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Systemic Medications and Their Impact on Dental Implant Osseointegration- A Review

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ABSTRACT:

Dental implants are a widely accepted treatment for rehabilitating partially or completely edentulous patients. However, implant failure remains a concern, especially in individuals on long-term pharmacological therapy. Evidence suggests that systemic medications such as NSAIDs, corticosteroids, bisphosphonates, SSRIs, PPIs, chemotherapeutic agents, and antihypertensives may impair osseointegration and peri-implant tissue health by affecting bone remodelling, angiogenesis, and immune responses. This review critically analyzes the impact of these drugs on implant outcomes, underlying mechanisms, and clinical evidence, while emphasizing risk assessment and management strategies to optimize implant success in medically compromised patients.

Introduction: Dental implants have significantly advanced prosthodontic rehabilitation by providing a reliable and esthetic solution for the replacement of missing teeth. The long-term success of implants depends on osseointegration, a biological process involving the direct structural and functional connection between the implant surface and alveolar bone. Although local factors such as bone quality, implant design, and surgical technique are well established, systemic conditions—particularly medication use—are increasingly recognized for their impact on implant prognosis. Several widely prescribed systemic drugs can influence bone metabolism, healing, and vascularization, thereby affecting osseointegration. Nonsteroidal anti-inflammatory drugs (NSAIDs) may delay bone healing by inhibiting prostaglandin synthesis, while corticosteroids can suppress bone formation and contribute to osteopenia [1]. Bisphosphonates, used in managing osteoporosis and metabolic bone disorders, inhibit osteoclastic activity and may compromise bone remodelling around implants [18,19]. Selective serotonin reuptake inhibitors (SSRIs) are linked to decreased bone mineral density, whereas proton pump inhibitors (PPIs) reduce calcium absorption and impair bone turnover [32,37]. Chemotherapeutic agents can hinder osteoblast function and angiogenesis, and prolonged antihypertensive therapy may alter bone remodelling through calcium and renal metabolism [50,59]. Recognizing these pharmacological effects is essential for identifying high-risk patients, optimizing treatment planning, and improving implant success rates.

Objectives: To evaluate how commonly prescribed systemic medications affect dental implant osseointegration and to highlight their clinical implications and strategies for optimizing implant success.

Conclusions: Systemic medications can significantly influence dental implant osseointegration by affecting bone metabolism, healing, and vascularization. Awareness of these drug–implant interactions enables clinicians to identify high-risk patients, tailor treatment planning, and implement strategies to enhance implant survival and achieve predictable long-term outcomes.

1. Introduction

Dental implants have transformed the field of prosthodontics by providing a reliable and functional solution for the replacement of missing teeth. The long-term success of implants relies heavily on osseointegration, a dynamic process in which the implant surface forms a direct structural and functional connection with the surrounding alveolar bone. While local factors such as bone quality, surgical technique, and implant design are well recognized, systemic factors—including patient health and medication use—play an

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increasingly important role in determining implant outcomes.

Various commonly prescribed systemic medications can significantly influence bone metabolism, healing, and vascularization, thereby affecting osseointegration. Nonsteroidal anti-inflammatory drugs (NSAIDs) can impede bone healing by inhibiting prostaglandin synthesis, while corticosteroids may reduce bone formation and increase the risk of osteopenia[1]. Bisphosphonates, frequently used for osteoporosis and metabolic bone disorders, inhibit osteoclast activity, potentially compromising bone remodelling around implants[18,19]. Selective serotonin reuptake inhibitors (SSRIs) have been associated with decreased bone mineral density and increased fracture risk, whereas proton pump inhibitors (PPIs) can interfere with calcium absorption and bone turnover[32,37]. Chemotherapeutic agents may impair osteoblast activity and vascular supply, and long-term antihypertensive therapy can modulate bone remodelling through effects on calcium metabolism and renal function[50,59].

Understanding the influence of these medications is essential for clinicians to identify at-risk patients, optimize treatment planning, and implement preventive strategies to enhance implant success. This review aims to systematically summarize current evidence on the effects of systemic medications on dental implant osseointegration, highlighting mechanisms of action, clinical implications, and considerations for improving patient outcomes.

2. Objectives

To evaluate how commonly prescribed systemic medications affect dental implant osseointegration and to highlight their clinical implications and strategies for optimizing implant success.

I) Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications for the management of pain and inflammation associated with dental procedures, including implant placement. Their therapeutic effect is primarily mediated through inhibition of cyclooxygenase (COX) enzymes, which catalyse the conversion of arachidonic acid to prostaglandins, key mediators of inflammation, vascular function, and bone metabolism. While NSAIDs are effective analgesics and anti-inflammatory agents, accumulating evidence suggests that they may adversely affect bone healing and osseointegration of dental implants when administered during critical periods of bone regeneration [1].

The process of osseointegration relies on a coordinated cascade of biological events, including an initial inflammatory response, angiogenesis, and the recruitment and differentiation of osteoprogenitor cells. Prostaglandins, particularly those produced via COX-2 activity, play a central role in these processes by regulating angiogenesis, osteoblast differentiation, and matrix mineralization. Preclinical studies have highlighted the importance of COX-2 in bone repair. Simon et al. demonstrated in animal fracture models that genetic absence or pharmacological inhibition of COX-2 severely impaired endochondral ossification, delayed bone healing, and reduced biomechanical strength of the regenerated tissue [2]. Similarly, Beck et al. showed that systemic administration of diclofenac, a non-selective NSAID, delayed callus formation and reduced mechanical stability in fracture models [3]. These findings emphasize the critical role of COX-2–mediated prostaglandin signalling in bone regeneration, which is directly relevant to the early healing phase following dental implant placement.

