrosion by F(−) than Ti alloy after F or hydrogen peroxide exposure.[136] Moreover, a significant increase in metallic ion release with potentially toxic values of Ti, Al and V ions after immersion at high fluoride concentrations was reported.[137] Significant differences were found, reaching nearly 100 times more titanium ions after contact with F (from 0.01 to 10 μg/L and from 0.01 to 1 μg/L for Ti and Al ions, respectively). Similarly, surface roughness increased threefold and changed significantly from a previous Ra of 10 nm to almost 30 nm after F immersion.[136]

2.1.4 | Other particle release generating factors

Although the contribution of Ti particles to the onset of peri-implantitis remains somewhat unclear, various mechanisms can contribute to titanium particle/ion release (mechanical wear by occlusion, mechanical treatments for dental cleaning, and peri-implantitis or lowering pH media by infection of inflammation)[45,145–147]; even in the absence of wear and fretting, Ti ion release has been observed due to the accumulation of ROS secreted by active macrophages. These factors can increase the chance of Ti particles during peri-implantitis diagnosis and may impact peri-implantitis treatments.[47]

Ultrasonic devices

Dental treatments such as ultrasonic scaling have been related to a higher release of metal particles.[148] Sandblasted discs (SB) were found to release more particles than sandblasted/acid-etched (SLA) and machined discs (M), and there were no reported differences regarding the mean size of the debris, thousand particles/mm^2, and mean size of particles for the M, SLA, and SB discs, respectively (48.5 and 7.57 ± 1.43 μm; 89.8 and 7.57 ± 2.75 μm; and 121.3 and 8.37 ± 2.94 μm). SLA particles induced a significant increase (40–70-fold increase) in the gene expression profiles of proinflammatory cytokines (IL1β, IL6, TNFα) in human bone marrow macrophages compared with 0.01 μg/mL LPS ($p < 0.001$).[148] Similarly, SLA particles significantly increased the number and total area of osteoclast TRAP$^+$ cells by nearly twofold compared with LPS-treated cultures and by sevenfold compared to controls (13.1% vs. 6.47% vs. 1.7%, respectively). A cytokine expression analysis concluded that SB particles significantly induced the strongest inflammatory signal versus SLA and machined particles.[148] Finally, Ti particles (SB and SLA) in animals were able to induce osteolysis and promote significantly more bone loss than in controls. Histologically, an increased presence of TRAP+ osteoclasts, inflammatory cells, and fibrous tissue was confirmed in the experimental bone compared with the experimental group. A clear relationship between Ti particles, increases in IL1β, IL6 and TNFα, and enhanced osteoclast formation and activity was reported.[148]

Ti particles can stimulate osteoclastogenesis directly or by a paracrine mechanism, synergistically increasing the expression of IL-6, IL1β, and TNFα.[149] Increased activity of osteoclasts by IL-6 is mediated by osteoblasts, and TNFα can be enhanced in macrophages in an autocrine and paracrine manner, leading to the secretion of more TNFα and IL-6. This paracrine stimulation of inflammatory cytokines is relevant because this chain reaction provides inflammatory signals to an extended range of macrophages with no direct contact with particles.[149,150]

Implantoplasty

A recent study compared the amount and characteristics of particles released during implantoplasty of three types of dental implants.[151] Most of the particles were of ultrafine size (<100 nm). More particles were released from blasted than from blasted and acid-etched surfaces, explained by different roughness and mechanical strengths.[151] Some implications can be drawn from this study. First, the submicron particle size might imply that the operator believed that the area was visually clean, whereas it was scattered with metal particles.[151] Second, Ti nanoparticles highly activate immune cells and promote the release of the inflammatory cytokines TNF-α, IL-1β, IL-6, IL-8, IL-11, and TGF-β. The risks and benefits of implantoplasty should be weighed for each implant or patient[151] and some authors categorize it as an aggressive process leading to increased Ti particle release.[67]

2.1.5 | Particle-associated periprosthetic osteolysis and evidence from the orthopedic field

Wear particles and ions from joint replacements and other orthopedic implants may result in a local chronic inflammatory and foreign body reaction.[152] Aseptic loosening and subsequent joint failure were found to occur in 6.2% of CoCrMo hip replacement patients[92] to approximately 10% of primary hip arthroplasty patients and constitute a serious concern and the main problem of modern endoprothesis.[44,84,99,153–156] There is evidence in the orthopedic medical field that hip implant lifespan and joint function depend greatly on the wear from mobile surfaces and the amount of wear particles.[82,157] Debris from orthopedic implants may cause aseptic implant loosening, and this phenomenon has been recently called particle-associated periprosthetic osteolysis (PPO).[157] This pathology seems to be initiated by a macrophage response to prosthetic wear debris that promotes the release and deleterious effects on bone of IL-1alpha, TNF-alpha, IL-1β, and MCP-1.[83–86] Other authors described the term adverse response to metal wear debris to include the spectrum of clinical and pathological changes as a consequence of metal wear accumulation in periprosthetic tissues. This entity implies cytotoxicity, tissue necrosis, macrophage activation, and heavy lymphoid infiltration as part of the innate and adaptive immune response.[25]

Titanium ions released by biocorrosion from orthopedic implants promoted in vitro differentiation of monocytes into mature and totally functional osteoclasts, a key factor in the mechanism of osteolysis.[31,44,54] Only 22.7% of the human monocytes tested increased their osteolytic activity after Ti exposure, whereas the remaining 80% were not activated.[31] This value was correlated with the percentage of patients suffering from aseptic loosening (10%–15%), and the authors explained that individual molecular variations in the signaling pathway may result in Ti "compatibility" or "incompatibility." On the other hand, the authors also found that exposure to Ti ions had a minor effect on the already matured osteoclasts under the physiological control of osteoblast-derived factors such as M-CSF and RANK-L.[31,55]

Osteoclastic cells differentiate from hematopoietic and circulating monocytes stimulated by the presence of M-CSF (macrophage-colony stimulating factor) and by the receptor activator of NF-KB ligand RANK-L expressed mainly by osteoblasts.[31] Typically, osteoclasts express cathepsin K (CATK) and tartrate-resistant acid phosphatase (TRAP). Under the conditions of an in vitro study design, Ti particles activated osteoclast differentiation out of their physiological pathway. It was reported that Ti ions might bind to phosphorylated proteins of a nonidentified pathway that promotes monocyte differentiation toward osteoclasts.[31] While 100 nM induced 1.7 and 2.4 times the TRAP expression of monocytes and osteoclasts, respectively, a concentration of 1 μM (concentration of titanium particles reported in patients with implant loosening) Ti particles increased monocyte TRAP expression by 5 times and induced 7.1 times the osteoclast expression in responsive individuals.[31] In summary, exposure to Ti particles promoted monocytes to differentiate into osteoclasts and lowered the resorptive capacity of the existing cells by 30%. Moreover, contact with Ti may disconnect the newly differentiated osteoclasts from physiological osteoblastic control (RANK-L and M-CSF) and increase the cellular recruitment of osteoclast precursors by releasing CCL17/TARC, CCL22/MDC, and other proinflammatory cytokines.[158]

Human osteoclasts may be able to corrode both Al and Ti and absorb these ions.[53,55,159] While Al ions were released into the surrounding extracellular medium, Ti ions stayed inside the osteoclasts, blinded to cellular structures or phosphorylated proteins, phospholipids, and nucleotides.[53] This affinity was hypothesized to interfere with cellular signaling pathways or modify extracellular membrane properties, affecting their cellular functions such as their ability to migrate, secrete proteins, or respond to stimuli.[53,160] Interestingly, after these osteoclasts underwent apoptosis, ions and Ti-protein complexes were finally released into the medium, contributing again to aseptic loosening and further osteoclast differentiation.[53] TiO_2 layers can be damaged during their use, but osteoclasts can also degrade this layer by secreting hydrogen protons into the resorption lacunae.[161] High amounts of H+ and low pH weaken the superficial layer and dissolve metal ions that spread into the surrounding area. A new metal surface is now exposed after the disappearance of the oxide layer, and this surface becomes more sensitive to corrosion under these acidic conditions.[53] Free metal particles are usually phagocytosed by macrophages, but they can also be taken up directly by osteoclasts in the resorption area and incorporated into the TRAP-containing transcytosis compartment.[53,162,163]

An in vitro study demonstrated that wear particles of 0.90–1.50 μm recovered from patients with aseptic loosening and used in an osteoblast culture increased ROS production, induced cell apoptosis in a dose- and time-dependent manner, and promoted several cytoplasmatic detrimental effects.[164] Chronic exposure of marrow-derived human mesenchymal stem cells to implant wear debris from joint replacement reduced the number of viable osteoprogenitor cells and led to an impairment in bone regeneration, poor bone quality, and potentially even further implant loosening.[165] The presence of titanium particles was the cause of increased osteoclast differentiation and bone resorption in a murine study.[166]

It is relevant to list the differences between the field of orthopedics and the dental field.[167] In orthopedics, implant placement is performed in a closed field, while in dental field, there is a transmucosal portion that communicates with the oral cavity in the presence of saliva and bacteria. The presence of saliva that can enter the peri-implant sulcus and the internal cavities of the implants can allow the elimination or reduction of the concentration of metallic particles. Second, some orthopedic implants have greater displacements than those observed between the abutments and dental implants, so the degree of wear may be higher. In third place, although the metallic alloys are similar and there is a predominance of titanium use, the biomechanics and the applied forces are clearly different.

In summary, osteolysis around prostheses can be explained by several factors, including higher recruitment of circulating osteoclast precursors, increases in the differentiation and activation of osteoclast precursors into functional and resorptive cells, or longer survival of osteoclasts in the metal-tissue interface area.[31,168] Some strategies have been formulated to reduce or modulate the adverse effects of Ti particles to improve the function and lifetime of implants: (1) interference with systemic macrophage trafficking and arrival at the implant area; (2) an attempt to change the proinflammatory macrophage phenotype from an M1 anti-inflammatory macrophage toward an M2 phenotype in the peri-implant area to help tissues heal; and (3) local inhibition of the transcription factor nuclear factor kappa B (NF-κB) by delivery of an NF-κB decoy oligodeoxynucleotide, thereby impairing the production of proinflammatory mediators.[152]

2.2 | Metal particles and oral diseases

A recent review[47] noted that even when more research was needed to clarify the relationship between peri-implantitis and titanium debris, several studies have shown that their presence might contribute to disease progression via different mechanisms. These include foreign body reactions, cellular responses of epithelial, gingival, inflammatory, and bone cells, epigenetic mechanisms such as DNA methylation, or modification of the oral microbiome to favor dysbiosis.[47] Particles and titanium ions may be related to deleterious effects such as mucositis around dental implants or contribute toward the development of bone resorption and peri-implantitis.[50]

2.2.1 | Findings from in vivo oral biopsies

An increasing number of publications have reported the presence of Ti particles in biopsies from areas with peri-implantitis.[39,51,52,145,169–178] A histopathological study showed abundant free or phagocytosed Ti particles by macrophages released after titanium corrosion processes.[170] The authors already reported the existence of macrophages loaded with Ti particles in the peri-implant tissues of human failed dental implants[169] and significantly higher amounts of Ti particles in the peri-implantitis group (fivefold increase) than in the control group as assessed by exfoliative cytology[179] (sediment test, 2.02 parts per billion vs. 0.41 ppb, respectively; supernatant test 2.44 ppb vs. 0.88 ppb, respectively). In another cytological study, 40 patients with single, unloaded anodized implants were analyzed to detect titanium particles by using a cytobrush during second-stage surgery.[171] Any of the patients belonging to Group 1 (mild mucositis) were positive for titanium particles, whereas 60% (12 out of 20) of the patients in Group 2 (moderate or severe peri-implant mucositis) presented Ti debris in their samples.[171] In the authors' opinion, the presence of Ti particles correlated with an increase in inflammation of the peri-implant soft tissues.[171]

Similarly, tissues surrounding pathological dental implants presented with significantly higher concentrations of Ti than periodontitis tissue (mean ± SD of 98.7 ± 85.6 μg/g vs. 1.2 ± 0.9 μg/g; $p < 0.001$). The authors concluded that these high levels of Ti particles in the peri-implant mucosa may potentially aggravate the inflammatory status and reduce the prognosis of treatment interventions.[180] The presence of Ti was detected in 9 out of 12 (75%) samples containing soft tissue and bone from peri-implantitis areas. In addition, high amounts of neutrophils and M1 macrophages were also observed.[52] The content of Ti measured in the biopsies exceeded by 18 times the viability threshold of macrophages.[181] The increased presence of Ti was reported in a study that compared submucosal samples of plaque from 30 patients with 20 peri-implantitis sites and 20 healthy sites (0.85 ± 2.47 vs. 0.07 ± 0.19).[39] The authors suggested an association between peri-implantitis and greater levels of dissolved titanium in the submucosal plaque.[39] Another study, in which samples were collected from dental ceramic and Ti implants with peri-implantitis, reported using synchrotron[174] that Ti particles, ranging from microns to 100 nm, were found in all analyzed samples, whereas ceramic particles were present in 5 out of 8 samples. The concentration of particles from both Ti and ceramic implants was estimated to be as high as 40 million particles/mm^3. The authors stated that even though dental implants do not have the amplitude of movement of orthopedic total joint replacements, the small continuous movements of occlusion can promote wear, while other environmental characteristics such as bacterial biofilm, ROS, low pH, fluoride, and other acids can enhance corrosion at the implant surface.[174] A lower percentage of Ti particles in the peri-implantitis biopsies was also reported, affecting 7 of 36 biopsies (19.4%) and having sizes between 9 and 54 μm.[175] Histology demonstrated a chronic inflammatory infiltrate dominated by plasma cells. The presence of foreign bodies of different origins was detected in 34 out of 36 samples, and in four cases (11.1%), foreign body multinucleated giant cells were identified. Ti debris was found in 90% of the peri-implantitis tissues from 10 patients under light and scanning electron microscopy.[176] The histopathological study reported a mixed chronic inflammatory infiltrate and areas where Ti was related to a significantly higher expression of RANKL, IL-33, and TGF-β.[176] The results were in concordance with other studies showing the presence of Ti in peri-implantitis samples.[52,177,178]

A recent cytological study in 41 patients detected Zr only in patients with zirconia implants, whereas titanium was found in all groups even in subjects with no titanium implants; Zr and Ti elements were not detected in patients after control of food intake and toothpaste. The authors remarked the need to analyze cross-contamination in metal particle detection tests.[182] Other recent research with soft tissue biopsies from orthopedic and dental implants concluded that nanoscale metallic particles play a role both in physiological and pathophysiological reactions of the immune system and may participate in osseointegration and disintegration of dental implants.[183] When the amount of particles crosses a threshold called "Critical Dose of Nanoscale Metallic Particles," a local intensification of inflammation is observed, with early death of immune cells and failed removal of debris, leading to further accumulation of nanoparticles and chronic inflammation. The authors claimed that mucositis and peri-implantitis could be related to the accumulation of metal nanoparticles in the bone bed as a precipitant factor for aseptic inflammation with an autoimmune component. Finally, cell reactivity and inflammation can be secondarily aggravated by bacterial colonization and biofilm formation. Moreover, clinical manifestations of mucositis might be related to microparticle accumulation due to mechanical loading and delayed cleaning of antigenic particles. The authors also recommended delayed dental implantation to achieve successful long-term osseointegration instead of immediate loading so that the immune system could to eliminate the metallic particles accumulated during the insertion before loading and before microbial contamination.[183]

2.2.2 | Findings from ex vivo oral biopsies

In a study using postmortem human bones with implants, 100% were positive for Ti ions detected by X-ray spectroscopy. Even areas 2.0 mm away from the implant presented a low quantity of Ti debris, and the authors concluded that Ti particles did not affect the bone remodeling process.[111] The content of Ti in 7 human jawbones was 3 times (significantly) higher in implant bones than in the control group without implants (1940 vs. 634 μg/kg, respectively), and samples with the highest content of titanium reached 37 700 μg/kg-bone weight.[11] The authors concluded that this amount was correlated to a concentration of 38 μg/mL, which was 3.8 times more than the cytotoxic threshold reported for TiO_2 nanoparticles (10 g/mL).[100] In human bone slides, the size of the Ti particles varied from 0.5 to 40 μm and were found at distances of 1.58 mm from the implant interface.[184] The authors noted that cell transportation of Ti particles 0.5–5 μm inside the bone marrow is possible and that particles smaller than 1 μm cannot be detected by transmitted light microscopy.[184] Moreover, they reported the findings of fibrosis of the bone marrow, avital bone tissues, and multinucleated cells near the implant surface. These histological changes were compatible with the advanced inflammation observed, including bone marrow injury during implant insertion.[184] Furthermore, the presence of MNGC in the peri-implant tissues was likely triggered by the release of Ti particles from implants to engulf debris, similar to the TRAP+ MNGCs described in the orthopedic field.[184,185]

2.2.3 | Damage to the epithelial barrier

The release of Ti particles may also compromise the oral epithelial barrier. It has been reported that debris released during implantation is able to activate DNA damage in epithelial cells via the DDR pathway.[128] These findings may suggest that a disruption of epithelial homeostasis may occur when Ti particles are scattered into a surgical wound.[128,186] After this epithelial barrier misfunction, accumulation of biofilm and bacteria may occur, triggering a larger inflammatory response able to increase implant corrosion and further spread of metal particles.[186] The combined presence of a biofilm layer and Ti debris results in a synergistic effect that promotes surface damage, thins the TiO_2 layer, lowers corrosion resistance, and favors Ti particle release.[187] A time-dependent reduction in cell viability and an increase in ROS production were found to be induced by the interaction of Ti particles and fibroblasts or mesenchymal stem cells (MSCs).[188] Increases in oxidative stress, alteration of MSC populations, and deteriorated bone regeneration were also observed. Indeed, Ti nanoparticles were able to chemoattract anomalous quantities of neutrophils, releasing large amounts of metalloproteinases that damaged collagen fibers and promoted deleterious effects on the epithelial barrier.[188]

2.2.4 | Changes in biofilm

Ti particles and/or ions may also induce changes in the microbiological composition of the oral biofilm and further contribute to microbial dysbiosis and peri-implantitis.[189] Ti particles were found to increase the levels of four bacteria: *Streptococcus anginosus*, *Prevotella nigrescens*, *Capnocytophaga sputigena*, and *Actinomyces israelli*. In detail, Ti ions increased the accounts of 16 bacterial species after 24 h, some of which were periodontal/peri-implant pathogens such as *T. forsythia*, *T. socranskii*, *E. nodatum*, *P. nigrescens*, and *Campylobacter* spp.[189] Increased levels of *T. socranskii*, *P. nigrescens*, *P. acnes*, and *Campylobacter* spp. have been reported in biofilm samples from peri-implantitis compared with healthy implants.[189–192] Ti particles may also increase bacterial biofilm virulence[189]: particles can increase the amount of bacteria present on the implant surfaces, and the consequent biofilm accumulation is able to enhance peri-implant tissue degradation over the long term. The biochemical explanation for these situations is not well known, but various authors have suggested that different charges between Ti and bacteria can force coaggregation by ionic bonding; TiO_2 layers are positively charged, whereas cell membranes are normally composed of negatively charged lipids.[189,193,194] Moreover, the dose-dependent effect of Ti ions raising levels of anaerobic periodontal pathogens may be related to the reduction in oxygen availability in bacterial biofilm that promotes a change to a more pathogenic anaerobic microbiota.[189,195]