Animal studies investigating NSAID effects on dental implants further corroborate these observations. Ribeiro et al. reported that selective COX-2 inhibition in rats significantly reduced bone-to-implant contact (BIC), indicating compromised osseointegration [5]. Additionally, Ribeiro et al. demonstrated that continuous administration of COX-2 inhibitors impaired bone healing even when implants possessed enhanced surface characteristics, such as aluminium oxide-blasted topography, suggesting that surface modifications alone may not fully overcome the negative impact of COX-2 inhibition [4]. Chikazu et al. confirmed the essential role of COX-2 in implant osseointegration, observing decreased peri-implant bone formation and compromised integration when COX-2 activity was pharmacologically blocked [6]. Collectively, these studies highlight that inhibition of prostaglandin synthesis during the early healing period can substantially impair

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the biological foundation required for stable implant integration.

Evidence from human studies, although limited, provides complementary insights. Alissa et al. conducted a randomized, double-blind, placebo-controlled trial investigating short-term ibuprofen administration following dental implant placement. While no statistically significant long-term reductions in bone integration were observed, subtle early differences in peri-implant healing were noted between the NSAID and placebo groups [7]. Winnett et al in a systematic review, concluded that prolonged or high-dose NSAID therapy may impair osseointegration, particularly when administered during the early inflammatory and osteogenic phases [8].

Recent studies provide additional information regarding NSAID effects. Kumchai et al. conducted a randomized, placebo-controlled pilot study evaluating naproxen during implant osseointegration, reporting reduced early bone formation in the NSAID group compared with placebo [9]. Corbella et al. in a retrospective cohort analysis, found that chronic use of anti-inflammatory medications, including NSAIDs, was associated with increased marginal bone loss and slightly reduced implant survival rates [10]. Interestingly, innovative approaches incorporating aspirin into biomaterial coatings on 3D-printed titanium implants demonstrated enhanced osteoblast differentiation, macrophage polarization toward pro-regenerative phenotypes, and improved osseointegration [11]. This suggests that not all NSAIDs uniformly inhibit bone healing; factors such as drug type, local delivery, dosage, and tissue environment can modulate the biological response.

NSAID-induced impairment of osseointegration is largely attributed to suppression of prostaglandin-mediated pathways critical for angiogenesis and osteoblast differentiation. Angiogenesis provides the vascular supply essential for nutrient delivery and osteoprogenitor recruitment, both necessary for matrix deposition and mineralization at the implant interface. Inhibition of COX-2–mediated prostaglandin synthesis during the early healing phase can therefore lead to delayed mineralization, reduced bone density, and compromised implant stability [1,2,5,6]. Additionally, NSAIDs may indirectly affect bone remodelling by modulating inflammatory cytokine profiles, reducing the recruitment of osteogenic cells, and altering the balance between osteoblast and osteoclast activity, further influencing osseointegration outcomes.

From a clinical perspective, the management of NSAID therapy in dental implant patients requires careful consideration. Short-term analgesic therapy immediately following surgery is generally acceptable, particularly for pain control in the first few days postoperatively. However, prolonged or high-dose administration during the critical early phase of osseointegration should be avoided, especially in patients with additional risk factors for impaired bone healing, such as osteoporosis, systemic diseases affecting bone metabolism, or concurrent use of medications like corticosteroids or bisphosphonates. Clinicians must weigh the benefits of analgesia against the potential risk of impaired osseointegration and consider alternative pain management strategies, including acetaminophen or localized anaesthetic protocols, when appropriate.

Preventive strategies to mitigate NSAID-related impairment of osseointegration include minimizing drug exposure during the first two to three weeks post-implant placement, careful monitoring of peri-implant healing, and ensuring optimal surgical technique with minimal trauma. Implant surface modifications and bone grafting procedures may partially compensate for reduced bone formation, although they do not fully negate the effects of COX-2 inhibition. In high-risk patients, clinicians may also consider delaying elective implant placement until NSAID therapy can be minimized or temporarily discontinued.

II) Corticosteroids

Corticosteroids are synthetic or naturally occurring steroid hormones widely utilized for their potent anti-inflammatory, immunosuppressive, and metabolic regulatory properties. They are commonly prescribed for autoimmune disorders, chronic inflammatory conditions, and in organ transplantation to prevent rejection. Glucocorticoids, the most clinically relevant subtype, exert their effects by binding to intracellular glucocorticoid receptors, which translocate to the nucleus and modulate transcription of multiple genes involved in inflammation, immune response, and metabolism. Despite their therapeutic indispensability, systemic corticosteroid therapy is consistently associated

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with deleterious effects on bone metabolism, raising significant concerns regarding dental implant osseointegration and long-term implant survival [12].

Bone remodelling is a tightly regulated physiological process involving a balance between osteoclastic bone resorption and osteoblastic bone formation. Glucocorticoids disrupt this equilibrium through multiple pathways. They directly inhibit osteoblast proliferation and differentiation, induce apoptosis of osteoblasts and osteocytes, and reduce the production of extracellular matrix proteins essential for bone mineralization. Simultaneously, they indirectly stimulate osteoclast activity by altering the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin, crucial regulators of osteoclastogenesis. The net result is a reduction in bone formation, enhanced bone resorption, and decreased bone mineral density, particularly in trabecular bone, which is critical for achieving primary stability and osseointegration of dental implants [13, 14].