While the pro-inflammatory effect of Ti particles may be negligible in a healthy periodontium, damage could be tremendous in combination with bacteria activating macrophages in a synergistic way.[87]

A retrospective human study was conducted to determine the relationship between the Ti levels in patients with dental implants in function for more than 10 years, their peri-implant microbiome, and their peri-implantitis levels.[172] Overall, 6 peri-implantitis cases, 9 healthy implants, and the presence of Ti particles in 40% of the cases were described. Dissolved Ti in samples was associated with peri-implant disease status ($p=0.02$) and correlated to the main component of the microbiome ($\rho=0.552$) and its alpha-diversity ($\rho=-0.496$). Interestingly, canonical correlation analyses found that while titanium levels were significantly associated with the microbiota composition ($p=0.045$), no association was found with the health or disease status of the implant was found.[172] The authors suggested an association between Ti particles and peri-implantitis due to their potential role in modifying the peri-implant microbiome structure and diversity.[172]

2.2.5 | Inflammasome activation

Inflammasomes are innate immune system receptors and sensors that play essential roles in BRONJ, periodontitis, gout arthritis, metal particle-induced osteolysis, bone healing, osseointegration, and osteoporosis. This complex system involves interactions between bone cells and immune cells.[196] They regulate the activation of caspase-1 and induce inflammation and cytokine release in response to infectious microbes and molecules derived from host proteins.[181,197] Caspase-1 leads pro-IL-1β, pro-IL-18 and pro-IL-33 to their active forms and release.[181] Inflammasomes are regulated by a two-step process that needs a first stimulus (priming) and a secondary stimulus (activation).[198] Activation of the inflammasome complex can occur by direct contact or through cell-surface interactions.[51] While some bacterial biproducts, such as LPS or other PAMP, act as first stimuli binding to a TLR receptor and can increase the production and accumulation of pro-IL-1β inside macrophages, a secondary stimulus[199] (PAMP or DAMP) is still needed to release the activated form of IL-1 β through inflammasome complex activation and caspase-1 activation.[181,200–203]

Despite the synergistic effect between bacterial biofilm and Ti particles that increases implant surface corrosion and wear as well as intensifies the inflammatory status of the tissues, metal particles may induce inflammation independently. The presence of Ti particles and their phagocytosis were related to the activation of the NLRP3 inflammasome and the consequent release of IL-1B.[204] Particles alone did not stimulate IL-1β secretion in human mononuclear cells directly due to the need for previous LPS signaling. When macrophages were exposed to Ti + TNFα, inflammasome activation and stimulation of IL-1β secretion occurred. Interestingly, that study confirmed that the NLRP3 inflammasome mediates the response to Ti particles by human macrophages and that this activation may occur in the absence of bacteria or LPS; in other words, it can be induced under aseptic conditions when TNFα is also present.[204]

Similarly, an in vitro study reported that metallic wear particles with adherent PAMPs could sequentially prime the NLRP3 inflammasome and that metal particles alone and independently of adherent PAMPs, were able to finally activate the inflammasome complex.[205] The authors also stated that PAMPs sources could come not only from local sources but also from bacteria from the gastrointestinal tract or from the oral cavity and entered into the systemic circulation.

As IL-1β secretion induced by wear particles activates macrophages and can be related to bone resorption around total joint replacements, the inhibition of inflammasome signaling might be a way to prevent wear particle-induced inflammation and the development of peri-prosthetic osteolysis.[204] A previous study from the same group stated that released metal ions can activate TLR signaling in a similar way to bacterial derived PAMPs.[206] In this sense, metal ions act like haptens able to activate the adaptive immune system similar to bacterial derived antigens. Interestingly, authors reported that septic loosening and aseptic loosening may share similar pathomechanisms and that the strict dichotomy to sterile aseptic and bacterial-caused septic implant loosening may be somewhat questionable.[206]

Other studies also reported that Ti nanoparticles were able to activate the NLRP3 inflammasomes by ROS and promote inflammation and tissue damage in the lungs (Table 1).[181,200–202] A possible feedback loop between ROS and NLRP3 inflammasome was found.[207] Mitochondria- derived ROS seem to be one of the main activation factor of NLRP3 inflammasome; inflammatory status caused by this activation mediates the recruitment of inflammatory cells like macrophages and neutrophils that finally would increase again the levels of ROS in the tissue.

It has been reported that inflammasome activation is based on NF-κB signaling and that different DAMPs could induce NLRP3 inflammasome mediated by ROS production, K^+ efflux, lysosomal rupture, or metal ions.[198] In this sense, metal ions could activate inflammasome through ROS production after NF-κB activation. Intense release of IL-1β caused by metal ions seems to reduce the levels of an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and, as a consequence, ROS production is increased.[93]

Other studies highlighted the need for LPS priming previously to metal ion exposure to induce IL-1β release, but, interestingly, the presence of bacterial endotoxins significantly increased the in vitro biological activity of metal particles via TLR2 and TLR4 binding. In this research, endogenous alarmins induced by particle-induced damage were not able to activate TLR.[208,209] On the contrary, in vivo priming was induced by alarmins or endogenous factors, by metal ions binded to TLR or mediated by PAMP or LPS generated by subclinical bacterial biofilm from implant surface.[198,210,211]

Certain metallic particles can induce activation with higher intensity. An in vitro study observed that TiAlV did not activate inflammasome-driven inflammatory reaction, while CoCrMo particles promoted marked activation.[212] Other study found that Cr^{3+}

and Ni^{2+} induced an intense inflammasome activation, whereas Co had no or limited effects in this pathway.[198]

Indeed, higher expression of the NLRP3 inflammasome was reported in periodontal diseased biofilms than in healthy biofilms.[181] Interestingly, Ti ions can act as secondary stimuli and trigger a proinflammatory reaction due to their activation of inflammasome complexes in human macrophages.[51] The inflammatory effect is also more intense when macrophages are first stimulated with bacterial LPS, and the proinflammatory environment disappears after filtration and removal of Ti particles.[51] The authors stated that the Ti concentration measured in three samples around dental Ti implants were high enough (varying from 7.3 to 38.9 μM) to stimulate macrophages to secrete IL-1β. However, a study reported that a strong inflammatory response was induced by Ti particles through the activation of macrophages and the release of TNF-α, IL-1β, and IL-6 independently of their association with bacterial LPS.[59] In this case, 50 ng/mL Ti nanoparticles evoked a more proinflammatory signal than Ti microparticles. The presence of *P. gingivalis* LPS did not increase the expression of proinflammatory genes or increase the release of more inflammatory cytokines.[59] Macrophages were clearly activated not only by LPS but also by phagocytosis of submicron Ti particles and increased inflammatory cytokine production (TNF-α, IL-1β, and IL-6). The combination of both factors synergistically elevated cytokine production to pathological levels.[64] This situation is more relevant in dental than in orthopedic fields because particle-activated macrophages can be easily exacerbated by the presence of bacterial LPS in patients with implant prostheses.[64] An in vitro study reported that the NLRP3 inflammasome can regulate osteoclast formation. Under infectious conditions, inflammasome activation promoted bone loss due to induced osteoclast formation mediated by IL-1B production, probably to eliminate injured bone or pathogens around bone. Meanwhile, under physiological conditions, the inflammasome seemed to inhibit osteoclast formation via pyroptosis and helped to maintain bone homeostasis.[213] Moreover, activation of the inflammasome stimulates M1 polarization.[196] These M1 cells can regulate osteoblast/osteoclast function through cytokines and promote bone resorption. Indeed, inflammasome can also modify the ratio Th17/Treg: increased amounts of Th17 cells can alter bone metabolism by inhibiting osteoblast function and activating osteoclasts.[196]

2.2.6 | Role of immune cells in bone metabolism and foreign body reaction

Macrophages and TiO_2 stimulation tests

An interesting study was designed to measure the association between peri-implantitis and the presence of non-allergy-related proinflammatory cytokines associated with TiO_2 particles (TNF-α and/or IL-1β) through a macrophage stimulation test.[42] From a sample of 60 patients, total TiO_2 stimulation test positivity frequency was 28.3% and 30.0% in the control group (without implants); a statistically significant difference ($p = 0.0014$) between positivity in non-peri-implantitis group (5.0%) and in peri-implantitis group (50.0%) was measured. The authors reported that patients with positive TiO_2 stimulation test had a OR = 19.0 of developing peri-implantitis and that the incidence of peri-implantitis in the positive stimulation test group was 90.9% versus 34.5% in the group of patients with negative test results.[42]

Relevantly, the authors explained that as macrophages are part of the innate, nonspecific immune system, they cannot learn sensitization; macrophages from human blood can react in vitro after contact with titanium particles and release proinflammatory cytokines above physiological limits, even when no titanium implant was previously present in these patients.[42] In conclusion, the authors reported a statistically significant relationship between a positive TiO_2 stimulation test and the presence of peri-implantitis.

Other studies with sensitivity tests reported that patients with positive test were 2.4 times more likely to lose at least one implant than patients with negative TiO_2 stimulation test.[42] In this study, positive patients presented higher levels of pro-inflammatory cytokines and no allergic signs but a tendency to excessive amount of local and even systemic inflammation caused by macrophages reaction to titanium. A delayed or impaired healing of titanium dental implants and a higher tendency of implant failures, related to a hyperactive macrophage response around the implant in the positive patients group was reported.[42,43] Other studies stated that excessive pro-inflammatory cytokines release by macrophages after interaction with TiO_2 particles may mediate the inflammatory and osteolytic process and enhance the risk of peri-implantitis.[99,214] For example, in vitro exposure of human macrophages to titanium-alloy particles for 48 h increased the release of TNF-α by 40 times and the release of IL-6 by 7 times ($p < 0.01$). Exposure to macrophages for 30 min was enough to activate transcription factors NF-κB and NF-IL-6. While inhibition of phagocytosis failed to reduce cytokine release, inhibition of tyrosine and serine/threonine kinase activity decreased the activation of transcription factors.[99]

A clinical retrospective study evaluated diagnostic markers to predict titanium implant failure. The authors concluded that IL-1β/TNF-α excessive release was strongly associated with implant failure and that some polymorphisms may constitute genetic risk factors for implant osseointegration. Both factors can be useful tools to determine individual risk values in dental implantology.[43] After multiple logistic regression analysis, both positive IL-1β/TNF-α release assays and some risk genotypes were significantly and independently associated with titanium dental implant failure.[43] While some risk genotypes had an OR = 1.57–6.01, excessive cytokine release increased the risk of implant failure by 12 times ($p < 0.0001$, OR = 12.01). The authors reported that TiO_2 stimulation led to a significantly higher release of IL-1β/TNF-α in patients with implant loss than controls, both in the early implant loss group and the late implant loss group.[43] The significant role of host factors, like the immune response to titanium or genetic polymorphisms may be a possible explanation to the fact that Ti particles induced inflammation and bone loss in a small percentage of patients.[43,215]

It seems clear that macrophages release IL-1β/TNF-α after detecting Ti particles and induce a strong inflammatory response triggering bone resorption.[43] These cytokines modify RANK-RANKL balance, promote osteoclastic activation, and produce damage to extracellular matrix by MMPs induction.[216] Like other cytokines, IL-1β/TNF-α may promote different effects based on their amount or on their short or long-term presence. For example, short-term inflammation with moderate to low levels of IL-1β/TNF-α may induce primary bone healing and favors implant osseointegration.[43,217] On the contrary, as explained before, long term or high release of these cytokines promotes inflammatory and osteolytic processes that increase the risk of implant failure and peri-implantitis.[43]

MNGCs

It was proposed to classify MNGCs into M1 cells with inflammatory functions or M2 cells with wound healing activity, following the criteria of macrophage polarization.[218,219] According to this concept, M1-MNGCs may act in the crestal portion of dental implants and react against pathogens or foreign body particles, whereas M2-MNGCs may remain in the apical portion of the implant in more stable bone.[218] MNGCs may not be able to resorb bone, yet they express M2 macrophage-like wound healing and inflammation-arresting molecules.[220] In fact, some MNGCs can dissolve the mineral phase of bone at the surface, such as osteoclasts, but others cannot degrade the matrix fraction of bone caused by the absence of a ruffled border and cathepsin K.[221] Additionally, the presence of infection or inflammatory cytokines significantly inhibited the formation of FBGCs in vitro.[220] The presence of an inflammatory status led osteoclasts to be stimulated as M1 macrophages, so the genesis of MNGCs with more M2-like phenotypes was downregulated in a pathway similar to M1/M2 macrophage polarization.[222] In detail, MNGC proliferation is enhanced by IL-4 and IL-13[223] and granulocyte macrophage colony-stimulating factor (GM-CSF) and significantly downregulated by IL-1β.[222,224] This fact would imply that MNGCs and osteoclasts are regulated in a reciprocal manner and that under implant failure conditions (infection or inflammation), osteoclastogenesis may be promoted and MNGCs are blocked.[222] Activated lymphocytes and mast cells can also be influenced by their IL-4 and IL-13 secretion and a change in macrophages into their M2 phenotype and their fusion into MNGCs to increase their phagocytic ability and avoid apoptosis.[223] In summary, the authors suggested that the promotion of MNGCs to block osteoclast formation may be relevant for orthopedic implant survival[222] because the M2 phenotype implies that the foreign body response that occurs with every medical device[222] may be more tolerant to the implanted material.[220]

MNGCs also communicate with other cell types, such as osteoclasts, and have the potential to secrete osteoclast-stimulating cytokines, such as interleukin-1α (IL-1α) and tumor necrosis factor-α (TNF-α).[225] At some point, MNGCs can switch their profile, stop releasing inflammatory cytokines, and begin to express strong fibrogenic and anti-inflammatory TGF-β. This expression of TGF-β induces fibroblasts to secrete collagen to encapsulate the foreign body under fibrous tissue.[226] Indeed, MNGCs can release other pro-healing growth factors, such as PDGF and VEGF.[227] Thus, MNGCs can also be involved in the initial proinflammatory activation and contribute to the downregulation of inflammation and the onset of healing or fibrotic processes.[225] Other authors reported that, during peri-implantitis, MNGCs can secrete cytokines such as CCL2, CCL3, and CCL5, for which osteoclasts express a large number or receptors, resulting in enhanced osteoclast activity and bone loss.[224] In conclusion, further research is needed to fully understand the role of MNGCs in bone metabolism and peri-implantitis.

T and B cells

T cells are a component of cell-mediated adaptive immunity, and they recognize antigens presented by antigen-presenting cells on the MHC complex.[228] T cells can modify bone metabolism because they are able to secrete OPG or RANKL and can regulate the local inflammatory environment.[228,229] There are three types of T cells, and their contribution to bone metabolism is different; regulatory T cells (Tregs) mainly contribute to lowering inflammation levels, while T helper cells (Th) and cytotoxic lymphocytes (CTLs) mainly promote inflammation.[228]

Treg secretion of the anti-inflammatory cytokines IL-4, IL-10, and TGF-B initiates the arrest of inflammation and reduces osteoclast activity and osteolysis.[229] In contrast, some types of Th cells, such as Th-2, Th-9, and Th17 cells, can release IL-9, IL-17, and other enzymes that trigger inflammation and tissue damage.[228,230] Moreover, excessive infiltration of CTLs is related to osteonecrosis[228,231] and these cells can increase osteoclast activity due to cytotoxic T lymphocyte-associated protein 4 (CTLA-4).[232]

B cells participate in adaptive humoral responses and can produce and release antibodies while presenting antigens to T cells.[233] Moreover, B cells can regulate bone metabolism by balancing the activity of osteoblasts and osteoclasts.[228] Pre-B cells, immature B cells, and antibody-secreting B cells (plasma cells) strongly inhibit osteoclast differentiation by blocking the RANK/RANKL system with an overabundance of OPG.[228] Some papers have reported that between 40% and 64% of the bone marrow production of OPG depends on B cells.[228,234] When B cells become activated under inflammatory conditions, they release RANKL and increase bone catabolic effects.[228,235,236]

Osteoblast- and B-lineage cells are the main sources of physiological OPG, and when aging reduces production by osteoblasts, B cells gain importance in OPG production to compensate for the RANK-RANKL-OPG quotient and counteract age-associated bone resorption.[237] Furthermore, aging decreases the capacity of these cells to avoid RANKL-mediated bone resorption.[237] A study in mice found that complete depletion of B cells led to osteoporotic bone and deficient levels of bone marrow OPG.[234] Regulatory B cells (Bregs) can secrete IL-10 to reduce osteoclast activation and metabolism.[233,238]

Interestingly, some studies have reported a local decrease in B-cell counts in osteonecrosis, while high numbers of activated B cells are presented in the blood.[228,232,239,240]

2.2.7 | Summary

Regarding the toxicity caused by Ti particles, other potential counterarguments have also been published in the literature.[41] Some metal nanoparticles like Ti dioxide have antimicrobial activity due to their oxidizing power by free radical generation.[241–243] Similarly, metal oxide particles have been tested as a carrier to delivery nanoantibiotics.[244] On the other hand, some protocol treatments for peri-implantitis like implantoplasty have some degree of outcomes even when promotes accumulation of Ti particles in the peri-implant tissues.[41]

Some authors have reported that an association between implant corrosion, the presence of Ti debris surrounding dental implants, and the appearance of biological implant complications may exist, but there is insufficient evidence to prove a unidirectional causal relationship.[40] Ti particles may be a common finding in healthy and diseased peri-implant mucosa or even in gums of patients without Ti implants. High concentrations of Ti particles around peri-implantitis lesions can be the consequence of the presence of biofilms and inflammation and not the trigger of the disease.[40] To identify the presence of Ti particles and to histologically compare the characteristics of peri-implantitis and periodontitis lesions, biopsies with granulation tissue were harvested from patients.[173] Ti particles were detected in all samples (100%) from the peri-implantitis patients, but no evidence of foreign body reaction indicating direct causal effects from the particles were found by the authors. Specifically, there was no evidence of Ti particles being phagocytized by macrophages or MNGCs in any sample.[173] The peri-implantitis granulation tissue was characterized by intense neovascularization and the presence of a chronic inflammatory infiltrate dominated by plasma cells, neutrophils, and higher proportions of macrophages compared to those in periodontitis samples.[173] Regarding this conclusion, the absence of MNGCs did not imply the absence of a foreign reaction or biological response. As explained below, the presence of inflammation or infection downregulates the proliferation of MNGCs.[220,222] In "classical" foreign body responses, the presence of MNGCs is one of the last steps after chronic inflammation and before the stage of fibrous encapsulation of harmful stimuli.[167,245] As stated previously in this article, the size of the particles influences the inflammatory response and the type of cell responsible for degrading them.[103] Only in the presence of very large particles (over 25 μm) will macrophages fuse into MNGCs to digest the particles in an extracellular manner in which MNGCs become more apparent.[103,104] Moreover, the increased numbers of neutrophils and macrophages and their higher activity due to the marker CD68 can be a mild biological response to the presence of Ti particles. Clinical data from the study did not corroborate the foreign body reaction theory as an etiological factor of peri-implantitis.[118,246] Nevertheless, this cannot imply that Ti particles do not drive biological responses because both terms are not the same, even though they share common words. Similar conclusions were drawn in a recent review about the role of the foreign body response in peri-implantitis.[167] The authors stated that there was no evidence for a unidirectional role of Ti particles as possible nonplaque-related factors in the etiology of peri-implantitis disease. Even when there is no evidence for this unidirectional role, there is increasing evidence supporting their deleterious effects on epithelial barriers, epithelial cells, bacterial dysbiosis, osteoblast/osteoclast coupling, bone mineralization, and immune cell function, from neutrophils to MNGCs. Some of these multifactorial mechanisms are summarized in Table 1.