Experimental studies and clinical observations demonstrate that chronic corticosteroid exposure compromises both the quality and quantity of alveolar bone. Preclinical data indicate that corticosteroids reduce bone turnover and impair angiogenesis, which are vital for the early healing phase around implant surfaces. Impaired angiogenesis limits the vascular supply needed for nutrient delivery and removal of metabolic waste, further hindering osteoblast function and matrix deposition. Consequently, initial bone healing is delayed, and osseointegration may be compromised, particularly in patients on long-term systemic corticosteroid therapy [12]. The severity of bone compromise correlates with cumulative corticosteroid dose, duration of therapy, and patient-specific factors such as age, sex, and pre-existing bone disease.

Clinical studies correlate these findings. Bell et al. conducted a retrospective analysis of patients receiving long-term oral corticosteroids and reported a significantly higher incidence of implant failure compared to corticosteroid-naïve controls [15]. Similarly, Chrcanovic et al. performed a meta-analysis examining dental implants in patients undergoing systemic corticosteroid therapy and found moderately reduced implant survival rates, particularly in patients with continuous therapy or high daily doses [16]. These findings underscore the direct relationship between corticosteroid-induced bone alterations and the biological foundation required for implant stability.

The risk of implant failure is also influenced by the route and formulation of corticosteroid administration. Oral corticosteroids, particularly at low to moderate doses, are associated with a measurable but comparatively lower risk of osseointegration impairment. In contrast, systemic high-dose therapy, prolonged treatment courses, and intravenous corticosteroids significantly increase the likelihood of compromised bone healing and implant failure. Local corticosteroid injections or short-term perioperative therapy generally carry minimal risk, provided cumulative systemic exposure is limited [12, 13].

Case reports provide valuable clinical insight into the challenges posed by corticosteroids. Cranin described the placement of endosteal implants in a patient with corticosteroid dependence, noting delayed bone healing and compromised implant stability [17]. These reports emphasize the need for careful patient selection, comprehensive preoperative evaluation, and meticulous surgical planning. Strategies to mitigate risks in corticosteroid-treated patients include optimizing bone quality prior to implant placement, minimizing corticosteroid exposure when clinically feasible, and considering adjunctive therapies such as bisphosphonates or anabolic agents to support bone formation.

Corticosteroids interfere with osseointegration through several key pathways. First, suppression of osteoblast proliferation and differentiation limits the deposition of new bone at the implant interface. Second, enhanced apoptosis of osteocytes and osteoblasts reduces bone matrix maintenance and compromises structural integrity. Third, alterations in RANKL/osteoprotegerin signalling enhance osteoclast-mediated bone resorption, further diminishing bone mass. Fourth, corticosteroid-induced reductions in vascular endothelial growth factor (VEGF) expression impair angiogenesis, limiting the vascular supply essential for bone regeneration and remodelling [13]. These mechanisms collectively establish a microenvironment that is suboptimal for implant integration, particularly in the early postoperative phase when osseointegration is most critical.

Journal of Chemical Health Risks
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The clinical implications of corticosteroid therapy on dental implants are profound. Patients receiving long-term systemic corticosteroids represent a high-risk cohort for implant failure due to impaired bone healing, reduced bone density, and altered trabecular architecture. Short-term perioperative corticosteroid use may be unavoidable for medical reasons, such as controlling systemic inflammation or preventing adrenal insufficiency. Nevertheless, prolonged therapy should be carefully evaluated, and risk mitigation strategies implemented to optimize implant outcomes. These strategies may include delaying implant placement until bone turnover and quality are optimized, performing preoperative bone augmentation procedures, or monitoring bone turnover markers to assess osseous health prior to surgery. Intraoperative techniques such as atraumatic tissue handling, achieving maximal primary stability, and minimizing periosteal stripping are crucial to enhance healing. Postoperative monitoring should be frequent, focusing on early signs of impaired osseointegration or peri-implant bone loss [15, 16].

Corticosteroids exert profound and multifactorial effects on bone physiology that directly impact dental implant therapy. Their suppression of osteoblast proliferation, induction of osteocyte and osteoblast apoptosis, enhancement of osteoclast-mediated bone resorption, and impairment of angiogenesis collectively compromise the osseous environment required for successful implant integration. Recognition of these risks, combined with comprehensive preoperative assessment, individualized treatment planning, meticulous surgical technique, and vigilant postoperative monitoring, is essential to improve implant outcomes in patients receiving systemic corticosteroid therapy. By integrating current evidence and adopting personalized therapeutic strategies, clinicians can optimize implant success while minimizing complications in this high-risk population.

III) Bisphosphonates (BPs)

Bisphosphonates (BPs) constitute a widely prescribed class of medications, primarily utilized for the management of osteoporosis, Paget's disease, multiple myeloma, and hypercalcemia associated with malignancy. Their therapeutic efficacy is largely attributed to potent antiresorptive activity, achieved through selective inhibition of osteoclast-mediated bone resorption, which results in increased bone mineral density and skeletal strength [19]. Among the commonly prescribed agents are alendronate, risedronate, and zoledronic acid, which vary in potency, pharmacokinetic profile, and route of administration. While the skeletal benefits of bisphosphonates, such as reduced fracture risk, are well established, their influence on alveolar bone remodelling and osseointegration presents significant considerations in the context of dental implant therapy [19, 21].

At the cellular and molecular level, bisphosphonates exhibit a strong affinity for hydroxyapatite crystals in bone, leading to preferential localization in areas of high bone turnover. Osteoclasts internalize these agents during bone resorption, which disrupts the mevalonate pathway, resulting in inhibition of prenylation of small GTPase signalling proteins, cytoskeletal disorganization, and ultimately osteoclast apoptosis [19]. This reduction in osteoclast activity suppresses normal bone turnover, which, although beneficial in preventing pathological bone loss, may compromise the dynamic remodelling required for optimal implant osseointegration. Dental implant integration depends on a delicate balance between osteoclastic resorption of necrotic bone and osteoblastic deposition of new bone at the implant interface. Excessive suppression of osteoclast activity, therefore, carries the potential to delay bone healing, interfere with primary and secondary stability, and predispose peri-implant bone to necrosis [18, 19].

Experimental studies have further elucidated the dual nature of bisphosphonate effects on bone healing. In animal models, local administration of zoledronic acid has been shown to increase early bone-to-implant contact, suggesting a potential role in enhancing initial osseointegration [30]. When inflammation, mechanical stress, or local infection is present, the suppressed bone remodelling induced by bisphosphonates can contribute to impaired bone healing and increase susceptibility to osteonecrosis [31]. Such findings emphasize the complex interplay between bisphosphonate pharmacodynamics, local bone biology, and the mechanical environment surrounding dental implants.

Clinical studies investigating implant survival in patients receiving bisphosphonates have reported variable outcomes. Retrospective and prospective analyses indicate that patients on low-dose oral bisphosphonates

Journal of Chemical Health Risks
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for osteoporosis can achieve successful implant therapy without significantly elevated rates of early implant failure [20, 25, 26]. Jeffcoat highlighted that controlled clinical studies revealed no adverse effects on alveolar bone around dental implants in patients receiving oral bisphosphonates [18]. Similarly, Scully et al. documented satisfactory osseointegration in patients on long-term oral therapy, reinforcing the notion that with careful patient selection, meticulous surgical technique, and thorough postoperative monitoring, implant therapy can be successful even in this population [24]. These findings suggest that low-dose oral bisphosphonates, particularly in patients without systemic comorbidities, may not be an absolute contraindication to implant placement.

Despite these positive outcomes, bisphosphonate therapy has been consistently associated with a serious complication: bisphosphonate-related osteonecrosis of the jaw (BRONJ). First characterized by Marx et al. BRONJ manifests as exposed necrotic bone in the maxillofacial region, persisting for more than eight weeks and often precipitated by dental surgery or trauma [23]. Risk factors for BRONJ include high-dose intravenous bisphosphonate therapy, invasive dental procedures, corticosteroid use, systemic comorbidities such as diabetes mellitus, and pre-existing periodontal disease [22, 28, 29]. The occurrence of BRONJ following implant placement, though uncommon in low-dose oral therapy, remains a significant concern, especially in patients receiving high-dose intravenous therapy for malignancy. Case reports and series have demonstrated implant failure and osteonecrosis in bisphosphonate-treated individuals, highlighting the need for rigorous preoperative risk assessment and careful postoperative management [27].

Several studies have explored the incidence and clinical course of BRONJ in patients receiving oral bisphosphonates. Lazarovici et al. reported instances of implant-associated osteonecrosis even with oral therapy, though the overall incidence remains low [22]. Brooks et al. demonstrated that risk increases with longer durations of bisphosphonate exposure, concomitant use of systemic medications such as corticosteroids or antiangiogenic agents, and the presence of local infection [28]. Animal studies reinforce these observations, indicating that peri-implant inflammation substantially elevates the risk of osteonecrosis in bisphosphonate-treated subjects [31]. These findings underscore the importance of optimizing periodontal and peri-implant health prior to and following implant therapy.

The duration, dosage, and route of bisphosphonate administration are critical determinants of implant success and osteonecrosis risk. Oral bisphosphonates prescribed for osteoporosis at low doses over short to moderate durations typically carry a lower risk, allowing for careful implant placement under stringent surgical protocols [18, 20, 25]. Conversely, high-dose intravenous bisphosphonates used in oncology significantly suppress bone turnover, and elective implant placement in these patients is generally contraindicated due to the elevated risk of BRONJ [22, 23]. Importantly, the long skeletal half-life of bisphosphonates means that even temporary discontinuation may not substantially reduce risk, rendering “drug holidays” of limited efficacy in preventing osteonecrosis [19].

Clinical strategies to mitigate bisphosphonate-associated risks in implant therapy emphasize comprehensive patient assessment and risk stratification. Patients should undergo thorough medical and dental history evaluation, including assessment of the type, dose, and duration of bisphosphonate therapy. Preoperative imaging with modalities such as cone-beam computed tomography can assist in evaluating alveolar bone quality and planning optimal implant placement. Surgical approaches should prioritize atraumatic techniques, achieve maximal primary stability, and minimize periosteal stripping to reduce the risk of compromised healing. Postoperative protocols should include stringent infection control, meticulous oral hygiene, and close monitoring of peri-implant bone levels, with early intervention in cases of inflammation or delayed healing [18, 25].

Emerging evidence also highlights the potential role of local bisphosphonate application in augmenting implant osseointegration while mitigating systemic risk. Animal studies suggest that targeted delivery of bisphosphonates to the implant site can enhance bone-to-implant contact and early stability without substantially affecting systemic bone turnover [30]. Nonetheless, the clinical translation of these findings requires further investigation, particularly with respect to the potential for localized osteonecrosis in the presence of peri-implant infection or mechanical overload.

Journal of Chemical Health Risks
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Bisphosphonate therapy exerts a dual and context-dependent influence on dental implant therapy. Low-dose oral bisphosphonates may allow for successful implant placement when combined with meticulous surgical planning and postoperative care. In contrast, high-dose or long-term therapy, particularly intravenous administration in oncology patients, substantially increases the risk of delayed osseointegration, implant failure, and BRONJ. Clinical decision-making should integrate individualized risk assessment, careful surgical planning, infection control, and vigilant postoperative follow-up. Future research should focus on identifying predictive biomarkers of osteonecrosis, refining surgical and pharmacologic protocols for safe implant placement, and evaluating the potential of local bisphosphonate application to optimize osseointegration while minimizing complications. A multidisciplinary approach involving dentists, oral surgeons, and medical specialists remains essential to safely manage implant therapy in this vulnerable population.