2.3 | Conclusion

Aseptic bone loss has been one of the largest concerns of orthopedic implants for decades and this pathology counts with abundant and solid scientific evidence. There is no doubt that the presence of titanium and other metal particles may stimulate the immune system, especially the macrophages, and that this activation lead to the release of cytokines and other pro-inflammatory substances that ultimately promote osteolysis and bone loss around the implant. Obviously, there are differences between orthopedic and dental fields, especially related to biomechanical aspects and presence of saliva and bacterial plaque. Nevertheless, these factors are precisely what brings even more relevance to the presence of particles and their associated effects in dentistry: First, Ti particles seem to induce damage to the epithelial barrier, to increase epithelial cell sensitivity to bacteria and finally to impair their barrier function against bacterial assault.[128,186] Second, bacteria and Ti particles can independently induce macrophage activation and cytokine expression, but their synergistic action is more powerful and triggers a more severe inflammatory state and extensive tissue damage.[42,64,180,206] Finally, the chronic presence of Ti particles and their associated chronic inflammation may generate a local immunosuppression status; macrophages show an impaired immune response to microorganisms due to damage of their respiratory burst processes and their reduced production of ROS.[247] These three mechanisms triggered by titanium particles appear to increase the severity of inflammation in oral tissues.

Also, bacteria and their metabolism can produce and accelerate the corrosive processes on exposed dental implant surfaces. However, microbial corrosion is only one of several types of corrosion that can occur on metallic surfaces, with galvanic corrosion being the most frequent. In addition, there are multiple sources of titanium particle release, even from the initial insertion of the implant; the installation of the prosthetic structure that favors galvanic corrosion when different metal alloys are used; and fundamentally, the continued wear at the interface between abutment and implant. A poor specificity for the association between the presence of particles and pathology has been reported.[41] More Ti particles have been found near implant surfaces and in samples from diseased sites, but these higher concentrations may also be the consequence of inflammation and corrosion caused by bacteria and inflammatory cells present in peri-implant lesions. Therefore, the presence of titanium particles can be a byproduct of a complex corrosive environment caused by plaque-induced inflammation. However, a dual role of titanium particles cannot be ruled out: a primary role generating an inflammatory reaction and associated bone loss in the absence of plaque, and a

secondary role with the appearance of particles after bone loss generated by bacteria and the titanium surface exposed to corrosion. At this point, it can be difficult to causally attribute the generated effects since it is a complex host response to foreign bodies with several feedback loops: Wear, corrosion, and environmental factors promote tribocorrosion, material degradation, and the release of titanium particles; these particles induce an inflammatory process, interfere with cell function, and can modify the composition and function of biofilm. Finally, biofilms also cause inflammation and further corrosion.[41]

In this regard it is relevant the association between sensitivity tests to TiO_2 and the occurrence of peri-implantitis in patients with a limited amounts of bacterial plaque. Those patients whose macrophages were reactive to titanium had 19 times higher risk of developing peri-implantitis than patients who were not positive to the sensitivity test. Tested positive patients seem to release significantly higher cytokine levels after contact with TiO_2 and these raised levels were significantly and independently associated with titanium dental implant failure.

As stated before, an association between biocorrosion, presence of titanium particles, and biological implant complications have been extensively reported, but so far, there is insufficient evidence to prove a unidirectional causal relationship.[40] Precisely because of this lack of evidence, the principle of prudence must lead us to be extremely attentive regarding the generating factors of titanium particles to avoid further inflammation around dental implants. Finally, clinical research on the topic is urgent and necessary to clarify the exact role of titanium particles in peri-implant bone loss.

3 | SURGICAL-RELATED FACTORS ALTERING BONE METABOLISM

Among the factors that can promote early implant failure, systemic diseases, bone quantity and quality, implant tridimensional malposition, surgical trauma, and contamination during surgical procedure can be included[217]; peri-implantitis and occlusal overload have been associated mainly with late implant failure.[43,217] Surgically triggered peri-implantitis may represent 4 out 10 cases of peri-implantitis[30] so surgical placement of the implant has a paramount relevance. Inadequate positioning of implants may increase by 48.2 times the risk for developing peri-implantitis mainly due to limited amounts of buccal hard tissues and keratinized mucosa and impairment of oral hygiene.[24,248] Some surgical factors like bone quality/density, implant insertion torque/ bone compression, and early bone remodeling have been previously described in a review by the same authors[249] and were out of the scope of this text.

3.1 | Osseodensification and bone drilling

During the evolution of implantology, many different osteotomy procedures have been proposed for dental implant site preparation. Several years ago, osseodensification (OD) was proposed to increase implant stability and enhance the quality of local bone.[250] A recent review of the literature concluded that the osseodensification drilling protocol was useful to raise implant insertion torque and BIC in vivo.[251] A meta-analysis study of three reports found that osseodensification not only induced favorable results on primary stability but also consistently increased the ISQ values after 4–6 months of implant fixation compared with conventional drilling.[252]

A study in 21 dissected human mandibles found a significant increase in implant torque and bone density by using osseodensification versus standard drilling (34.9 Ncm ± 19.1 and 23.6 Ncm ± 9.8, respectively).[253] An in vitro study in the low-density pig tibia found higher insertion torque and RFA values in the OD group than in the underdrilling group, improving the primary stability in low-density bone.[254] OD also enhanced BIC and bone mineral density in an in vitro study in bovine rib bones compared with conventional drilling but found no differences regarding the bone expansion obtained during both drillings.[255] A multicenter clinical trial of 56 patients compared OD versus conventional drilling, where the authors reported higher torque values and higher ISQ values independently of the anatomical area and time analyzed (baseline, 3 and 6 weeks).[256] A meta-analysis compared the primary stability of implants placed with OD versus the osteotome technique, piezosurgery devices, underdrilling and conventional drilling.[257] Significantly higher primary stability could be reached with any of these three implant preparations (OD, osteotome, and underdrilling) compared with conventional drilling.[257] Another systematic review and meta-analysis reported that OD may increase the primary stability, BIC and RAF values of implants based on limited data from animal studies. Additional clinical reports are needed to recommend the technique with stronger evidence.[258] Last, another review concluded that there is weak evidence that any of the drilling techniques analyzed were superior and could increase osseointegration and survival of low-density bone implants.[259] Another in vitro study in sheep found that implants placed with the OD protocol presented higher values of BIC and bone area fraction occupancy (BAFO) than conventional drilling protocols.[260] Moreover, the authors found bone remnants that could enhance the bridging between the implant surface and the new bone.[260]

Other studies highlighted possible deleterious effects of bone densification.[261] A preclinical study in rats concluded that excessive osseo-densification promoted osseo-destruction. It was observed the appearance of micro-fractures and an area of osteocyte necrosis caused by the misfit-induced stress of osseodensification. Implants placed with high misfit by osseo-densification produced high interfacial pressures over 200 Mpa exceeding the compressive strength limit of bone (100 Mpa).[262] This fact induced peri-implant bone resorption demonstrated by the increase of TRAP+ and Cathepsin K staining and the absence of new bone formation. As a consequence, some of these implants showed crater-like crestal bone loss with fibrous inflamed granulation tissue and finally, implant mobility.[261] The authors explained that dense bone and densified bone are

not equally stiff and that a compressed cancellous bone with their trabecular network compacted is weaker and less able to provide support to an implant than the same natural bone with similar density and BV/TV.[261] Similarly, undersized osteotomies causing high interfacial stress showed a significant drop in BIC while conventional osteotomies increased their BIC during secondary stability phase.[263,264] The authors emphasize that bone depends on the viability of osteocytes embedded in the bone matrix and that excessive osseodensification or high misfit can be detrimental for long-term peri-implant bone stability.

To obtain more osteogenic bone remnants, a new instrument for osteoshaping was introduced.[265] Due to their low speed (50 rpm), site preparation and autologous bone chip collection can be performed at the same time, also maintaining the cell viability of osteocytes.[265] This new device was designed to be reversed upon removal and collect larger particles of bone around 100 μm.[266] While high-speed drills may increase bone temperature up to 80°C and were higher than 40°C in a circumferential area of 150 μm around the osteotomy; on the contrary, low-speed drilling kept bone temperature under 40°C and prevented osteocyte thermal necrosis. The absence of irrigation allowed to recover not only bone chips but also stem-cell populations, connective tissue stroma and blood.[266] This preclinical study found that conventional osteotomies were filled with less bone and at later stages than the ones prepared at low speed with the new design, showing an osteoid matrix positive for aniline blue, cathepsin K and Osterix.

Other animal study in rats reported that bone debris retained in the osteotomy surface led to early peri-implant bone formation relative to that in controls.[265,267] Moreover, data from rodent studies revealed that osteotomies performed with osseoshaping under low speed had a small number of apoptotic osteocytes compared with that in conventional high-speed osteotomies.[268] Additionally, the area surrounding conventional high-speed drilling was TRAP positive in staining and presented with larger bone resorption than the osteotomy conducted with the low-speed device. In summary, osteotomies at low speed may be more osteogenic, may preserve more viable cells and may induce a faster implant osteointegration than those performed at high speed with conventional tools.[268]

The benefits of low-speed drilling without irrigation have been reported in the literature for some time[269] (i.e., reducing damage to host bone, enhancing bone healing, and providing a useful amount of living bone for regenerative procedures). A study in 19 patients reported that low-speed drilling provides a useful and easy source of human alveolar bone-derived cells (hABCs).[269] The comparison between healing sites (less than 3–4 months of healing) versus healed sites showed no differences, although cultured cells obtained by drilling grew faster and reported higher explant success in the healing sites than in the healed sites. Indeed, the origin of the alveolar bone sample did not alter the cell viability, and both groups were positive for the expression of osteogenic markers such as bone sialoprotein (BSP), osteopontin (OP), and tissue nonspecific alkaline phosphatase, which are relevant proteins for cell attachment, extracellular matrix, and mineralization.[269] A recent review of low-speed drilling[270] showed that it provided a greater quantity and higher quality of autologous bone with better morphological properties and greater osteotomy precision and was more time-consuming. However, no difference was observed when compared to conventional drilling for osseointegration, marginal bone loss, or implant success rate.[270] No differences in crestal bone loss were found in 16 patients and 30 implants comparing low-speed drilling versus high-speed drilling after 3 months.[271] The main benefit of low-speed drilling may be the capacity to recover viable cells from autogenous bone in cases where implants are to be placed simultaneously with bone regeneration.[270]

4 | GRAFTING MATERIAL-RELATED FACTORS ALTERING BONE METABOLISM

4.1 | Influence of physiochemical properties of the biomaterial

Some interactions between cell and biomaterials may be modulated by the physiochemical properties of the biomaterial.

4.1.1 | Effect of pore structure

A porous structure with an internal network is relevant for cell migration, attachment, proliferation, differentiation, growth, and nutrient transportation.[272] Optimal pore size requires a balance between biological and biomechanical effects. Large-pore size biomaterials may reduce the surface area for cell attachment but may increase cell infiltration and osteogenic differentiation.[272,273] Moreover, an excessively porous structure will compromise the biomechanical resistance of the scaffold. On the contrary, small pore sizes seem to promote lower cell infiltration and migration, leading to induce a more intense cell aggregation in the surroundings of the biomaterial rather than inside.

4.1.2 | Stiffness

Cells are able to detect mechanical stimuli and react to them by activating biochemical signals to promote specific cellular responses or remodeling their cytoskeleton. In fact, variations in cell morphology or modifications in the stiffness of the extracellular matrix may induce different effects on cell behaviors[272] Moderately stiff matrices (10 kPa) promoted myogenic differentiation, whereas rigid matrices with stiffness around 100 kPa tended to induce osteogenic differentiation.[274,275] In this way, cell adhesion and differentiation are favored by scaffold stiffness, but there seems to be a plateau beyond that; the increase in stiffness no longer provides higher cell adhesion.[272] Evidence seems to indicate that cell attachment and osteogenic differentiation are stiffness dependent.

4.1.3 | Material composition

The composition of the biomaterial also affects cell behavior, such that the more it resembles the extracellular matrix, the better cell attachment will occur. Other properties, like biomaterial surface topography and surface wettability, may induce alterations in cell biology through contact guidance.[272] In this sense, osteoblast cells are able to attach better to rough surfaces, while fibroblast cells have more affinity for smoother surfaces.[276] Finally, the effect of biomaterial/scaffold degradation is also relevant; ideally, this degradation would be synchronized with the replacement of natural tissues. Composition and stiffness are important factors in this process because degradation may imply a loss of resistance, and this should not jeopardize the success of tissue regeneration.

4.2 | Ideal characteristics of biomaterials

Ideally, the best biomaterial would be biocompatible, bioinert, bioactive, bioresorbable, bio-adoptable, and sterilizable.[277] Bone biomaterial should be nontoxic and avoid the activation of inflammatory or immune responses.[278] In fact, biocompatibility is the opposite of eliciting inflammation, the more biocompatible, the less inflammation.[277] Indeed, the function of the biomaterial should not be to fill the bone defect but provide support and function to the bone while resorbing. Moreover, their biodegradability should be controllable and their rate of resorption should match with the rate of new bone growth.[277]

Bone substitutes and scaffolds can perform different roles.[272] This material should be osteoinductive, providing volume inside its porous structure for vascularization and new bone formation. The material must allow and promote the entry of blood vessels and nutrients without compromising the integrity of its structure. Osteoconduction is another essential characteristic in a biomaterial and it is related to their biocompatibility and biodegradability. The biomaterial structure should be suitable for cell migration, proliferation, and differentiation, it should integrate with vascularization and with the surrounding bone (osseointegration) and ideally, it may undergo resorption at a similar rate as bone repairs or regenerates.[272] Finally, biomaterials should have mechanical properties closer to the tissue they are intended to replace.

4.3 | Behavior of different types of biomaterials

4.3.1 | Anorganic bovine bone

In most cases, anorganic bovine bone (ABB) induces the formation of new bone in contact with the external surface of the biomaterial without the presence of gaps, fibro-connective tissue, or MNGCs.[279] Osteoclasts can resorb this xenograft, but their resorption rate is slow.[280] The persistence of residual graft particles may not interfere with new bone formation in the area, and no adverse effects were reported.[279] ABB did not increase the production of inflammatory cytokines,[281] have shown biological affinity to osteogenic cells and can promote osteogenic differentiation.[279]

4.3.2 | Porcine collagenated bone

This biomaterial has been demonstrated to be highly biocompatible and osteoconductive due to its microporosity providing support for cell adhesion and differentiation. The onset of graft resorption was observed 1 week after placement and their degradation did not interfere with new bone growth nor caused side effects.[282] Other authors reported also a high angiogenic potential in addition to the aforementioned high rate of resorption and replacement for newly formed bone.[283] For example, a 24.5% of residual graft particles were reported after 4 months of implant insertion and graft with porcine xenograft.[284]

Macroporous calcium phosphates like hydroxyapatite, biphasic calcium phosphate, or beta-tricalcium phosphate are synthetic bone graft substitutes. Synthetic bioceramics tend to partially integrate into natural bone and induce osteoblast proliferation, differentiation and deposition of inorganic matrix. However, bone substitutes derived from CaP may be clinically limited by their fragility, their unpredictable resorption rate and by their lack of capacity to keep their volume and to sustain mechanical loading.[285]

The interconnected porous structure of porous hydroxyapatite enhance the attachment of mesenchymal cells, bone morphogenetic proteins, and angiogenesis and induced a strong osteoconduction.[286] Calcium phosphate is an alloplastic biomaterial with good biocompatibility and osteo-conductive that induce bone formation around the graft; their particles are resorbable and are gradually replaced by the newly formed bone.[279] The stimulation of macrophages with CaP-based biomaterials lead to a reduction in the expression of inflammatory mediators like IL-1β and to a increment of anti-inflammatory cytokines (IL-10, IL-1rα) and growth factors (VEGF, PDGF, EGF, BMP-2, and TGF-β1).[287] A pro-osteogenic environment is therefore created, further detected by osteoclasts which reduce their metabolism and resorptive capacity and therefore allowing bone formation. While ABB presents a slow resorption rate, other substitutes like nanocrystalline hydroxyapatite or tricalcium phosphate have fast resorbable rates.[288] Finally, bioglass augmented collagen deposition and its porous structures make it a good scaffold that increase the formation of osteoid matrix and bone but with a reduced fracture resistance.[279,289]

4.4 | Bone response to biomaterials

In addition to other biological processes, the bone remodeling cycle is regulated by a myriad of chemical conditions, such as growth factors, hormones and cytokines, or physical mechanisms, such as the transfer of energy from physical charge to bone, which also cause a biological response. These locally or systemically produced molecules act synergistically to balance bone turnover.

Consequently, when a biomaterial is inserted into tissue to promote regeneration, it triggers a series of responses that depend on both the biological environment and the physico-chemical properties of the inserted biomaterial. Obviously, after introducing an exogenous material into the body, the first main responses that are triggered are immunological and inflammatory. The viability of the graft will depend on the resolution of these phases. Among other factors, macrophages play a critical role during these processes, not only because they are required to clear the local sites of debris, including dead cells/microorganisms, but also because they release a series of inflammatory mediators and catabolic enzymes that are responsible for the early and acute inflammatory response in the wound. Moreover, these macrophages mediate the transition from a catabolic inflammatory environment to an anabolic regenerative situation, according to their M1 or M2 polarization.[290]

It is important to understand that the processes that occur around any exogenous substance introduced into the bone will be very similar, independent of the biomaterial used. The body does not recognize families of biomaterials[291] and will behave based on each biomaterial's physicochemical characteristics. Therefore, it is understood that the process of osteoconduction that occurs around a biomaterial particle is similar to the process of osseointegration that occurs on the surface of a titanium implant, and the body's response is mediated by the same pathophysiological mechanisms.

For example, the same family of biomaterials (i.e., allografts) processed industrially through different procedures generates different surface characteristics that trigger a different biological response. The same biomaterial coated with a specific biological factor, such as PLGA, modifies the intimate tissue response in the recipient bone.[292] The same biomaterial placed in a mixed mesenchymal environment, such as muscle or connective tissue versus bone tissue, triggers an opposite tissue response.[288] Under these various conditions, the cells of the immune system are programmed to be able to resorb some substances but unable to eliminate others. Notably, when these biomaterials need to be reabsorbed, they undergo resorption at various rates under two primary mechanisms: physical–chemical dissolution in the medium or phagocytosis promoted by specific or nonspecific cells of the immune system.

Therefore, to understand the influence of biomaterials on the homeostasis of new bone formation after grafting, it is didactically necessary to understand the previously defined properties of a biomaterial and how these biological processes could occur temporo-spatially.

After surgical trauma, the rupture of blood vessels, the extravasation of the vascular components and angiogenesis and its extension along the wound comprises the first event and, in turn, the commencing event for tissue repair, consolidation, and maturation of the grafted area. During the development of new tissue, the formation of the vascular micronetwork through nonvascularized tissue is a key factor,[293] and this microvascular density and its distribution will condition not only the viability of the graft but also the subsequent processes of osteoconduction and so-called osteogenesis through the formation of osteoid lines since reparative bone formation is produced by a mesenchymal model.[294] Not all biomaterials induce the same formation of the vascular network.[295] This vascular formation is not only conditioned by the biomaterial used but also by the combination of biomaterials used, so that the contribution of autogenous bone in the graft composite, in different concentrations, raises the microvascular density of the regenerated area, possibly due to the osteoinductive effect that these biomaterials provide.[296]

Neovascularization entails a transcendental phenomenon and is the contribution of both cells from the bloodstream, such as monocytic precursors that will lead to the formation of osteoclasts, and second, perivascular cells, which will have a double function, either by continuing to extend the vascular network, transforming into new endothelial cells, or by propagation to adjacent tissue, becoming stromal mesenchymal cells, which later act on functional demand and will end up becoming osteoblast precursors. It has been suggested that the detection of the protein encoding the Musashi-1 (MSI1) gene in this biological environment is an early marker for preosteoblastic precursors.[297] These osteoblastic progenitor cells have been found in close proximity to a specific subpopulation of endothelial cells (type H).[298] The number of preosteoblasts linked to endothelial cell type H decreases with age, likely explaining the lowered bone regeneration potential in elderly people.

As previously stated, the higher the microvascular density, the greater the cell density, which implies different repair and remodeling speeds according to the chosen biomaterial. It has also been shown that bone neovascularization comprises three tissue compartments of a graft. After 6 months of graft maturation, it is possible to observe neovascularization in the nonmineralized tissue, the so-called microvascular network, and in the new mineralized bone structure (in the form of vessels inside the osteons), as well as colonization of the old particles from the remaining biomaterial through its ancient channels of Havers, or in the center of its old osteons. Therefore, all biomaterials of natural origin end up being revascularized if they are not eliminated.[299] After the induction of vascular neoformation, the resorptive phenomena of both damaged native bone and placed biomaterials occur in combination with the new bone neoformation phenomena. It is evident that three of the properties that an ideal biomaterial must possess are combined: osteogenicity, osteoconductivity, and replacement of the resorption phase by native bone. However, these processes may be dependent on each other and, in some cases, even conceptually antagonistic.

Concerning resorption, native bone reparation through the bone remodeling process is well defined; the first step that occurs is the damaged-native tissue resorption process, promoted by osteoclasts, that later forms new bone through the apposition of new osteoid lines generated by osteoblasts positioned on the surface to be repaired. In fact, when autogenous bone chips are used as biomaterials, it is rare to visualize remnant particles in biopsies obtained after 6 months of graft maturation. Entirely, this native biomaterial undergoes complete resorption. However, this phenomenon is totally different from what can be observed on exogenous particles used as biomaterials. Conceptually, these exogenous biomaterials should be reabsorbed and replaced by new vital bone, but the reality

is that these particles are observed as islets that have allowed bone apposition on most or all their surface, showing a tissue integrity similar to that of the patient's own bone. This occurs due to the great osteoconductive potential of some biomaterials (undoubtedly different for each biomaterial according to its structure and its physical–chemical characteristics). This does not mean that the organism does not identify these exogenous particles as foreign particles and does not intend to eliminate them, but it seems that the bone remodeling unit balance is opposite to that which occurs in the damaged native bone. This means that bone neoformation occurs first, and then resorption of the biomaterial occurs only for the portion of the biomaterial that is exposed to the nonmineral component of the bone. In this sense, it is very interesting to observe that in biopsies taken from grafted areas after 6 months of maturation, MNGCs were found only on exogenous biomaterial particle surfaces, and osteopontin expression (key protein for cell adhesion and activation) is synergistic with TRAP 1 expression (molecules used for immunohistochemical labeling of osteoclasts), always and exclusively observed on the surface of the remaining biomaterial particles, which could indicate a biological demand for these exogenous particles being resorbed.[300] It is obvious, on the other hand, that those particles that have been totally surrounded by new mineral bone structure, due to their high osteoconductive potential, can never be reabsorbed by osteoclasts if the elimination of all the neoformed bone structure does not occur beforehand. For these reasons, it has been proposed that in the processes of bone regeneration based on the use of biomaterials such as scaffolds, osteoconduction and resorption of biomaterials may be antagonistic properties; consequently, a greater potential for bone formation may imply more persistence of the biomaterial in the organism (less resorption) and that a greater and earlier resorption of the biomaterial might lead to poorer results in the final osteogenesis of the grafted area.

Therefore, perhaps the scientific community should rethink the potential of various graft types and keep in mind that very osteoconductive particles surrounded by new mineral bone structure may not undergo resorption.[301] It is also relevant to highlight that resorption of bovine bone may not be necessary to obtain successful osseointegration.[280] However, regarding biomaterial resorption, there are opposite views. A slow resorption rate of xenogenic biomaterials could be useful when a higher bone graft stability is clinically advantageous for successful dental implant positioning, like pneumatized maxillary sinus, or for space maintenance in bone augmentation of severe atrophies.[279] On the other side, some clinicians prefer a fast remodeling rate, leading to the formation of autologous bone in substitution of the biomaterial. The paradigmatic case of this situation is alveolar preservation when a higher contact between native bone and implant surface is relevant.

Ideally, bone substitutes should be progressively replaced, allowing bone growth that will later enter its modeling and remodeling phase. But these materials do not always undergo controlled resorption and degradation.[288] Biomaterials can be reabsorbed by osteoclasts or by chemical breakdown. Osteoclasts are able to resorb ABB, but these cells carry out this process with less efficiency than in the case of natural bone.[302] On the contrary, severe resorption of ABB may occur when these particles become engulfed in soft tissue.[288] Soft tissue-mediated resorption can occur due to a foreign body response in which giant cells stimulate fibrous tissue formation or through the stimulation of RANKL provided by fibroblasts.[288,303]

Another ideal characteristic of a biomaterial should be that it provides a framework for bones to continue their bone deposition and bone resorption process.[280] Indeed, the capacity to form new bone should be commensurate with the resorption rate of the biomaterial, but the long-term persistence of the biomaterial also has possible negative effects. Thus, some clinicians prefer to place implants only in pristine bone and not in biomaterials or biomaterial composites without bone structure. Some authors reported that the presence of 25%–30% of remaining graft particles may impair normal bone healing and even implant osseointegration due to disrupted vascularization and limited cell nutrition.[280,304] Another problem could be the lack of biomechanical properties of the augmented area, as it is more like a composite than a homogenous bone structure.[280] On the contrary, a biomaterial with a slow resorption rate may be beneficial on some occasions because the grafted biomaterial can maintain the volume of the augmented area, provide support, and resistance to compression, avoiding soft tissue collapse. Low-resorption biomaterial can form a cancellous bone network acting like a stress shield against pressure from the maxillary sinus mucosa or gingival tissues.[280] These biomaterials can maintain the mechanical strength of the graft during healing and remodeling and balance their resorption rate with the patient's capacity to form new bone.[301]

It is also important to highlight a dual behavior depending on where the biomaterial is located. Anorganic bovine bone that was surrounded by fibrous tissue rather than embedded in bone can undergo resorption in a preclinical model.[288] In this sense, anorganic bovine bone inserted into recipient bone promoted a resorptive action that was TRAP1-positive osteoclast mediated; nevertheless, the same biomaterial placed in a different mesenchymal context (muscle in the back) of the same animal promoted a foreign body reaction mediated by CD68-positive multinucleated giant cells, suggesting that the biomaterial response is relative to the housing.[305]

Nonetheless, the persistence of the exogenous biomaterial in the organism, contrary to what was postulated years ago, is not a drawback since this biomaterial is capable of integrating new vital bone into its surface through an intimate structural union, while it is capable of both revascularization and cell colonization.[300] This phenomenon of integration composed of biomaterial and new bone formation is due to the important role of osteoconduction, which is the only property that is shared by all families of biomaterials. Osteoconduction is such a capital process that without it, osteogenesis is not possible, not even providing viable cells in the graft composites that are placed. Osteoconduction is, therefore, necessary for osteogenesis in tissues undergoing repair.

Osteoconduction, also called osseointegration in dentistry when it refers to dental implants, occurs through a cascade of events that depend on the physical–chemical characteristics of the biomaterials (highlighting wettability conditions, which regulate fluid absorption) and, consequently, of the different proteins contained in those fluids. These procedures include fibrin attachment, as well albumins and other stabilizing and osteoconductive proteins in turn. However, the adhesion of certain proteins such as osteocalcin or glycoproteins such as fibronectin, OPN, and sialoproteins plays a fundamental role in the bone-forming potential of the different biomaterials, since they are responsible for promoting cell adhesion, differentiation, and activation, as well as subsequent promotion of the mineralization of the new osteoid matrix deposited on the surface of the biomaterial.

After the absorption and stabilization of proteins on the surface of the biomaterial, osteoblastic precursors migrate to the surface of the biomaterial particles. When these cells contact this surface, a series of molecular events occur, such as the interaction of the proteins vitronectin (which is located in the cell sealing areas) and OPN (located on the biomaterial surface) through the protein complex RGD (arginine-glycine-aspartate). After this interaction, there is a cascade of cellular events that will end in activation of the α-actin rings, which in turn will modify the cellular cytoskeleton, transforming into cuboid-active osteoblasts. Next, these osteoblasts will polarize their nuclei toward the microvascular capillaries contained in the nonmineral structure of the bone, forming in their distal part a ruffled border through which the organic matrix will be secreted in intimate contact with the surface of the biomaterial. This collagen-rich matrix is not "bone" per se but will mineralize over time. This whole mineralization process is orchestrated by noncollagen proteins produced by late-stage osteoblasts and osteocytes. Finally, these active osteoblasts will migrate toward the closer blood vessel, creating new bone in their distal ruffled portion. Some of these osteoblasts are embedded in the newly formed matrix, differentiating into preosteocytes and mature osteocytes, while other osteoblasts undergo apoptotic death. The intimal contact between biomaterials and newly formed bone is easily observable under light microscopy or ultrastructural studies, as well as the formation of different cement lines according to the different phases of osteoblastic activation.[306] Due to the process described, it is important to understand that new bone formation in adult humans does not begin until the osteoblasts are differentiated and show the ability to secrete osteoid matrix, and this only occurs after the osteoconductive phenomenon. Therefore, osteogenesis is a process that occurs after osteoconduction and is not dependent on the presence of cells in the graft material, which in addition to not being viable long term, if the graft is particulate, do not have the ability to form an osteoid matrix by themselves.

A very interesting finding that can be observed in this new mature bone is osteocyte recolonization inside the particles of the biomaterial, both in the osteocyte lacunae and the lacunocanalicular system. This event occurred in 75% of patients who were grafted with anorganic bovine bone.[300] Such osteocyte recolonization can be observed not only histologically in this biomaterial but also in any biomaterial that has a system of channels and pores, such as allografts or phylogenic biomaterials.[307] The degree of bone penetration of any biomaterial depends on its ability to act as a spacer and conductive structure for the newly formed bone. The porosity of the material provides an excellent basis for vascularization and cell penetration. Growth of bone tissue in pores is only possible if the pore diameter is at least 100 μm, and the formation of osteon-like structures requires a pore diameter of 200 μm.[308] In this sense, the demonstrated osteopontin distribution within the lacuna-canalicular system of the remaining biomaterial particles, otherwise not observed in the newly formed vital bone, is of paramount importance. Ultrastructural immunohistochemical studies have consistently highlighted that while most noncollagen proteins are dispersed homogeneously throughout the bone, osteopontin distribution is more prominent in cement lines in bone remodeling.[309] This is quite important since the distribution of this protein defines the matrix–matrix and cell–matrix barriers.[310]

If the syncytium of the remnant biomaterial particles is cellularly recolonized by osteocytes and, as discussed above, the three resulting tissue compartments in the newly formed bone (mineral structure, nonmineral structure, and remaining biomaterial) are vascularized, it can be hypothesized that the mature graft may be able to modulate biomechanical stress into biochemical signals by establishing a network of osteocytes along the entire dimension of the newly formed bone.

At this point, the scientific and clinical community must rethink the importance of biomaterial resorption and whether it maintains the dimensional stability, vitality, and biomechanical function of the newly formed bone structure after being subjected to a functional load. Despite the efforts and investments to develop different biomaterials, an ideal single-bone graft substitute has not yet been developed. Clinicians need to understand the properties of each bone graft substitute to make an appropriate selection according to specific clinical requirements.

5 | DRUG-RELATED FACTORS AFFECTING BONE METABOLISM

Progress in osseointegration mechanisms has led to the inclusion of implant treatments in a very large part of the population. This fact implies that an increasing number of implants are placed in patients with systemic diseases and under chronic drug treatment. After implant placement, patients may receive systemic drugs that could either impair or enhance osseointegration.[311] Some of these drugs are anabolic bone agents, such as parathyroid hormone (PTH) peptides, simvastatin, prostaglandin EP4 receptor antagonist, vitamin D, and strontium ranelate, and others act as anticatabolic bone-acting agents, such as calcitonin, bisphosphonates, the RANK/RANKL/OPG system, and selective estrogen receptor

modulators.[311] An update about the effect of some of these systemic medications on bone metabolism and osseointegration is depicted in this section.

5.1 | Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are very commonly prescribed drugs for treating depression, anxiety disorder, and other conditions. These drugs tend to increase the levels of brain serotonin by preventing the reuptake of 5-hydroxytryptamine (5-HT).[312] As osteoblasts and osteoclasts have receptors for serotonin and can be exposed to this substance by autocrine, paracrine, or endocrine pathways, the levels of serotonin can affect bone metabolism.[313–315] Most of the in vitro studies found serotonin to exert a positive effect on osteoblast proliferation, differentiation, and mineralization[316–318] while others reported inhibitory effects on osteoblastic cells.[319–321] In detail, a study in rats found that low levels of serotonin inhibited osteoblast proliferation, differentiation, and mineralization whereas this role was mitigated at high 5-HT concentrations.[320] An association between bone mineral density reduction and an increased risk of bone fracture due to the use of reuptake inhibitors has been reported.[322] Additionally, the use of SSRIs in a murine model delayed bone healing by reducing osteoblastic differentiation and mineralization.[323] Indeed, the use of SSRIs has been related to a negative impact on bone health, and SSRIs have been associated with significantly higher rates of all-cause revision (OR 1.24) or aseptic revision (OR 1.24) after total shoulder arthroplasty.[324] A recent review and metanalysis observed a significant decrease in bone mineral density after using SSSRIs with a mean effect of 0.28 (95% CI = 0.08, 0.39).[313] A retrospective comparison did not show a significant difference in the time of bone fractures to union between patients with chronic SSRI use and patients who had not been on SSRIs (time to heal 6.1 vs. 6.0 months).[323] Daily use of SSRIs in adults over 50 years was associated with a twofold increased risk of clinical fragility fracture, lower bone mineral density at the hip, and a trend toward lower bone mineral density at the spine.[325]

Research regarding SSRIs and dental implants is scarce, but some evidence toward a negative impact on osseointegration has been reported.[312] A systematic review and meta-analysis of the literature found an association between SSRI use and an increased implant failure rate.[326] Implant failure was significantly higher in individuals taking SSRIs ($p < 0.01$) than in controls, with an estimated difference of 7.5%. Indeed, the fixed effects model estimated an odds ratio of implant failure in the experimental SSRIs group against failure in the control group of 2.92 ($p < 0.05$).[326] One study involving 490 patients (51 using SSRIs) and a follow-up between 3 and 67 months reported that treatment with SSRIs was associated with an increased failure of osseointegrated implants.[327] Therefore chronic use of SSRIs increased the risk of dental implant failures with a hazard ratio of 6.28 ($p = 0.03$); the failure rates for patients using SSRIs reached 10.6% of the implants, whereas the failure rate was 4.6% for nonuser patients.[327] A similar retrospective cohort study with 2055 osseointegrated dental implants in 631 patients (109 implants in 36 SSRI users) concluded that SSRIs increased osseointegration failure.[328] The implant failure rate in the SSRI group was 5.6%, while it was 1.85% in the non-SSRI users (OR: 3.123).[328] Similarly, a retrospective study analyzed the evolution of 352 patients of both genders with 680 dental implants, of whom 110 patients (and 230 implants) were SSRI users.[329] The authors concluded that patients taking SSRIs showed increased failure of dental implants. In detail, the total number of complications did not reach statistical significance, but 14 patients from the group of SSRI users presented with loosening of the implants or peri-implantitis (6.08%), while in the control group, there were 10 patients with implant loosening or peri-implantitis (2.22%).[329] If data were disaggregated, the authors found that 27% of diabetic patients who were also taking SSRIs suffered dental implant failures versus 13.4% of diabetic patients who were not taking SSRIs.[329] It was found in a clinical retrospective study of 771 patients and 1820 implants that patient users of antidepressants were under higher risk of implant failure than nonusers.[330] In detail, the frequency of implant failure in patients using SSRIs was 6.3% versus 3.9% in nonusers. In the same study, 33.3% of patients using tricyclic antidepressants had failed implants, while 31.3% of patients taking serotonin-norepinephrine reuptake inhibitors (SNRIs) showed implant failure. While smoking yielded an increased odds ratio of implant failure of 5.221, that with the use of antidepressant drugs reached 4.285.[330]