IV) Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed antidepressant medications indicated for depression, anxiety disorders, and various psychiatric conditions. Their pharmacological action is mediated by blocking the serotonin transporter, thereby increasing extracellular serotonin levels in the central nervous system, which contributes to mood regulation and stabilization. While SSRIs provide substantial psychiatric benefits, their long-term use has been associated with systemic skeletal effects that may interfere with bone physiology, osseointegration, and ultimately the prognosis of dental implant therapy [32].

The influence of SSRIs on bone homeostasis is mediated through the serotonergic system, which functions in both central and peripheral tissues. Serotonin regulates bone metabolism by acting on osteoblasts and osteoclasts. Experimental studies have shown that serotonin promotes osteoblast differentiation through activation of the 5-HT2B receptor and the MAPK signalling pathway, which enhances matrix deposition and mineralization [33]. However, inhibition of serotonin reuptake reduces the availability of serotonin for these pathways, thereby impairing osteoblast proliferation and bone formation. Warden et al. demonstrated that pharmacologic inhibition of the serotonin transporter leads to reduced bone accrual during growth, highlighting its importance in skeletal development and maintenance [34]. Beyond osteoblasts, serotonin also regulates osteoclast differentiation and actin cytoskeleton organization, implicating the serotonergic system in both bone formation and resorption. Dysregulation of these pathways under chronic SSRI therapy can therefore result in imbalanced remodelling and decreased bone mass [35].

Animal studies provide further support for these mechanisms. Howie et al. investigated the effect of sertraline on bone regeneration using a calvarial defect model and found significant impairment of bone healing, with delayed osteoblastic activity and suppressed new bone formation [40]. These findings suggest that SSRIs compromise bone regenerative potential, which is critical during the early stages of implant osseointegration.

Clinical evidence mirrors these biological observations. Wu et al. reported in a large cohort study that patients taking SSRIs had a significantly higher risk of dental implant failure compared with non-users [32]. Carr et al. similarly found a strong association between SSRI use and implant failure in their retrospective cohort analysis, noting that the risk was particularly pronounced during the early healing phase [36]. Chandra et al. further corroborated these findings in a retrospective study, reporting that patients on SSRIs exhibited impaired implant prognosis compared with controls [38]. Together, these studies consistently suggest that SSRI use is a relevant pharmacologic risk factor for osseointegrated implant complications.

Additional research has examined how SSRIs influence peri-implant tissues and inflammatory responses. ALHarthi et al. observed that individuals on chronic SSRI therapy demonstrated higher salivary levels of interleukin-1β, as well as increased periodontal and peri-implant inflammation, compared with controls [39]. This indicates that the adverse effects of SSRIs extend beyond impaired bone remodelling to include modulation of host inflammatory responses, which may further jeopardize peri-implant health and long-term implant stability.

The negative impact of SSRIs on implant prognosis also appears to be dose- and duration-dependent. Long-term users show greater impairment of bone healing and higher risks of failure than those on short-term or low-

Journal of Chemical Health Risks
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JCHR (2025) 15(6), 2725-2740 | ISSN:2251-6727

dose therapy [32, 36, 38]. Furthermore, the presence of concomitant medications known to affect bone metabolism, such as proton pump inhibitors or anti-inflammatory agents, may compound the detrimental effects. Corbella et al. demonstrated that patients on multiple drug regimens, including SSRIs, experienced significantly poorer implant outcomes compared to those not taking these medications, highlighting the additive risks of polypharmacy [37].

From a mechanistic standpoint, SSRI-induced reduction of osteoblast activity, delayed mineralization, and altered osteoclast function collectively disrupt the delicate balance of bone remodelling required for successful osseointegration [33, 34, 35, 40]. Additionally, the elevated inflammatory milieu in peri-implant tissues of SSRI users contributes to marginal bone loss and compromised tissue stability [39]. Systemic reductions in bone mineral density, particularly in long-term users, further exacerbate these effects, placing SSRI patients at a disadvantage for implant therapy.

The clinical implications of these findings are significant. Patients on long-term SSRI therapy should be considered at higher risk for implant complications and require thorough preoperative assessment, including evaluation of bone density and quality through cone-beam computed tomography or similar imaging modalities. Risk stratification is essential, especially in elderly patients or those with coexisting osteoporosis. Surgical techniques should focus on minimizing trauma, achieving maximum primary stability, and ensuring optimal bone-to-implant contact. Use of implants with enhanced surface modifications may provide additional benefits in improving osseointegration in these cases.

Postoperative management must include strict infection control, maintenance of peri-implant tissue health, and regular follow-up to monitor bone levels. Given the psychiatric risks associated with discontinuing SSRIs, temporary withdrawal of therapy is not a practical option in most cases and should not be attempted without medical consultation. Instead, a multidisciplinary approach involving coordination with psychiatrists and medical practitioners, combined with careful surgical planning and stringent follow-up, represents the most effective strategy to optimize outcomes for patients receiving SSRIs.

SSRIs are indispensable agents in psychiatry, but they present clinically relevant risks for implant dentistry due to their effects on bone remodelling and peri-implant health. By reducing osteoblast proliferation, altering osteoclast differentiation, delaying mineralization, and heightening inflammatory responses, SSRIs increase the probability of implant failure, particularly with long-term use or concurrent medications that further impair skeletal physiology. Careful patient selection, individualized treatment protocols, and meticulous long-term monitoring are essential to mitigate these risks and improve implant success rates in this vulnerable patient population.