On the other hand, another retrospective study did not find an association between SSRI use and an increased risk of dental implant failure.[331] In this study, 931 dental implants from 300 patients were analyzed; implant failure data were higher for SSRI users than for nonusers (12.5% vs. 3.3%, respectively), and the Kaplan–Meier analysis showed a statistically significant difference in the cumulative survival rate of implants from the different groups ($p < 0.001$). In contrast, the multivariate GEE model did not show a significant association between the use of SSRI drugs and implant failure ($p = 0.530$).[331]

Another recent retrospective study[332] found that patients using nonsteroidal anti-inflammatory drugs (NSAIDs) presented significantly higher levels of peri-implantitis than control patients, whereas the researchers did not find an influence on implant survival or an augmented risk of peri-implantitis in patients taking SSRI drugs, proton pump inhibitors, or antihypertensive medications.[332] The authors concluded regarding SSRIs that even when the association between SSRIs and implant failure or peri-implantitis is biologically plausible, there is a need for more research to confirm these findings.[332]

As stated above, serotonin can regulate osteoblast/osteoclast balance and so SSRIs may modify the activation and differentiation of osteoclasts[315] and reduce osteoblast differentiation and mineralization.[326] This negative impact on bone metabolism regulation was verified by a reduction of osteoblast marker genes like alkaline phosphatase, osteocalcin, and Osterix.[319,326] Based on these

facts, SSRIs may have detrimental effects on bone mineral density and trabecular microarchitecture due to their anti-anabolic skeletal effects.[326,333]

Wu et al.[327] explained that SSRIs were associated with implant failures due to the interference of the medication in the peri-implant bone metabolism after implant loading. Serotonin has a relevant role in the anabolic response of bones to mechanical loading[327,334] and SSRIs might impair or inhibit bone remodeling around functional implants after mechanical loading and lead to bone mass loss around the implants.[327,334] Specifically, a preclinical study in rats concluded that serotonin was able to regulate the anabolic response of the appendicular skeleton to mechanical loading. As serotonin may stimulate canonical Wnt/β-catenin-dependent bone formation, their deficiency may lead to an impairment of bone turnover, with bone resorption exceeding bone formation. In sum, a reduction in serotonin (5-HT) tone might be accompanied by a deterioration of the biomechanical properties of bone.[334]

In sum, even when there is evidence of the negative effect of SSRIs on peri-implant bone metabolism, further studies on comprehensive effects of serotonin and SSRIs are needed. Patients taking this medication should be closely monitored if they are going to undergo dental implant treatments.

5.2 | Proton pump inhibitors

Proton pump inhibitors (PPIs) are a widely prescribed class of medications used to treat a wide variety of pathologies related to acid production in the stomach. Omeprazole, a drug belonging to this class, is among the top 10 most prescribed drugs in the United States, where approximately 7.8% of the population is prescribed this medication,[335] and its use is increasing in Europe.[336] These medications are used to treat primary or prevent recurrent peptic ulcers, to counteract gastroesophageal reflux or to eradicate *Helicobacter pylori* (in combination with antibiotics).[336]

Several adverse clinical effects related to PPIs have been reported in the literature, especially during the past decade.[337] Chronic use of this medication has been associated with an increased risk of bone fracture, acute and chronic kidney disease, gastrointestinal infections, deficiencies in vitamin B12 and magnesium,[337,338] and gastric cancer[336] among others. A recent review only found statistically significant differences between PPIs and the increased appearance of gastrointestinal infections, highlighting the need for more quality research in the field. In the meantime, clinicians should consider exercising greater vigilance with PPI use.[337] Above all, the chronic use of PPIs may, because of acid suppression, decrease the absorption of vitamins, and nutrients, and this chronic situation can lead to states of vitamin B12, iron, calcium, and magnesium deficiencies and finally to a negative calcium balance, bone loss, and osteoporosis.[312]

The association between PPIs and increased fracture risk is based on some potential mechanisms, such as hypochlorhydria-associated malabsorption of calcium or vitamin B12, gastrin-induced parathyroid hyperplasia, and osteoclastic vacuolar proton pump inhibition.[339] While some studies have found a link between chronic PPI use and an increased number of bone fractures,[340] other reviews have claimed no need for periodic bone mineral density (BMD) measurements among PPI users.[339] One study found that PPI use was related to a reduction in trabecular BMD but without changes in cortical BMD measured by quantitative computer tomography.[341] Even when there were changes only in the trabecular component of the bone, the authors stated that PPI use might increase the risk of fractures in older populations, caused by these detrimental effects on cancellous bone.[341] Similar conclusions can be drawn from other research[342,343]: lower trabecular bone scores (TBS) were found among patients after chronic exposure to PPIs than in equivalent control patients. A slight reduction in BMD was found, and the study suggests that PPI can impair the quality of the trabecular bone, but this effect may be reversible.[342] In a similar manner, patients without a risk factor for osteoporosis and under treatment with PPIs obtained lower femoral T scores than the control group, and they presented an increased risk of developing osteoporosis and osteopenia.[343] In contrast, other research did not find a relationship between long-term PPI treatment and variations in BMD or bone strength that was sufficient to elevate the risk of bone fractures.[344] A literature review and meta-analysis indicated that all the included studies showed a higher risk of fractures after PPI use. Menopausal status plus the intake of PPIs was also associated with an increased risk of bone fractures (by 1.93-fold).[345]

As in the case of SSRI, the evidence between PPIs and osseointegration is more limited. A systematic review of the literature found an association between PPIs and a higher implant failure rate (increase of 4.3% in the PPIs group vs. control) ($p < 0.01$).[326] The estimated odds ratio of a failure in the experimental group (PPIs users) against a failure in the control group was OR = 2.02 ($p < 0.05$).[326] A retrospective cohort study of 799 patients and 1733 dental implants analyzed the failure rates of patients taking PPIs (58 patients and 133 implants).[346] Data from the study suggested that PPI use might be associated with a higher risk of implant failure. In detail, 6.8% of the implants showed a lack of osseointegration in patients taking PPIs versus 3.2% of failures in patients not taking PPI drugs (higher risk HR = 2.73).[346] After a comprehensive review of the literature, a link between PPI consumption and impaired bone regeneration was suggested, but quality studies are needed to avoid influencing the results by confounding factors.[347] Another review found that PPIs exerted a negative but variable effect on the bone around dental implants but that there was a positive relationship between the medication and soft tissue attachment levels around teeth.[348]

A retrospective cohort study of 3549 implants in 994 patients collected data on 179 dental implants that failed.[349] Among other risk factors, such as bruxism, smoking, and low-density bone, the intake of PPIs was associated with an increased rate of implant loss (12% implant failure in the PPI group vs. 4.5% in the non-PPI group, $p = 0.034$).[349]

Another study measured the influence of the long-term use of PPIs and long-term dental implant failure or peri-implantitis[350] through a retrospective cohort study of 933 implants placed in 284

patients. The authors found no correlation between PPI use and implant failure (odds ratio [OR], 0.801) or peri-implantitis (OR, 0.801). Even though PPIs may alter bone metabolism, the anti-inflammatory effects of PPIs may exert a protective role, reducing the incidence of peri-implantitis.[350] PPIs were also found to be a protective factor (OR = 0.08) against peri-implantitis in a clinical study with 240 randomly selected patients from a university clinic study conducted to identify risk or protective factors in peri-implantitis.[351] Opposite results were described in another cohort study with 1918 dental implants in 592 patients and 69 implants placed in 24 users of PPIs.[352] While the failure rate was 8.3% for the PPIs group, only 1.9% of non-osseointegrated implants were measured in the opposite group. The odds of implant failure were 4.60 times higher for patients taking PPI medication than for normal patients, so the authors concluded that PPI intake may be associated with a higher risk of early implant loss.[352]

Despite the fact that the literature provides some contradictory data, the only systematic review with meta-analysis reported the existence of an association between the use of PPIs and implant failure.[326] Further studies are needed to determine if the impaired bone metabolism is mediated by PPIs or other confounders.[326,347] As a general recommendation, the administration of PPIs should be carefully analyzed, and if possible, the use of PPIs after implant insertion should be limited.[347]

5.3 | Antihypertensives

In the orthopedic field, long-term use of loop diuretic medication has been associated with significantly higher rates of all-cause revision of total shoulder arthroplasty (OR 1.44) and aseptic revision (OR 1.43).[324] The possible mechanisms by which antihypertensives (AHTNs) impact bone metabolism may be related to the inhibition of the catabolic effect of osteoclasts by blocking their β2 adrenergic receptors (beta-blockers), to the increase in bone formation due to the higher calcium absorption at the distal convoluted tubule (thiazides) or by shifting the balance toward bone formation by blocking the renin-angiotensin system (ACE inhibitors).[326,353]

In a review about medication related to dental implant failure, only one study on AHTNs reached the inclusion criteria.[326] An increased survival rate was found among the patients using antihypertensive medication (0.6% of failed implants in the AHTN group vs. 4.1% in the control population).[353] Other retrospective study reported higher ISQ in patients taking antihypertensive medication (75.7 ± 5.9) compared with healthy patients (73.7 ± 8.1).[354] But this higher implant stability was only statistically significant in patients taking renin-angiotensin system inhibitors, while patients taking beta blockers showed a tendency to higher ISQ but without reaching statistical significance. Another study analyzed the association of hypertension, antihypertensive drugs, and the absence of osseointegration of dental implants.[355] On the contrary, this study concluded that neither the presence of hypertension nor the use of antihypertensives were associated with dental implant failures.[355] Specifically, the success rate in the hypertensive group for medicated users was lower (92.5%) than that for nonmedicated users (94.1%), without a significant difference ($p = 0.939$).[355] A retrospective study reported higher bone loss, greater pocket depth, and higher prevalence of peri-implantitis in patients under antihypertensive treatment (0.66 mm of bone loss and 30.8% of patients with peri-implantitis) than in healthy patients (0.34 mm of bone loss and 9.1% of patients with peri-implantitis).[356] Calcium channel-blocking agents may induce gingival hyperplasia with alterations in MMP metabolism and failure of collagenases activation.[356] Finally, a recent systematic review about the topic, included only 3 studies and 959 patients.[357] The authors concluded that patients under antihypertensive treatment had comparable success rate and implant stability than patients not taking medications. This limited evidence points to the need for further studies to elucidate the effect of this medication on bone metabolism and implant survival.

5.4 | Nonsteroidal anti-inflammatory drugs

Other medications, such as NSAIDS or oral bisphosphonates (BP), did not reach statistical significance in a recent systematic review.[326] A retrospective cohort study focused on whether the biological complications after implant placement were associated with the perioperative use of NSAIDS by analyzing data from 468 patients.[358] Patients who had used NSAID medication perioperatively experienced 44% implant loss, while the non-NSAID cohort lost 38% of the implants. Indeed, the presence of 3.2 times more radiographic bone loss, greater than 30% of the vertical height of the implants, was measured.[358] According to this study, dental implant osseointegration can be impaired by the negative effect of NSAIDs on integration during bone healing. Conclusions from a literature review[359] showed that NSAID drugs may negatively affect the osseointegration of dental implants, but the quality of the clinical studies is poor, as is the quality of the evidence. Specifically, an inhibition of bone formation around orthopedic implants is associated with selective COX-2 inhibitors.[359]

6 | DIET-RELATED FACTORS ALTERING BONE METABOLISM

6.1 | Vitamin deficiencies

It has been reported that approximately 25% of the US population may have a suboptimal intake of vitamins A, C, D, and E, as well as calcium, magnesium, and potassium in their diet and that approximately 2 billion people around the world may be affected by micronutrient deficiencies.[360] Some publications have shown the influence that several micronutrients may have on the alveolar bone.[360] Specifically, a positive influence on bone health with a reduced risk of fracture has been associated with calcium, fluorides, magnesium,

potassium, vitamin B6, vitamin D, and zinc.[360,361] In contrast, deleterious effects on alveolar bone have been partially attributed to fat-, carbohydrate-, and cholesterol-rich diets and reduced calcium intake.[360,362]

6.1.1 | Magnesium

Magnesium controls calcium influx at the cell membrane and is crucial for vitamin metabolism, specifically for the conversion of vitamin D and B1 into their active forms, and it is also involved in the synthesis of hormones, proteins, bone mineralization, and muscle contraction processes.[363]

Some studies have reported that magnesium deficiency results in impaired bone metabolism. A study analyzed the evolution of implants placed in rats after a diet with a 90% reduction in magnesium intake.[364] This deficiency led to reduced magnesium serum levels and increased values of PTH and deoxypyridinoline (DPD), a bone resorption marker.[365] Consequently, the animals showed a loss of systemic bone mass, thinner cortical bones, and lower values of implant removal torque.[364] Another similar study highlighted that bone impairment (less densitometric analysis and lower torque values) occurred in statistically significant values when the reduction in magnesium intake reached 90% but not at 75% reduction.[364] Both studies concluded that a magnesium-deficient diet had a negative influence on bone metabolism and bone systemic density, as well as on the bone tissue around the implants.[364,366]

6.1.2 | Vitamin C

Vitamin C exerts relevant functions in collagen metabolism. A deficiency in this vitamin may impair the healing of the gingiva, peri-implant mucosa, and alveolar bone.[360] Vitamin C has been shown to induce an increase in collagen type I by human fibroblasts in a dose-dependent manner, enhancing extracellular matrix contraction. Thus, reinforcement of the collagen network by increased collagen cross-linking and maintenance of an optimal collagenic density in the dermis is expected after vitamin C supplementation.[367] Moreover, some preclinical studies have demonstrated that vitamin C potentially accelerates bone healing after fracture, increases type I collagen synthesis, and reduces oxidative stress values by neutralizing ROS.[368] Three preclinical studies reported that vitamin C was effective in lowering oxidative stress induced by inflammation after injuries due to a reduction in endogenous or exogenous ROS that improved tissue composition in ligaments, tendons, and bone.[369-371] Indeed, vitamin C promotes the activation of leukocytes and macrophages in the healing area, and their deficiency can retard the healing time and reduce the resistance to infection.[372]

Preclinical studies have shown that vitamin C also promotes faster development of chondrocytes and reduces scar tissue formation.[368] Clinical studies have also reported higher values of bone mineral density, better healing of bone fractures from increased osteocalcin levels, and increased osteoblastic differentiation and bone formation with the inhibition of osteoclastogenesis via Wnt/β-catenin signaling.[368,373] This study in rats also found that vitamin C reduced the expression of osteoclast differentiation genes, such as receptor activator of nuclear factor kappa-B, receptor activator of nuclear factor kappa-B ligand, tartrate-resistant acid phosphatase, and cathepsin K.[373] Improved bone healing can be assumed based on data from this animal study.[373] However, more evidence from clinical trials is needed to corroborate data from preclinical studies.

A randomized controlled clinical trial with 128 patients was designed to evaluate the effects of vitamin C supplementation on wound healing after different oral surgery procedures, including dental implants and dental implants with guided bone regeneration.[374] The authors found that vitamin C supplementation enhanced postoperative healing at 7 and 14 days in patients undergoing dental implant surgeries or GBR procedures.[374]

An increased intake of vitamin C among other nutrients (such as β-carotene, α-tocopherol, α-linolenic acid and others) as part of a diet with an abundance of fruits and vegetables was associated with a reduced pocket depth after scaling and root planning in non-smoking periodontal patients.[375] Similarly, high consumption of flavonoids (an abundant metabolite found in some berries and citrus) was inversely correlated with pocket depth and salivary IL-1β concentration in patients undergoing periodontal maintenance.[376]

A study in rats concluded that supplementation with vitamin C suppressed alveolar bone resorption stimulated by a rich cholesterol diet.[377] Whereas the rats without vitamin C supplementation and with a high-cholesterol diet showed bone resorption and osteoclast differentiation, the rats with vitamin C intake showed lower values of periodontal 8-hydroxy deoxyguanosine, less bone resorption, and less damage to the periodontal tissues, as a result of reduced oxidative injury.[377]

6.1.3 | Calcium

Approximately 99% of the total calcium in the body is located in bones and teeth, mostly as hydroxyapatite, and <1% is located in soft tissues and body fluids.[363] Three hormones are in charge of maintaining serum calcium concentration: PTH, 1,25-dihydroxycholecalciferol, and calcitonin.[363] Low consumption of calcium and vitamin D induces serum hypocalcemia, initiating stimulation of PTH and consequent osteoclastogenesis and bone resorption.[363]

6.1.4 | Zinc

Zinc is a cofactor for several enzyme systems relevant to wound healing, including DNA and RNA polymerases, proteases, and carbonic anhydrase.[372] Zinc has been associated with a positive effect on bone formation due to the stimulation of osteoblast proliferation,

differentiation, and mineralization and a reduction in osteoclastic bone resorption and osteoclastogenesis.[378] Supplemental intake of zinc and genistein was recommended as a preventive way to avoid osteoporosis in human subjects, as these elements have been related to increased bone mass.[379] In detail, zinc seems to inhibit bone loss through the cessation of osteoclast-like cell formation from bone marrow cells due to the stimulation of IGF-1[378] and by increasing the apoptosis of mature osteoclasts.[380] In the same way, zinc shows a reductive effect on osteoclastogenesis induced by receptor activator of nuclear factor (NF)-kappa B ligand (RANKL).[380] Moreover, zinc can liberate vitamin A from liver storage, helping in immune function, whereas zinc deficiency impairs the speed of wound healing.[372]

6.1.5 | Vitamin E

Vitamin E is a lipid-soluble antioxidant that inhibits cyclooxygenase, lipoxygenase, and phospholipase A2 protein kinase C activity and tumor necrosis factor-alpha formation, and it reduces the formation of C-reactive protein.[363] As a result, vitamin E has anti-inflammatory and anti-thrombotic properties; it promotes a lower release of prostaglandin E2, leukotriene B4, and thromboxane A2, decreases the formation of ROS species and impairs leukocyte adhesion.[363] Moreover, vitamin E diminishes the expression of the receptor RANKL in osteoblasts and inhibits osteoclastogenesis.[360,372]

6.1.6 | Vitamin A

Vitamin A or its active metabolite retinoic acid is an osteopromotive factor that stimulates endogenous mechanisms of bone repair.[381] It is able to enhance the effect of BMP-2 on the osteogenic differentiation of adipose-derived stem cells.[381] Indeed, vitamin A has a role in the homeostasis of the immune system, immune cell differentiation, activation, T-cell regulatory function, and the removal of leukocytes from tissue.[363]

6.1.7 | Vitamin B

B vitamins are a group of water-soluble substances, including thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9), and cobalamin (B12).[363] Deficiency of vitamin B6 and B12 might promote osteoclast activity and bone resorption and might impair endothelial function and blood vascularization to the bone.[382] A study concluded that lower levels of osteocalcin and alkaline phosphatase were found in patients with vitamin B12 deficiency, suggesting that the activity of osteoblasts was affected and that bone metabolism is at some point dependent on vitamin B12.[383] A meta-analysis also stated that structural deterioration of bone was found in patients with elevated homocysteine levels and low values of vitamin B12 and folate and that vitamin B6 was also under optimal values in patients presenting with hip fractures.[384]

6.2 | Vitamin D

Vitamin D is an extremely important vitamin for bone metabolism and is well known for its role in calcium homeostasis, as adequate vitamin D levels are a prerequisite for calcium absorption. It also acts as an antioxidant with anti-inflammatory activity because it acts directly on immune cell cytokine expression.[385] Unfortunately, its major source of synthesis in the human body is via direct sun exposure. With populations increasingly staying indoors and the number of desk jobs continuously rising, vitamin D deficiency is one of the most prevalent vitamin deficiencies in humans worldwide. Unfortunately, foods in general have extremely low levels, and supplementation therefore becomes a requirement when deficiency is present. Epidemiological studies have reported that 47.9% of the global population had vitamin D deficiency with serum values of 25(OH)D < 50 nmol/L and 76.6% presented serum values lower to the recommended (25(OH)D < 75 nmol/L).[386]

Vitamin D deficiency is most known for its associations with osteoporotic and menopausal women. Proof of the relevant role of vitamin D in bone metabolism is evidenced by the fact that the benefits on the skeleton of calcium consumption from dairy products intake (milk, yogurt, and cheese) may be dependent on vitamin D serum levels.[386,387] A study reported that dairy products were related to significantly higher BMD in adults with sufficient vitamin D serum levels whereas dairy intakes were not associated with higher BMD among the vitamin-D insufficient patients.[388] Similarly, another study reported that dairy intake was protective against BMD loss among vitamin D supplement users but not among nonusers.[387] Besides this function in bone metabolism, few people realize, however, their role as risk a factor of onset or progression of other diseases including depression, dementia, Alzheimer's disease, asthma, cancer, cardiovascular disease (CVD), and diabetes, among others.[389] Vitamin D is essential for gastrointestinal calcium absorption, mineralization of osteoid tissue, and maintenance of serum ionized calcium levels. It is also important for other physiological functions, such as muscle strength, neuromuscular coordination, and hormone release.[389] More recently, vitamin D deficiency has also been associated with increased early dental implant failure, and associations with other dental-related complications are increasing.[249,390–398] Optimizing levels prior to surgery therefore becomes fundamental for maximizing bone metabolism and wound healing.

6.2.1 | Understanding vitamin D and optimum levels

Serum 25-hydroxy vitamin D (25-OHD) is a reliable marker of vitamin D status, and a level below 20 ng/mL defines deficiency. Levels above 30 ng/mL are required to maximize the bone-health and

nonskeletal benefits of vitamin D (Table 2). For individuals undergoing any type of dental-related procedures, levels between 40 and 60 ng/mL are generally recommended since it is known that following a period of stress (e.g., simply a dental surgical intervention), levels may decrease significantly.

Unfortunately, foods do not contain sufficient levels. Examples are cod liver oil fish liver oils (250 μg/100 g), fresh caught salmon (12.4 μg/100 g vitamin D3), tuna (7.2 μg/100 g vitamin D3), egg yolk (7.8 μg/100 g), and milk, cheese or yogurt (1.3–2.9 μg/100 g).[399] These are low levels considering that deficiency should be treated with 5000–10 000 IU/day for a 4–12-week period to restore levels to sufficient values. Since an adequate intake of vitamin D (15 μg/day set by the European Food Safety Authority) is hard to achieve through diet alone, dietary supplements of vitamin D are usually recommended.[400] This recommended intake should be increased 10 μg/day in elderly people or in all age groups when solar UVB is scarce.[399]

According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) guidelines, supplementation is recommended to maintain levels above 30 ng/mL.[401] The Endocrine Society in the United States recommends achieving a concentration of more than 30 ng/mL (>75 nmol/L) of serum 25(OH)D, considering the optimal range of 40–60 ng/mL (100–150 nmol/L). The Endocrine Society also advocates an intake of 1500–2000 IU/day (37.5–50 μg) in all adults and that obese patients (BMI > 30 kg/m^2) should take three times the normal adult daily vitamin dose.[401]

6.2.2 | Dental-related complications associated with vitamin D deficiency

Vitamin D plays an important role in supporting the immune system and integration of various biomaterials. It is also relevant for decreasing general oxidative stress and minimizing additional inflammation caused by surgery. As expressed previously, vitamin D is also heavily involved in biomaterial integration and other metabolic processes, such as bone remodeling. Therefore, complications specific to vitamin D deficiency have been observed in the dental field.

In 2009, the first animal study investigating the role of vitamin D in dental implant osseointegration was conducted.[395] Utilizing a rat model, implants were placed in both normal control and vitamin D-deficient animals and subjected to implant push-out tests as well as histological analysis. The push-out tests revealed an approximate 66% decrease in value in the vitamin D-deficient group and revealed significantly lower BIC values as early as 14 days postimplant placement. It was concluded from this study that the effect of vitamin D deficiency was unexpectedly profound. It was further stated that future clinical research would benefit patient care by further evaluating the link between vitamin D deficiency and the potential for early or late implant failure.

Following years of initial preclinical studies demonstrating the marked impact of vitamin D deficiency on osseointegration, additional clinical studies began linking vitamin D deficiency with implant failure. These began initially as case reports. In 2014, Bryce and MacBeth reported that vitamin D deficiency was a suspected causative factor in the failure of immediate implants.[391] The assessment of vitamin D levels prior to implant surgery has been advised in such studies, especially in patients who have undergone either long-term hospital care or a recent traumatic injury/event.[391] Additionally, in the same year, it was also noted that low vitamin D deficiency was a risk factor for not only implant osseointegration but also bone grafting procedures.[392]

In 2016, Fretwurst et al.[393] reported that several implants were removed or lost for unexpected reasons in a dental university clinic. These patients were then sent for various blood analyses to investigate a potential cause. In each case report, extremely low serum vitamin D levels (serum vitamin D level < 20 μg/L) were reported in all cases. This research group reported that after a six-month period of healing and vitamin D supplementation (all cases > 46 μg/L), implants were successfully osseointegrated in all cases following adequate supplementation.[393] It is recommended that future randomized clinical trials be conducted to investigate the association between vitamin D deficiency and implant failure, osteoimmunology, and early implant complications.[393]

In 2019, Mangano et al. published a retrospective study of 1740 implants placed in 885 patients.[394] Implant failure rates were assessed along with other known complications associated with dental implant failure, such as smoking and periodontal disease. In that study, it was reported that heavy smoking (defined as 15 cigarettes per day) was found to be associated with an increase of about two times in early implant failure (3.4% vs. 6.1%, $p = 0.473$). Similarly, patients with generalized periodontal disease had more early implant failures than patients without periodontal disease (3.3% vs. 6.1%, $p = 0.386$). Interestingly, severe vitamin D deficiency (defined as serum levels <10 ng/mL) was reported to be associated with nearly 3.82 times increase in overall implant failure rates compared to controls (2.9% vs. 11.1%, $p = 0.105$).[394] The low number of patients with severe deficiency of vitamin D (<10 ng/mL) is one of the main limitations of this study, which could not demonstrate a significant relationship between low serum levels of vitamin D and an increased risk of early dental implant failure. Despite this, a clear trend between low serum vitamin D values and early implant failure has been reported, and so further prospective clinical trials with larger samples are needed to better understand the influence of vitamin D.[394]

TABLE 2 Vitamin D concentrations in humans at deficient, optimal, and toxic levels.

Status	Serum 25 OH (ng/mL)	Vitamin D concentration (nmol/L)
Severe deficiency	<10	<25
Deficiency	<20	<50
Insufficiency	21–29	50–74
Sufficiency	30–100	75–250
Optimal	30–60	75–150
Toxic	>150	>375
Presurgical	40–60	100–150

Moreover, a recent systematic review concluded that it is difficult to prove a direct relationship or causality between low serum vitamin D levels and early dental implant failures. The small number of clinical trials and their limited number of patients make it necessary to carry out future research to clarify the specific role of vitamin D deficiencies.[402] Conclusions from other systematic reviews were the opposite: serum vitamin D levels in patients may play a relevant role in osseointegration, marginal bone loss, and dental implant survival.[403]

On the other hand, the association between vitamin D deficiency and marginal bone loss (MBL) has shown more clear results.[404] This cohort study found a significant correlation between low vitamin D serum levels and increased MBL after 12 months of loading ($p < 0.001$). Moreover, significant differences were reported among the three groups regarding their MBL: 1.38 ± 0.33 mm in group 1 (deficient vitamin D levels), 0.89 ± 0.16 mm in group 2 (insufficient vitamin D levels), and 0.78 ± 0.12 mm in group 3 (sufficient vitamin D levels).[404] MBL in groups of patients with sufficient and insufficient serum vitamin D levels were within the margins of physiological marginal bone loss, while MBL was higher in patients with a deficiency of vitamin D, and this deficiency seems to increase physiological marginal bone loss.[403]

Vitamin D intake was also associated with a reduction in mesial and distal marginal bone loss in a retrospective study on osteoporosis and dental implants.[405] Vitamin D supplementation seems to have positive effects on peri-implant bone formation.[405]

As long as clearer evidence-based conclusions are not available, prevention with determination of vitamin D levels and supplementation prior to dental implant placement may be recommended if the serum levels of the patient is not withing the normal range.[403,406]

6.2.3 | Dental supplemental recovery program

Owing to the impact of vitamin D deficiency-related complications and failures in dentistry, it has generally been recommended to treat vitamin D-deficient patients with supplementation prior to surgery. Following extensive research, a presurgical supplemental program with dozens of antioxidants, high-dose vitamin D, and their related cofactors has been introduced to the market (DentaMedica, StellaLife). Bone-related support includes vitamin K, magnesium, calcium, manganese, and boron, among other nutrients. The 6-week program is designed to boost presurgical levels (10 000 vitamin D IU/day) for 4 weeks prior to surgery and then provide 2 weeks of maintenance postsurgery. A clinical trial by Paz et al. in 2021[407] found that over 80% of the incoming patients for implant therapy were deficient in vitamin D. Following the 4-week supplemental period, all patients taking DentaMedica exhibited favorable levels of vitamin D (40–60 ng/mL or 100–150 nmol/L) prior to implant surgery. It was concluded that this simple solution may prevent complications that may arise because of deficiencies in vitamin D and other antioxidants.

6.3 | Influence of diet

While high-fat diets are associated with impaired bone metabolism, vegan or vegetarian diets may also promote negative effects on bone.[408] Physical activity and diet may be the most relevant factors affecting BMD and fracture risk.[409] Vegan diets have been advised in order for individuals to avoid CVDs caused by high-fat diets common in Western countries; however, the cessation of animal-based food consumption is an unnatural pattern with no precedents in the evolution of *Homo sapiens*.[408,410,411] While vegan diets may be healthier than standard diets, yielding lower rates of obesity, diabetes, and CVD,[412] they are not associated with reduced all-cause mortality rates.[410,411,413] Indeed, most of these benefits may be biased by higher consciousness about health and lower use of salt, tobacco, alcohol, and drugs.[408,414,415] In contrast, veganism is associated with dysfunction of the neurological, psychological, musculoskeletal, hematological, and immunological systems.[408,416] As the main sources of vitamin D, B12, B2, and niacin come from animal-based food, vegans without drug supplementation can suffer from an increased risk of bone fractures, sarcopenia, depression/anxiety, anemia, neurocognitive impairment, and immune compromise.[408,416–418] Moreover, as vegan diets are rich in grains and legumes with high amounts of phytates reducing gum absorption of nonsodium minerals, mineral deficiencies of calcium, zinc, iron, iodine, and magnesium are common in vegans.[419–421] As reported before, calcium, magnesium, and vitamin D are key factors for bone metabolism. Deficits in these factors have been documented in vegan diets[420,422] and as a consequence of low vitamin D, calcium absorption is reduced and bone formation is hindered.[408] A properly planned vegetarian diet with nutritional supplements may increase BMD and reduce the risk of osteoporosis and fractures.[409] Increased risk of bone fractures and reduced BMD at the femoral neck and lumbar spine[416] among vegan/vegetarians have been reported.[408] Reduction in BMD was more evident in vegans than in vegetarians[416,421] and became significant in population aged >50 years,[416] as decreasing bone mass caused by age may be compounded by a longer period under a vegan diet. Reduced whole body BMD was also assessed in vegan/vegetarian versus omnivore diets.[416] Another study reported a 3.94 times higher risk of osteopenia and a 2.48 times higher risk of lumbar spine fracture in vegans than in omnivores.[423] A meta-analysis of 20 studies reported a significantly higher relative risk of bone fracture in vegan/vegetarian populations than in the normal population (RR = 1.316), being even higher in vegan subgroups (RR = 1.439).[416] Interestingly, fracture rates were more frequent in the Caucasian population than in Asians due to the smaller, thicker, and denser bones and to the higher consumption of soy products rich in proteins and isoflavones in the Asian population.[416] More research is needed to elucidate these controversies regarding bone metabolism in vegan patients. Similarly, in the absence of publications regarding the influence of these diets on peri-implant pathology, prudence is advisable in the treatment of these patients by taking a correct medical history to prevent possible nutritional deficits.

7 | HOST-RELATED FACTORS ALTERING BONE METABOLISM

7.1 | Smoking

Smoking is likely one of the most widely explored factors affecting bone metabolism and long-term tissue stability.[424] To highlight these negative effects, the increased risk associated with tobacco from long-term longitudinal and cross-sectional studies has been vastly explored. In a follow-up study of 22 years, smoker patients presented nearly a doubled risk for implant failure or removal (HR = 1.81).[425] The presence of peri-implantitis in smoker patients was 2.6 times more frequent than in nonsmoker patients (OR = 2.63; 30.5% of patients vs. 18.2% of patients, respectively) (Figure 4).[426,427] These increased rates of complications can be attributed to a delay in healing potential, a higher tendency toward postoperative infections, and greater peri-implant bone loss.[424] Smoking may also induce greater changes in the oral microbiome with an increased level of pathogenic species such as *P. gingivalis*,[428] altering the host–microbial interaction[424] by impairing the normal peri-implant tissue blood supply and thereby lowering neutrophil chemotaxis and phagocytosis. Additionally, smoking increases the levels of proinflammatory cytokines/proteins such as TNF-α, IL-β1, IL-6, and AGEs, exacerbating the effects of hyperglycemia.[424,429]

Cigarette smoking is also considered an independent risk factor for the development of osteoporosis and is significantly related to lower BMD, and the lifetime cumulative bone loss is associated with a 50% greater rate of hip fracture.[430] Smoking also has a central role in bone loss and is significantly associated with lower BMD, involving all skeletal sites,[431] independent of age, sex, and genetic disposition.[432] Noxious effects of smoking on bone have been related to tobacco dose, duration of the smoking habit, and body weight.[431,432] There is evidence of the deleterious effects of smoking on bone integrity after promoting an imbalance in bone turnover processes that may lead to osteoporosis, osteoarthritis, bone fracture, delayed bone healing and extended hospital stays.[433,434]

The effects of smoking can be divided into indirect and direct mechanisms (Figure 5).[430] Body weight, the PTH-vitamin D axis, gonadal hormones, and oxidative stress are considered indirect mechanisms, whereas the RANKL-RANK-OPG pathway, the Wnt/β-catenin signaling pathway, and the aryl hydrocarbon receptor (AhR) pathway are considered direct mechanisms.[430]

Body weight is negatively associated with long-term smoking,[430] although with a tendency toward central obesity.[435] It has been reported that nicotine is able to inhibit food ingestion due to the secretion of serotonin and dopamine, reduce the levels of leptin (anabolic bone factor), enhance lipid oxidation, prevent the conversion of androgens to estrogens, and therefore reduce adipose tissue and body weight.[430]

Smoking has also been related to a downregulation of vitamin D serum levels (both 25-hydroxyvitamin D (25-OH-D) and 1,25-OH2-D) and to the inhibition of PTH release.[430] There is evidence of gastrointestinal calcium absorption caused by smoking due to changes in calciotropic hormones leading to altered

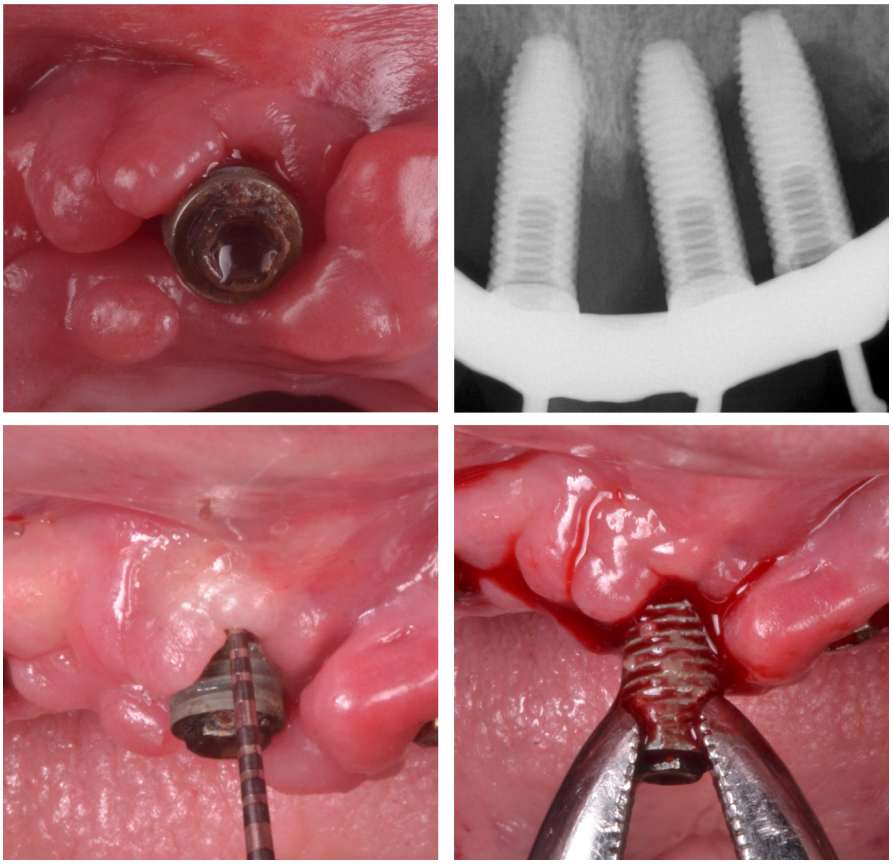

FIGURE 4 Failed implant in smoker patient (>10 cigarettes per day).