V) Proton pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) are among the most widely prescribed medications globally, used predominantly for the management of gastroesophageal reflux disease, peptic ulcer disease, and other acid-related gastrointestinal disorders. Their mechanism of action involves the irreversible inhibition of the H+, K+-ATPase enzyme within gastric parietal cells, which leads to profound suppression of gastric acid secretion. While this pharmacological effect is highly beneficial in protecting the upper gastrointestinal tract, increasing evidence has raised concerns regarding the unintended systemic consequences of long-term PPI use, particularly with respect to bone metabolism and the potential impact on dental implant therapy.

The suppression of gastric acid secretion has a direct bearing on mineral absorption, most notably calcium. Adequate gastric acidity is essential for the solubilization and intestinal absorption of calcium salts, which play a fundamental role in bone mineralization and skeletal homeostasis. Prolonged PPI use leads to hypochlorhydria, which compromises calcium absorption, and may also impair the uptake of other essential nutrients such as vitamin B12, iron, and magnesium [42]. These deficiencies contribute cumulatively to reduced bone mineral density, impaired bone strength, and an increased risk of osteoporotic fractures, particularly among elderly and postmenopausal populations [41, 44]. The clinical implications extend to dental implants, where sufficient bone quality and density are critical for primary stability and long-term osseointegration.

Journal of Chemical Health Risks
www.jchr.org
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Beyond effects on nutrient absorption, PPIs may also act more directly on bone cells. Osteoclasts, which mediate bone resorption, rely on proton pumps similar to those found in gastric parietal cells. Mizunashi et al. demonstrated that omeprazole can inhibit osteoclastic proton pumps, thereby reducing bone resorptive activity [43]. Although this might suggest a protective effect against bone loss, physiological bone remodelling requires a balance between osteoclast-mediated resorption and osteoblast-driven bone formation. Disruption of this balance through chronic inhibition of osteoclast function may impair the bone's capacity to remodel and adapt to mechanical stresses, an essential requirement during the osseointegration phase of implant healing. In this context, reduced remodelling may paradoxically compromise peri-implant bone turnover, leading to delayed integration and potential implant failure.

Clinical studies have increasingly documented associations between systemic PPI use and dental implant outcomes. Chrcanovic et al. in a large cohort analysis, reported a significant increase in dental implant failure rates among patients using PPIs compared with non-users [16]. This finding has been supported by retrospective clinical investigations, such as those by Altay et al. and Masri et al. both of which demonstrated elevated risks of early implant failure in chronic PPI users [45, 46]. These consistent reports indicate that PPI therapy can negatively influence the biological processes required for osseointegration, reducing implant survival in susceptible patients.

Experimental studies have provided further mechanistic insight into these clinical outcomes. Tekin et al. explored the biomechanical and biochemical effects of systemic omeprazole administration on titanium implants in animal models, showing that PPIs significantly reduced bone-to-implant contact and bone mineralization in the peri-implant region [47]. These findings confirm that PPI exposure adversely affects both the biological environment and the mechanical integration of implants, thereby explaining the increased failure rates observed clinically. Collectively, this evidence highlights that PPI-induced alterations in bone metabolism are not only theoretical but have tangible consequences for implant stability and success.

Several interrelated mechanisms explain why PPIs compromise implant outcomes. The foremost is impaired calcium absorption secondary to chronic gastric acid suppression, which reduces mineral availability for bone deposition [42]. In addition, inhibition of osteoclastic proton pumps disrupts bone remodelling dynamics, while secondary nutrient deficiencies, such as hypomagnesemia and vitamin B12 deficiency, further weaken skeletal health and impair healing capacity [43, 44]. These mechanisms act synergistically, compromising bone turnover and the ability of peri-implant bone to adapt under functional loading, thereby reducing the likelihood of long-term implant survival.

Given these risks, the management of patients undergoing dental implant therapy while on long-term PPI treatment requires careful risk stratification and clinical planning. Prior to implant placement, a thorough evaluation of systemic bone health is essential, including bone mineral density testing and biochemical assessment of calcium, vitamin D, and magnesium levels. Identification of deficiencies allows for preoperative optimization, which may involve supplementation, dietary counselling, or coordination with the patient's physician to address underlying metabolic imbalances. In terms of surgical management, minimally invasive techniques that maximize primary stability and bone-to-implant contact are particularly important in PPI users, where osseointegration may be delayed. Rigorous postoperative monitoring is equally vital, allowing for the early detection of compromised healing or marginal bone loss, both of which are more likely in this population.

While discontinuation of PPI therapy has been suggested as a potential mitigating measure, this approach must be undertaken cautiously and in consultation with the patient's treating physician, as abrupt cessation can exacerbate gastrointestinal symptoms and undermine treatment compliance. In many cases, reduction of PPI dose or the use of alternative therapies may be a more realistic approach. However, given the widespread use of PPIs and their potential to impair implant success, their presence in a patient's medication history should always trigger a more cautious, individualized approach to treatment planning.

While PPIs remain invaluable for the management of acid-related gastrointestinal disorders, their long-term

Journal of Chemical Health Risks
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use is associated with adverse effects on bone metabolism, which have significant implications for dental implant therapy. Impaired calcium absorption, altered osteoclast function, and secondary nutrient deficiencies contribute to compromised osseointegration and increased implant failure rates, as confirmed by both clinical and experimental studies [45, 46, 47]. Careful preoperative evaluation, surgical precision, postoperative monitoring, and interdisciplinary collaboration remain essential in mitigating these risks and ensuring favourable implant outcomes in patients reliant on chronic PPI therapy.

VI) Chemotherapy

Chemotherapy, widely recognized as a cornerstone in the treatment of malignant diseases, is designed to inhibit tumor growth by targeting rapidly dividing cells. While this therapeutic approach is highly effective in reducing tumor burden, its cytotoxicity extends beyond malignant tissues and affects normal proliferative cells, including those in the oral mucosa, bone marrow, and bone-forming osteogenic cells. As a result, chemotherapy has far-reaching implications on bone physiology, wound healing, and osseointegration, all of which are essential for the long-term stability of dental implants.

The mechanisms by which chemotherapeutic agents influence bone metabolism are closely related to their mode of action. These agents interfere with DNA replication, mitotic spindle formation, and cellular proliferation, and although the primary intent is to inhibit tumor growth, osteoblasts and osteoclasts, due to their relatively high turnover, are inadvertently affected. In vitro studies have confirmed that drugs such as methotrexate, cisplatin, and 5-fluorouracil reduce osteoblast proliferation, inhibit differentiation, and impair mineralization [49]. The balance between osteoblastic bone formation and osteoclastic resorption is thus disrupted, leading to compromised bone quality. Beyond direct cellular effects, chemotherapy induces systemic alterations that further impair tissue repair. Myelosuppression is a frequent consequence, leading to leukopenia and thrombocytopenia, which increases susceptibility to infection and delays healing. Furthermore, mucosal toxicity, manifesting clinically as oral mucositis, predisposes patients to peri-implant inflammation and secondary infection, creating an unfavourable environment for successful osseointegration [55].

Clinical evidence mirrors these mechanistic insights. Retrospective studies and case reports consistently suggest that chemotherapy is associated with an increased risk of early implant failure compared with non-exposed individuals. Cobo-Vázquez et al. demonstrated that while dental implants placed in chemotherapy patients exhibited a slightly higher rate of early complications, overall survival remained acceptable when surgical timing and infection control were optimized [48]. Historical reports by Steiner et al. and McDonald et al. similarly documented cases of delayed osseointegration and peri-implant complications during or shortly after chemotherapy [50, 51]. These findings were further corroborated by Kovács, who studied implant survival in oral cancer patients undergoing chemotherapeutic treatment [52, 53]. The results highlighted that implants placed prior to chemotherapy cycles had significantly better outcomes, whereas those placed during active cytotoxic therapy showed higher failure rates. Such data reinforce the importance of proper scheduling and underline that timing relative to oncologic therapy is critical in determining long-term implant success.

The systemic effects of chemotherapy on bone healing are not limited to dentistry but extend to other surgical contexts as well. Orthopaedic literature has provided important corroborative evidence. Avedian et al. studying tumor endoprostheses, reported that chemotherapy impaired the initial compressive osseointegration of orthopaedic implants, further validating that cytotoxic therapy broadly compromises osseointegration capacity across skeletal sites [54]. This consistency across specialties underscores that the negative impact of chemotherapy on bone healing is a generalized phenomenon rather than a localized dental concern.

In clinical practice, therefore, the timing of implant placement in relation to chemotherapy emerges as one of the most critical determinants of success. Implants are best placed during periods of hematologic stability and mucosal integrity, typically after the completion of chemotherapy cycles and recovery of blood counts. Proceeding with elective implant placement during active cytotoxic therapy or in the immediate post-cycle

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 2725-2740 | ISSN:2251-6727

phase carries substantial risks of infection, delayed healing, and early implant loss. Preoperative work-up should always include a haematological assessment to ensure adequate white cell and platelet levels, as well as imaging to evaluate bone density and quality, which may be compromised after systemic treatment.

Another consideration relates to long-term oncologic management. Patients who have completed chemotherapy remain at risk of cancer recurrence, which could necessitate further chemotherapy or adjunctive radiotherapy, both of which may indirectly compromise the health of existing implants. Wood B et al has emphasized the importance of close interdisciplinary collaboration in such cases, where dental surgeons, oncologists, and primary physicians jointly determine the appropriate timing for implant therapy and plan for contingencies in the event of disease relapse or further cytotoxic exposure [56].

To mitigate risks and improve outcomes in patients with a history of chemotherapy, several strategies have been recommended. Surgical timing is paramount, with delay until after haematological recovery serving as the most effective preventive measure. Assessment of bone density and structure helps guide implant selection and may indicate the need for adjunctive grafting techniques in cases of compromised bone. Employing atraumatic surgical techniques minimizes soft and hard tissue trauma, reduces healing burden, and lowers infection risk. Stringent infection control, both pre- and postoperatively, remains critical given the immunosuppressed state of many chemotherapy patients. Prophylactic antibiotics, when appropriately indicated, and meticulous oral hygiene further safeguard against peri-implant infection. Multidisciplinary care is essential, with dental professionals liaising closely with oncologists to fully understand the patient's chemotherapeutic regimen, anticipated side effects, and systemic status during the perioperative period [55, 56].

While chemotherapy presents undeniable challenges to implant therapy, it does not preclude successful rehabilitation. With appropriate patient selection, careful timing, rigorous infection control, and collaboration across specialties, implant survival rates can remain high, even in this medically compromised population. However, the cumulative evidence strongly supports a cautious and individualized approach, as outcomes are heavily influenced by treatment schedules, systemic health, and the quality of perioperative care.

VII) Antihypertensives

The relationship between antihypertensive therapy and bone physiology has been highlighted in multiple studies, with evidence suggesting that certain classes of antihypertensives may exert either protective or detrimental effects on skeletal health. Angiotensin II, a central component of the renin–angiotensin system (RAS), has been shown to accelerate osteoporosis by stimulating osteoclast activity and enhancing bone resorption [63]. This finding has provided a rationale for the use of RAS inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which have been demonstrated to reduce osteoclast activation and preserve bone mass. Clinical studies further support this protective role, as patients on RAS inhibitors have shown improved bone mineral density (BMD) and reduced fracture risk [61, 62].