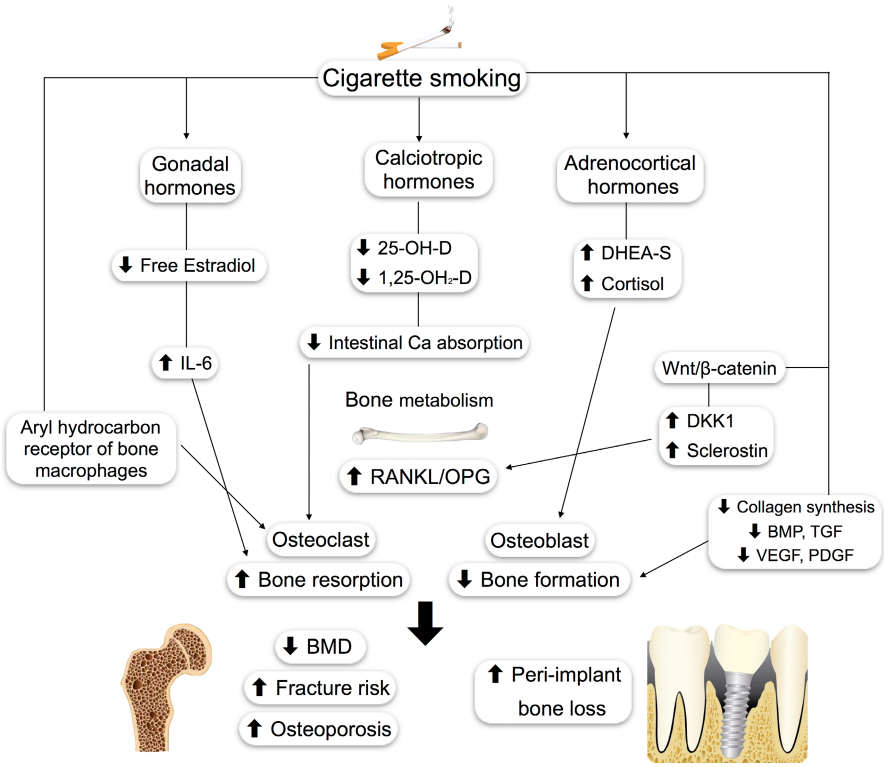

FIGURE 5 Direct and indirect effects of smoking on bone metabolism.

bone metabolism.[436] It is well known that vitamin D is crucial for bone homeostasis and can modulate calcium absorption, while PTH can regulate calcium levels by bone resorption and kidney reabsorption.[430]

Both estrogen and testosterone have essential functions in bone metabolism; while testosterone promotes osteoblastic proliferation and differentiation, estrogen inhibits osteoclast differentiation and bone resorption.[430] Evidence of reduced free serum estradiol and early onset of menopause among smokers was previously reported, leading to a chronic deficiency state of estrogen that impairs bone health.[431] Cigarette smoking effectively reduces free estradiol levels by reducing estrogen production, enhancing hepatic metabolism of estradiol, and increasing the serum levels of sex-hormone binding globulin. The effects of smoking on testosterone are more controversial and need further research, but low levels of testosterone have been related to damaged trabecular bone and an increased risk of fractures.[431]

Smoking has also led to increased levels of ROS and consequently increased osteoclast activity, reduced osteoblast metabolism, and lowered bone mass.[431]

Smoking can exert direct effects on osteoblasts by binding to specific cell receptors such as nicotinic acetylcholine and androgen receptors and their AhRs.[430] As smoking impairs long-term bone metabolism, monitoring bone formation markers (hydroxyproline (HYP) and type I collagen N- and C-terminal propeptides (PINP and PICP/CICP) in the blood, osteocalcin, or bone-specific alkaline phosphatase) or bone degradation markers can be helpful to detect bone damage before the individual reaches more severe degrees of osteoporosis.[430] Human studies have also reported reduced values of OPG in smoking patients, which increases the RANKL/OPG quotient and bone resorption.[437] Indeed, the RANKL-RANK-OPG pathway is under indirect control by gonadal hormones and the PTH-vitamin D axis, and other factors, such as interleukins and prostaglandins, may interact with this pathway and modulate bone metabolism. Specifically, estrogen and androgen can increase OPG levels, downregulate the RANKL/OPG ratio and reduce osteoclast differentiation.[430]

The Wnt/β-catenin signaling pathway has a dual role in bone metabolism, and its activation reduces the RANKL/OPG ratio and impairs osteoclast differentiation and bone resorption. Moreover, it is also able to promote bone formation and matrix mineralization and facilitate the differentiation of osteogenic mesenchymal stem cells.[438] Smoking periodontal patients show increased levels of DKK1 (expressed by osteocytes and mature osteoblasts) and sclerostin (expressed by osteocytes), which are potent targets able to block the Wnt/β-catenin pathway and further upregulate the RANKL/OPG ratio with excessive osteoclast activation and bone loss.[430]

The activation of AhR on bone marrow macrophages leads to strong osteoclastic differentiation and bone resorption and may be one of the key mechanisms of smoking-induced osteoporosis.[430]

Not only does smoking have a negative effect on osteogenesis, but it also has detrimental effects on bone angiogenesis.[431] An in vitro study reported a dose-dependent inhibitory effect of nicotine on osteoblast cell proliferation and on the amounts of several growth factors involved in osteogenesis and angiogenesis, such as PDGF-AA, VEGF, BMP-2, and TGF-β1.[439] Indeed, smoking has been associated with impaired wound healing and defective connective tissue turnover.[440] Cigarette smoking leads to impaired wound contraction and disrupted collagen metabolism with reduced synthesis

of collagen due to a smoking-induced alteration in vitamin C serum levels and a change in the inflammatory cell response with significantly higher quantities of neutrophils and elevated levels of MMP-8 and -9.[440]

Indeed, smoking can diminish bone vascularization and impact immune functions. Cigarettes have been related to lower gingival inflammation due to a reduction in angiogenesis and the bleeding response to plaque.[441] Moreover, tobacco induces oral bacterial dysbiosis, compromises innate cell function, and promotes a protease-antiprotease imbalance in gingival tissues. Similarly, a study on 120 patients smokers and nonsmokers with and without periodontitis concluded that smokers showed less vascular density and a lower vessel caliber than nonsmokers.[442] In detail, the mean microvascular density in smokers with periodontitis was 325.4 versus 412.13 per mm in nonsmoking periodontal patients. Indeed, vessels in smokers ranged from 4.7 to 6.1 μm, while nonsmokers' vessels were measured between 6.2 and 9.2 μm.[442]

Some of these negative effects have been directly related to nicotine. A reduction in collagen and noncollagenous protein synthesis after nicotine treatment of fibroblasts was reported.[443] Interestingly, nicotine presented a bimodal effect on osteoblast differentiation of human alveolar bone marrow-derived mesenchymal stem cells (hABMMSCs).[444] While low doses of nicotine under 1–2 mM promoted cell proliferation and between 1 μM to 1 mM did not alter significantly the ALP activity, doses above 2 mM inhibited in vitro osteoblast proliferation (in a significant way at doses of 5 mM and above) and reduced ALP activity and ALP, OCN, BSP, Runx2, and Collα1 expression.[444] ALP has a relevant role in bone calcification, and ALP activity is useful to measure osteoblast differentiation and activity; Runx2 is another key factor for osteoblast differentiation, as it regulates the expression of several osteoblast genes, including ALP, OCN, OPN, BSP, and Col1α1.[444] Zhao et al.[445] conducted a study to analyze the influence of hABMMSCs on implant patients. Cells from nonsmoking patients showed a significantly higher proliferation rate, higher osteogenic potential, higher ALP activity, and lower adipogenic potential.[445] In detail, ALP staining in the nonsmoker group was 76.8% versus 22.4% for the smoker group, while mineralization markers, including ALP, Col-I, and Runx2, were also expressed at significantly higher levels after 1 and 2 weeks. After 8 weeks of ectopic bone formation, bone matrix formation in the nonsmoker group showed threefold higher values than that in the smoker groups, by H&E staining (78.1% vs. 17.4%) ($p < 0.05$) as well as by immunohistochemical staining (33.6% vs. 8.9%) ($p < 0.05$).[445] Cigarette smoke exposure led to the activation of RANKL mediated by NFκB signaling pathways in mouse bone cells and was involved in the activation of resorption-induced genes such as RANKL, suggesting a potential mechanism for tobacco smoke-induced RANKL gene expression.[446] It was reported that only 10 days of exposure to smoke in rats lowered osteoclast activity, inhibited osteoblast differentiation, and modified the levels of bone remodeling genes. After 3 months of smoke exposure, a relevant impairment of bone structure was reported.[446]

Cigarette extracts have also been linked with a significant reduction in ALP activity and bone matrix mineralization.[434] Oxidative stress caused by the combustion of cigarette components may be one of the main factors reducing the osteogenic differentiation of bone-forming cells.[434] A study in murine animals found relevant cellular and molecular alterations of healing bone fractures due to smoking. These included a reduction in skeletal stem cell populations, disrupted chondrogenesis, increased levels of proinflammatory cytokines, and an infiltrated population of immune cells that provoked a higher initial inflammatory status.[447]

Another relevant consequence of smoking is the impairment of host defenses, both cell-mediated immunity and humoral immunity.[424] Cigarette smoking has been related to altered protease release, respiratory burst, chemotaxis, and phagocytosis of PMNs. The levels of secreted ROS can be lowered or raised depending on tobacco doses and pathogenic stimuli, and they also seem to reduce the formation of neutrophil extracellular traps (NETs).[448] Moreover, PMNs exposed to tobacco showed reduced motility, velocity, and directionality.[449] Indeed, it was reported that atypical cell death of human neutrophils with features of apoptosis, autophagy, and necrosis after exposure to cigarette smoke extract was observed.[450]

The effects on acquired immunity have been reported, but their mechanisms are still unclear. Cigarette smoking may alter the Th1/Th2 balance toward an overabundance of Th2 cells, exacerbate the inflammatory production of mediators such as IL-4, IL-5, IL-9, IL13, IL-17B, and IL-25, promote tissue destruction and increase the severity of periodontal or peri-implant lesions.[451]

Smoking is also correlated with increased levels of advanced glycation end products (AGEs) in the peri-implant sulcular fluid of patients with peri-implantitis. Smoking patients with peri-implantitis were found to have AGE values of 552.8 ± 87.2 pg/mL ($p < 0.01$) compared to nonsmokers with peri-implant diseases (141.6 ± 64.9 pg/mL) and without peri-implantitis (88.1 ± 27.3 pg/mL). With these data, the amount of AGEs may be correlated with the severity of peri-implantitis and the smoking history of the patient.[429] AGEs are hazardous molecules formed after oxidation and glycation of lipids and proteins, and their formation is augmented under inflammatory conditions, chronic hyperglycemia, or cardiovascular or renal diseases.[429] When the receptor for AGEs (RAGEs) reacts with ligands generated by tobacco smoke, promotion of the oxidative stress status in both periodontal tissues and pulmonary tissues is observed. Further harmful smoking interactions other than AGEs-RAGEs lead to an increased generation of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) in blood and gingival crevicular fluid may have a key role in the onset and increased severity of periodontal and peri-implant diseases.[429]

In summary, the negative effects of nicotine on osteoblast proliferation and differentiation at low doses and their cell death promotion at higher doses demonstrate their negative effect on bone metabolism and explain the risk posed by smoking in the onset of alveolar bone loss and periodontal and peri-implant diseases.

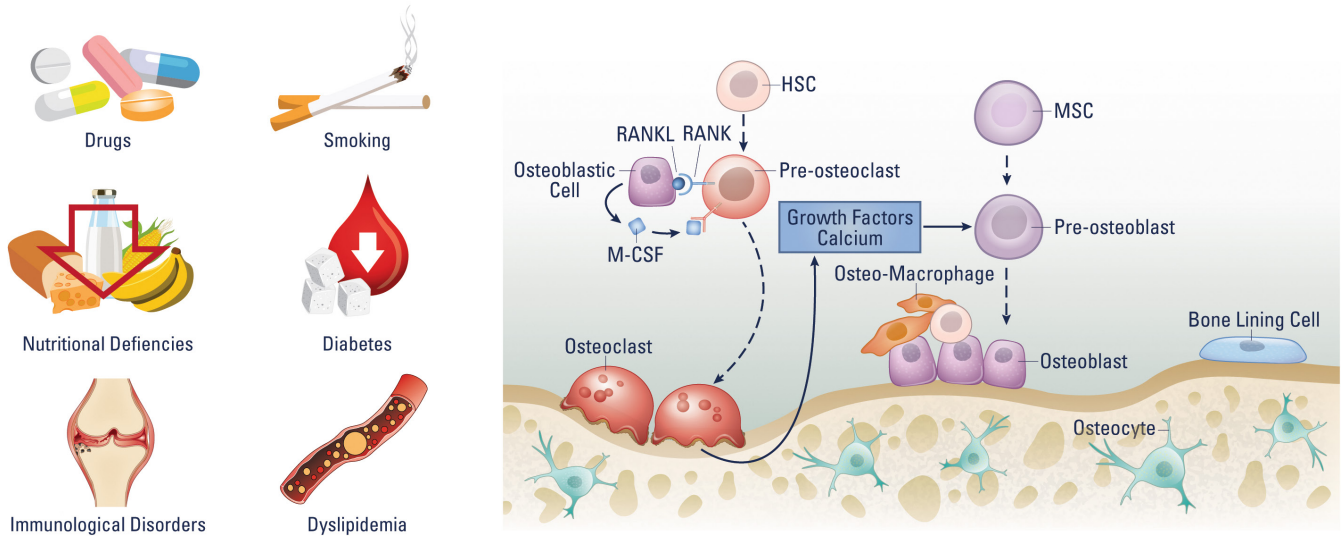

FIGURE 6 Host-related factors affecting bone metabolism.

7.2 | Metabolic syndrome

So-called metabolic syndrome is a cluster of biological factors characterized by abdominal obesity, dyslipidemia, hypertension, and type 2 diabetes mellitus (Figure 6).[452] This group of pathologies has been associated with an increased risk for other chronic diseases, such as CVDs, chronic kidney dysfunction, arthritis, different types of cancer, and early death.[452–454] The estimated prevalence of metabolic syndrome (MetS) is between 25% in developed countries[455] and 30% in the United States.[452]

Obesity may promote a state of systemic inflammation with high counts of monocytes, neutrophils, and adipose tissue macrophages that lead to a systemic inflammatory status.[456–459] These cytokines and the accumulation of cholesterol in macrophages modify the quotient of M1/M2 macrophages, leading to an M1 proinflammatory environment and thereby increasing the numbers of monocytes/macrophages in circulation.[249,458,460] Moreover, the higher adipogenesis of fat cells inside the bone marrow impairs osteoblastogenesis, and additional secretion of fatty acids can lower osteoblast activity and promote osteoblast apoptosis.[461,462] As a consequence, an inverse correlation between bone mass and bone marrow fat has been published.[461–464] Data from animal studies reported more bone resorption, less bone mass, less bone formation, and higher levels of bone turnover markers in animals with diets rich in fatty acids or cholesterol.[462,465,466] Other disruptions in obesity might be caused by the downregulation of the Wnt signaling pathway, leading to the promotion of adipogenesis and lower osteoblast proliferation, differentiation, and maturation.[462,465] In animal studies, hyperlipidemia induced by a high-cholesterol diet resulted in lower alveolar bone density and higher bone resorption, as revealed by the higher numbers of tartrate-resistant acid phosphatase-positive osteoclasts.[377]

The persistence of chronic inflammation in adipose tissue has been related to the onset of insulin resistance and fat accumulation inducing a local increase in macrophages.[467] Whereas VEGF may enhance chronic inflammation and contribute to the progression of MetS,[467,468] HGF shows anti-inflammatory properties with anti-fibrotic and anti-apoptotic functions.[424,467]

In MetS, weight gain is associated with the infiltration of fat by macrophages, and these cells may be an important source of inflammation in obese adipose tissue.[469] There is a tendency of adipocytes to become larger when stimulated by proinflammatory cytokines (MCP-1, TNF alpha, and IL-6) released by activated macrophages.[467] HGF may exert its anti-inflammatory effects by inhibiting NF-kB signaling, which may reduce the inflammation mediated by M1-polarized macrophages in tissues. Thus, it has been reported that HGF suppresses the production of IL-6 by bone marrow-derived macrophages and the expression of MCP-1 in vitro.[467,470] While this situation persists, Mets induces low-grade systemic inflammation[455] with several systemic implications. For example, Mets may affect the periodontal condition by worsening the pocket depth and by acting as a predisposing factor to alveolar bone loss.[455] The link between systemic low-grade inflammation and periodontal and bone metabolism may lie in the influence of proinflammatory cytokines and oxidative stress on periodontal tissues.[455,471,472]

Reduction of inflammation in adipose tissues promotes an increase in the secretion of adiponectin, having beneficial effects not only in obesity, atherosclerosis, type 2 diabetes, fatty liver, and insulin resistance[467] but also in bone metabolism.[473] It was reported that the anti-inflammatory properties of adiponectin can suppress the negative effects of oxidized high-density lipoprotein HDL (oxHDL) on bone tissues. Oxidation of HDL can affect bone mineralization through an inflammatory pathway, as increased values of inflammatory markers such as IL-6, TNF-α, and NF-κβ (p65) and reduced values of the mineralization marker COL1A2 have been measured.[473]

From the data of this study, the presence of osteoblast demineralization can be explained by the inflammation associated with the oxidation of HDL. NF-κβ activation by augmented IL-6 and TNF-α leads to diminished values of ALPL and COL1A2, which are relevant bone matrix proteins necessary for the formation of hydroxyapatite crystallized matrix vesicles and deposition to form hard bone. As a result, a relevant reduction in mineralization by osteoblasts can be expected.[473]