In contrast, thiazide diuretics exert a direct anabolic effect on bone metabolism by stimulating osteoblast differentiation and promoting mineralized nodule formation, thereby enhancing bone formation and potentially improving osseointegration [64]. Beta-blockers have also been associated with skeletal benefits, as they reduce sympathetic nervous system activity, which in turn decreases bone resorption. These systemic effects suggest that antihypertensive drugs may influence not only cardiovascular outcomes but also bone physiology, thereby exerting an indirect impact on dental implant survival and stability.

Several retrospective and cohort studies have evaluated the clinical outcomes of dental implants in patients receiving antihypertensive therapy. Wu et al. reported that patients on antihypertensive medications demonstrated comparable or even improved survival rates of osseointegrated implants relative to non-medicated controls, indicating a possible protective effect [66]. Similarly, Rawen Tonini et al. observed high long-term success rates of implants placed in hypertensive patients under medication, reinforcing the notion that implant therapy in this population is safe and effective [67]. More recently, Masri et al. conducted a large retrospective cohort study and found that while

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(6), 2725-2740 | ISSN:2251-6727

systemic hypertension itself was not a contraindication for implant therapy, early healing dynamics varied depending on the class of antihypertensive used [57]. This highlights that the pharmacological diversity within antihypertensive therapy may explain differences in implant outcomes across studies.

The role of specific drug classes has been further clarified by mechanistic and clinical studies. Saravi et al. demonstrated that patients on RAS inhibitors and beta-blockers exhibited favourable implant stability, suggesting enhanced osseointegration [58]. The skeletal protective effects of RAS inhibition combined with the bone-preserving properties of beta-blockers through sympathetic modulation provide a plausible explanation for these findings. However, Corbella et al. in a larger retrospective study, found mixed outcomes, reporting no significant association between antihypertensive use and implant loss, while emphasizing the importance of stratified analysis by drug class [37].

Beyond implant survival, long-term success is also determined by peri-implant bone maintenance. Carlos et al. reported that marginal bone loss around implants correlated with systemic conditions such as hypertension and its pharmacological management, indicating that antihypertensive therapy could indirectly modulate peri-implant bone health [60]. Seki et al. evaluated clinical parameters of anodized implants in patients on antihypertensives and found no significant detrimental effects, supporting the clinical safety of these medications [59]. These findings collectively suggest that systemic disease status plays an important role in peri-implant bone outcomes, but antihypertensive therapy itself may not be harmful and in some cases may provide protective benefits.

The mechanistic basis for these observations lies in the diverse actions of antihypertensive drugs. ACE inhibitors and ARBs mitigate osteoclast activation by blocking the effects of angiotensin II, thereby preserving bone mass [63]. Beta-blockers decrease sympathetic signalling in bone, reducing resorptive activity, while thiazide diuretics promote osteoblast-driven bone formation and mineral deposition [64]. Calcium channel blockers, on the other hand, have shown less consistent evidence, with some reports indicating neutral or mildly beneficial effects. This pharmacological diversity explains the variability in clinical outcomes, with some studies showing protective effects on implant stability while others report neutral findings.

From a clinical perspective, the current body of literature suggests several important implications. Hypertension itself is not a contraindication for dental implant therapy, and patients on antihypertensive therapy can achieve outcomes comparable to or even superior to those of non-medicated individuals. Certain drug classes, particularly RAS inhibitors, beta-blockers, and thiazide diuretics, may exert beneficial skeletal effects that enhance osseointegration and long-term implant survival. The risk of implant failure does not appear to be significantly elevated in patients taking antihypertensives, though systemic factors such as patient age, comorbidities including diabetes or osteoporosis, and concurrent medications must be carefully considered. Long-term success rates remain high, reinforcing the clinical feasibility of implant therapy in this population [66, 67].

Overall, the evidence suggests that antihypertensive drugs, while prescribed primarily for cardiovascular management, may also have meaningful implications for bone health and implant outcomes. Their role in modulating bone metabolism underscores the importance of interdisciplinary care, where both systemic disease management and implant planning are carefully integrated to optimize treatment success.

3. Conclusion

Dental implants are a predictable and successful option for oral rehabilitation, with survival rates exceeding 90% in healthy individuals. However, the widespread use of systemic medications presents emerging challenges that can compromise implant outcomes. Drugs such as NSAIDs, corticosteroids, bisphosphonates, SSRIs, PPIs, chemotherapeutic agents and antihypertensives can adversely affect bone metabolism, vascularity, immune response and soft tissue healing—all critical factors for osseointegration. NSAIDs may inhibit bone healing through COX-2 suppression, corticosteroids reduce osteoblastic function, bisphosphonates impair bone turnover and healing, SSRIs alter serotonin-mediated bone remodelling, PPIs interfere with calcium absorption, chemotherapeutic drugs damage osteogenic tissues and antihypertensives can influence bone turnover. These findings emphasize the importance of

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2725-2740 | ISSN:2251-6727

comprehensive preoperative assessment and individualized treatment planning.

Preventive strategies include thorough evaluation of the patient's medical and drug history, consultation with the physician to adjust high-risk medications when possible and adoption of minimally invasive surgical techniques with extended healing time in susceptible patients. Regular follow-up with radiographic and clinical monitoring is essential for early detection of complications and long-term maintenance of peri-implant health. Maintaining good oral hygiene, ensuring adequate bone quality and controlling systemic conditions enhance implant success.

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