It is clear that, in general, hyperlipidemia and osteoporosis are linked in many of the same patients.[474] There is evidence of an inverse relationship between cholesterol values and BMD, and there is also an association between low bone quality and diet-induced hyperlipidemia.[474,475] The increased risk of osteoporosis in patients diagnosed with hyperlipidemia might be attributed to the inflammatory status and oxidative stress promoted by cholesterol and fatty acids, which lead to greater osteoclastic activity with less bone formation and vascularization.[474,476] It has been reported that statins may have protective effects on bone, as these substances seem to increase the expression of BMP-2[474,477] and protect osteoblasts from apoptosis.[478] A previous review of the literature concluded that simvastatin was beneficial in the treatment of osteoporosis and had a positive effect on bone fracture healing.[479] In detail, simvastatin promotes bone formation by inducing osteoblastogenesis (activity, differentiation, and reduced apoptosis of osteoblasts) and inhibiting osteoclastogenesis (number, activity, and differentiation of osteoclasts).[479] Indeed, the authors noted that the controversy about simvastatin and its role in bone metabolism is due to differences in dosage and route of administration of the drug.[479] Finally, a study on 4138 users of statins analyzed the deleterious effects of the combination of statins with other potentially harmful drugs on bone metabolism.[480] In this study, the most commonly used BMD-reducing drugs were proton pump inhibitors (PPIs), and the authors found that osteoporosis was more frequent in patients who were prescribed both PPIs and statins or both statins and levothyroxine than in patients only under treatment with statins.[480] The authors advised that PPIs and levothyroxine should be prescribed with caution to patients taking statins due to the increased risk of osteoporosis and BMD reduction.[480]

While there is increasing evidence regarding the association between excess lipids and bone dysfunction/osteoporosis, the mechanisms of lipotoxicity in tissues remain unclear. Inhibition of insulin signaling, reduced bone cell viability, or upregulation of osteoblast apoptosis are common effects.[481] Recently, a further explanation of how hyperlipidemia may impact bone metabolism through alterations in lipophagy was described.[481] It was found that osteoblasts can activate autophagy during the mineralization process to degrade and recycle cellular damaged components, and their inhibition leads the cells to reduce their function[481,482] or even induce bone loss during the remodeling stages.[483] A high-fat environment also stimulates autophagy in osteoblasts.[484] It is important to note that autophagy is also a stress response mechanism for survival and that its overactivation or persistence may induce cells to enter into programmed cell death as a consequence.[481,485] On the other hand, lipophagy is part of lipid metabolism, and triglycerides and cholesterol are degraded into lipid droplets and later into free fatty acids,[481] which are further used in cell ATP generation. Physiological autophagy is crucial to equilibrate lipid metabolism as well as for the maintenance of cellular energy homeostasis and to protect cells from toxic lipid accumulation.[481] Failing lipophagy leads to an excessive presence of lipids inside the cells and tissues, and pathologies such as hepatic steatosis or atherosclerosis then follow.[481] While lipophagy can be positive for osteoblast differentiation in an initial high-fat environment, higher concentrations of fat in the tissues can promote the reverse effects; the promotion of autophagy/lipophagy inhibits osteogenic differentiation, and the inhibition of both processes slightly improves osteogenesis.[481] The authors explained that excessive fat accumulation promotes damage to proteins and cellular organelles that cannot be catabolized by autophagy. A dysfunctional oxidative process induces the accumulation of damaging substances inside the cells to the point of altering their function or even apoptosis.[481]

Metabolic syndrome and periodontal diseases have been clearly linked.[486–489] Individuals with MetS are 38% more likely to present periodontal diseases than a normal population without these pathologies.[487] Indeed, a dose–response gradient between the number of pathologies of MetS and periodontal diseases was found.[488] While the presence of 1 component of MetS implied a periodontal disease OR = 1.14, the presence of 4 or 5 elements increased the OR to 2.02.[488] The biological explanation regarding this connection has been related to an increased inflammatory response and the higher systemic oxidative stress caused by Mets.[490,491] A significant component of this exacerbated inflammation may be macrophages, as these cells are key not only for periodontal inflammation but also for osteoclastogenesis, alveolar loss and tissue homeostasis.[492–494] It seems that MetS leads to a systemic hyperinflammatory state with a higher release of substances such as IL-6, M-CSF, MCP-1, and RANKL that favors alveolar bone loss.[239]

Recently, a possible reduction in periodontal inflammation caused by MetS was published[492]; saturated fatty acids in conjunction with bacterial LPS may promote the production of acid sphingomyelinase (aSMase) and ceramide (CER), increasing LPS-induced inflammatory signaling.[492,495] The sphingomyelin (SM) hydrolysis pathway is involved in the crosstalk between LPS and saturated fatty acids (SFAs), such as palmitic acid (PA), in macrophages.[495] Palmitic acid and LPS may have a synergistic effect on inflammatory cytokines released from bone marrow macrophages in metabolic syndrome-related periodontitis.[239] It seems that PA amplifies the inflammatory effects and the expression of TLR-related signaling factors such as TLR2 and CD14 triggered by LPS.[239] A test model in mice showed that a pharmacological inhibitor of aSmase, such as imipramine, was able to block the synergistic effect of LPS and saturated fatty acids (SFAs) on macrophage inflammatory signaling and, thus, a downregulation of proinflammatory and pro-osteoclastic gene expression was reported.[492] Based on data from this study, the authors reported that imipramine (1) reduced macrophage-mediated alveolar bone loss, (2) reduced osteoclastogenesis induced by

periodontitis and MetS, (3) lowered periodontal inflammation stimulated by periodontitis and Mets, (4) reduced the upregulation of pro-inflammatory cytokines (IL-6, IL-1α, IL-1β, COX-2, and TNFα) and (5) lowered pro-osteoclastogenic factors and CER in macrophages. Similarly, imipramine also reduced the infiltration of leukocytes in periodontal tissues and their associated bone resorption.[492]

Another component of the metabolic syndrome with several alterations in wound healing and bone metabolism is diabetes mellitus. The core of the evidence shows that hyperglycemia, especially at severe stages, may pose a higher risk of implant failures and peri-implantitis.[496] Peri-implantitis is associated with a reduction in bone formation and bone quality.[497] Some studies reported rates of 10% to 20% of implant failures in diabetic patients versus the normal rate between 1% and 3% in the normal population.[498] In contrast, other reviews found no differences in the implant failure rates between diabetic patients and healthy patients.[499,500] Even when long-term studies report no survival differences, a delayed healing process and higher marginal bone loss have also been observed.[312,500] Moreover, these results are mainly in well-controlled diabetic patients; therefore, close follow-up for maintenance in these patients is encouraged.[312]

7.3 | Chronic inflammatory status and ROS

When a continuously harmful stimulus that activates immune responses persists over time, it may create a chronically inflamed environment that inhibits bone regeneration/repair due to the constant secretion of inflammatory mediators by cells.[228] A possible link between altered immune responses and increased immune cell infiltration leading to uncontrolled inflammation has been found in damaged bone tissues, such as osteonecrosis.[228,501] Bone healing requires satisfactory cleaning of debris, removal of harmful stimuli and adequate regulation of inflammation.[228] Both excessive or insufficient inflammatory responses have detrimental effects on bone repair; excessive inflammation promotes very high levels of inflammatory cytokines, ROS, including O_2^-, $HO^\bullet$, H_2O_2, and proteases.[228,502] For example, during the first stages of bone healing, TNF-α and IL-6 signal for osteoblast progenitors to arrive at the healing area, but long-term release of the same mediators impairs osteogenesis and promotes bone damage.[228,503] Specifically, IL-6 is essential at early stages of bone healing because it promotes angiogenesis, stimulates the production of VEGF and other growth factors, and favors osteoblast and osteoclast differentiation.[503] While the absence of IL-6 may delay the mineralization of fractures, elevated serum levels are also correlated with impaired bone healing.[503] In a similar manner, TNF-α is able to promote or suppress osteogenesis based on its concentration, exposure time, and type of cell it acts on.[504] Short-term release of TNF-α favors the recruitment of essential MSCs for bone healing, promotes matrix mineralization, and recruits osteoclasts by inducing osteocyte apoptosis[505]; all of these factors are key to both intramembranous and endochondral bone formation.[503,506] In contrast, systemically high chronic levels of TNF-α promote tissue damage and have been related to bone volume loss, reduced bone mechanical strength, and the onset of chronic diseases such as rheumatoid arthritis.[503,507]

A reduction in the inflammatory response may lead to incomplete debris clearance and the persistence of damage-associated molecular patterns (DAMPs). These DAMPs keep the inflammatory status elevated, as they are recognized by pattern recognition receptors activating inflammatory responses.[228,503,508]

Reactive oxygen species are the common term for molecules derived from oxygen that are formed by redox reactions or electronic excitation.[509] ROS have a strong antibacterial capacity and can destroy DNA, proteins, and cell membranes without producing drug-resistant bacteria.[492] Related to dental implants, ROS are mediators between the implant and the host environment. The amount of ROS and oxidative stress can be dependent on implant properties, especially the size of their degradation particles, mechanical properties, or wettability.[498] In this way, ROS may have positive and negative effects. Research in new materials can use ROS production to shift macrophage polarization to M2 and arrest the previous inflammatory status, avoid inflammation around peri-implant tissues due to a promoted antibacterial effect, or stimulate faster wound healing.[498] In contrast, excessive accumulation of ROS may induce a chronic inflammatory status and imbalance the ratio between bone regeneration and bone loss.

Some medical conditions can alter the amounts of ROS. Diabetes mellitus, as a chronic disease, promotes a local increase in proinflammatory cytokines such as TNF-alpha and IL-6. It also modifies the RANKL-OPG ratio and triggers bone resorption.[510] Moreover, diabetic patients have a greater tendency toward systemic and local infections affecting both wound healing and bone repair.[312] Various negative effects of hyperglycemia on bone can be related to excessive production of ROS.[511,512] The presence of high amounts of ROS can lead to osteoblast dysfunction (among others, impaired cell attachment, alterations in their morphology, lower cell proliferation, and differentiation), apoptosis[513] and, finally, delayed and impaired bone healing after implant placement[513,514] or even compromised osteogenesis of porous titanium implants.[513] Markers for oxidative stress have been found in diabetic animal studies, leading to a reduction in the trabecular bone and osteoid volumes as well as to arrested bone formation, defective bone mineralization, and reduced osteoblastic activity.[512] After cellular damage, the activation of inflammatory cells can also induce an overproduction of ROS and consequent harmful oxidative stress.[368] This imbalance between ROS and antioxidants creates a hostile environment for healing, with impaired cell viability and proliferation, and may even promote apoptosis.[368,515]

Moreover, delayed tissue healing in diabetic patients involves a wide number of mechanisms, including hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis, and neovascularization, high levels of metalloproteases, damage from ROS and advanced glycation end-products (AGEs), lowered host immune resistance, and neuropathy.[516] In detail, the impaired vascularization present in diabetes has negative effects on wound healing due to

limited perfusion and angiogenesis.[516] Then, hypoxia can amplify the inflammatory response and increase the amount of oxygen free radicals[516,517] that are added to an excess of ROS and AGEs already generated by hyperglycemia.[511,512] Chronic hypoxia may induce deleterious effects on bone. Recently, it was suggested that hypoxia, through hypoxia-inducible Factor 1 alpha (HIF1α), increased RANKL-induced osteoclast formation by upregulating the mitogen-activated protein kinase (MAPK) pathways.[228] This fact seems to corroborate the possible key role of hypoxia in pathological bone loss episodes.[232] Otherwise, chronic hypoxia might change the effects; an animal study reported that constant hypoxia with levels of oxygen at 1% lowered osteoclast formation and their resorbing function without modifications in cell viability.[232] Moreover, these hypoxic conditions also inhibited RANKL-induced osteoclastogenesis through the regulation of NFATc1.[232] Finally, diabetes also induces defective T-cell immunity, impaired leukocyte chemotaxis, phagocytosis, and antibacterial capacity, leading to incomplete clearance of debris and bacteria and delayed repair.[516]

Interestingly, peri-implant chronic stimulation caused by titanium debris promotes a state of chronic inflammation and oxidative stress that may lead to a reduced immune response of macrophages to bacterial elements such as LPS.[247] Implant surface reactivity also plays an important role in ROS production mediated by nanoparticles.[518] Titanium particles can induce the secretion of moderate quantities of ROS by the nicotinamide adenine dinucleotide phosphate oxidase-1 pathway. This acquired immunosuppression may be a risk factor for further implant-related infections. Authors have explained that rapid oxygen consumption and high amounts of ROS production are common responses of macrophages under acute infections to oxidize and neutralize pathogens.[247] However, these levels of ROS can be toxic to cells and damage tissues.[247,519] Chronification of both the harmful stimuli and secretion of ROS can activate NF-κB and other pro-inflammatory mediators that lead the tissue to a low-grade, chronic inflammatory state.[520,521] This chronic inflammation means that even when wear particles are clearly pro-inflammatory, the damage to the immune function of macrophages as well as to their respiratory burst and to their proliferation prevent them from acting.[247] As a result, local immunosuppression in peri-implant tissues arises with suppression of the fast and potent mechanism of ROS production by macrophages, making these tissues more susceptible to infections.[247]

7.4 | Role of TGF

The TGF family represents key proteins in bone homeostasis. It was reported that systemic or topical application of TGF has anabolic effects on bone healing in vivo.[522] On the other hand, impaired bone healing and reduced bone mineral content have been observed in patients with chronic inflammation and elevated TGF-β_1 serum levels.[522] Increased levels of TGF-β1 have been measured in peri-implantitis or periodontitis tissues (even 100 times the normal levels)[523] compared to healthy tissues, and the epithelium of failing implants has also shown remarkable elevations in TGF-β1.[176,524] Moreover, increased secretion of TGF-β1 has been reported in the orthopedic field related to prosthetic wear and the presence of metal particles, which lead osteoblasts to further increase their production.[525] TGF-β1 has a dual function during wound and bone healing, and both its abundance and absence can be related to impaired wound healing.[176,526] At early stages, TGF-β1 enhances angiogenesis and collagen formation by fibroblasts and collagen and noncollagen bone proteins by osteoblasts,[522] and it attracts inflammatory cells such as mast cells, lymphocytes, and neutrophils. It can also promote proinflammatory cytokine release and arrest cell- or humoral-mediated responses.[176] Other authors have attributed TGF-β1 to moderate tissue destruction by alleviating the immune response.[524] Secreted by bone cells, bone matrix is a relevant reservoir of the latent form of TGF-β1.[522] When bone resorption occurs, acidification of the media leads to activation of the TGF-β reservoir and the promotion of bone formation.[522,527] During the early stages, TGF-β1 is a potent inducer of osteoblast proliferation and chemotaxis in immature osteoblasts,[522] but this effect is present only at low concentrations of this factor and during short periods of time.[522,528]

Nevertheless, in patients with chronic inflammation who may have constantly elevated levels of active TGF-β1 secreted by activated macrophages, TGF-β1 might be responsible for a reduction in bone mineralization.[522,529,530] In fact, TGF-β is released by tissues during chronic inflammation and fibrotic diseases such as liver, cardiac, or renal fibrosis and can be one of the factors leading to the reduced bone density exhibited by some of these patients.[522,529,530] Indeed, the use of TGF-β1 as a stimulus seems to increase RANKL secretion and downregulate OPG in human osteoblasts.[522] Chronic overexpression of TGF-β2 in vitro promotes intense age-dependent bone loss that resembles the low-density bone reported in osteoporosis or hyperparathyroidism.[522,531]

7.5 | Other immune disorders

As peri-implantitis shares pathways with host immune disorders, a possible relationship between both entities has been proposed.[496] Nonetheless, the underlying mechanism remains unclear, and evidence is scarce. Cytokines and immune cells have a key role in the maintenance of peri-implant tissues, and the balance between their pro- and anti-inflammatory functions is crucial for implant survival.[532] Increased numbers of macrophages and dendritic cells have been found around failing implants.[532] A 10-year follow-up study reported an increased failure rate in patients with autoimmune diseases (HR = 5.61 $p = 0.04$ in the univariate analysis) caused by their impaired healing and reduced resistance to infection. In any case, the small sample of the study needs further research to clarify the evidence.[533]

Periodontal diseases and rheumatoid arthritis have been linked for decades, and there is some evidence of their relationship. Rheumatoid arthritis (RA) and chronic periodontitis are both chronic inflammatory pathologies that present with an exacerbated inflammatory

reaction that promotes the destruction of bone and other connective tissues.[534] A similar cell infiltration and quantity of inflammatory mediators have been reported[535,536] and in both diseases, TNF-α is a key factor regulating osteoclastogenesis and osteoblastogenesis.[536] Some studies have reported no difference in TNF-α values in saliva among patients with RA and periodontitis.[536–538] This fact may be explained by the long-term use of disease-modifying anti-rheumatic drugs (DMARDs) that may improve the periodontal condition due to their host modulatory effect.[536]

A close relationship between inflammatory diseases and periodontitis has been described in a recent systematic review and meta-analysis[539]: Patients with inflammatory bowel disease, being a high-risk population in dentistry, had a higher chance of developing periodontitis (OR = 2.65; ranged from OR = 2.22 in Crohn's disease patients to OR = 3.52 in ulcerative colitis patients). Moreover, periodontitis was a significant risk factor for the development of ulcerative colitis but not Crohn's disease.[539] Several hypotheses have been proposed to explain the relationship between RA and periodontal disease.[540,541] The "two-hit model" proposes that *P. gingivalis* disrupts immune tolerance to citrullinated proteins through PPAD, leading to a destructive inflammatory condition in periodontal tissues with macrophage activation, T-cell proliferation, and subsequent cytokine release, along with B-cell proliferation and the release of anti-citrullinated protein antibody (ACPA). Finally, in susceptible patients, the second hit occurs when these ACPAs react against the increased levels of citrullinated proteins in the synovium,[540] leading to a local and systemic increase in proinflammatory mediators. Other theories attribute the damage to a disbalance in cytokine production, especially TNF-α. In other cases, the tissue damage may be related to excessive neutrophil infiltration and activation; under these situations, neutrophils can secrete and form NETs to avoid infection spread, but these enzymes, cytokines, and ROS damage collaterally adjacent tissues, increase the inflammatory response, and expose autoantigens.[542,543] Increased TNF-α and the presence of NETs have been reported in both RA and periodontal diseases.[540] Further research is needed to obtain a full understanding of these pathologies.

8 | CONCLUSION

Peri-implant bone metabolism can be affected by a multitude of local predisposing factors and systemic drivers. For primary preventive measures, it is critical to survey certain implant-, site-, and patient-related factors that demonstrated favoring peri-implant bone loss during the initial healing and that are orchestrated immediately after implant placement and last until the supra-crestal connective tissue height is established after rehabilitation delivery. For the secondary/tertiary prevention of peri-implantitis, these factors must also be controlled. Accordingly, it is encouraged that implant surgeons perform a comprehensive risk assessment before implant therapy is initiated, aiming at identifying underdiagnosed diseases such as autoimmune disorders or chronic elevations of inflammatory cytokines that might be exacerbated by additional immunological conditions to minimize postoperative (bone loss or early implant loss) and biological (peri-implant mucositis or peri-implantitis) complications.

CONFLICT OF INTEREST STATEMENT

The authors have no direct conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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