

The Influence of Systemic Medications on Osseointegration of Dental Implants

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Abstract



Dental implants are routinely used to treat edentulism. Their success depends on osseointegration, the direct functional and structural interlocking of implant and bone. The osseointegration mechanism is similar to bone remodeling and healing. Thus, chronic use of systemic medications that can interfere with bone turnover and healing may affect osseointegration, resulting in premature implant loss. The aim of this narrative review is to analyze the reported effects of systemic medications on osseointegration.

Dental implants have been used to treat, routinely and predictably, partial and complete edentulism in dentistry for the last 30 years. The clinical success of dental implants depends on osseointegration, defined by Brånemark as “a direct connection between living bone and a load-carrying endosseous implant at the light microscope level.”¹ The success rate for dental implants is high, with routine reports of 90–95% success. Clinical research into implant dentistry has identified peri-surgical acute infections, surgeon inexperience, lack of initial implant instability, lack of patient compliance, uncontrolled parafunction, smoking, poor oral hygiene, uncontrolled diabetes² and head and neck radiation as factors contributing to failed osseointegration.^{3–8} However, there are relatively few absolute contraindications to implant therapy; they are recent myocardial infarction and cerebrovascular accident, valvular prosthesis surgery, immunosuppression, uncontrolled bleeding issues, active treatment of malignancy, drug abuse, psychiatric illness and intravenous bisphosphonate use.³ Therefore, the vast majority of the population is considered medically eligible for implant therapy. A large proportion of the population suffering from chronic conditions are under medical management that includes long-term use of medications. Yet, relatively little is known about the effects of chronic medication use on the success of dental implants and osseointegration. Successful osseointegration of dental implants requires normal functioning of native biological activities that occur during bone remodeling, the dynamic process of bone resorption by osteoclasts and new bone formation by osteoblasts.⁹ Thus, any events that can alter bone repair and bone healing may, in turn, alter successful osseointegration and ultimately lead to premature implant loss or peri-implant complications. Although chronic use of multiple systemic medications can affect bone healing and repair, the potential effects of long-term prescription of such medications on osseointegration of dental implants have not been adequately investigated.

In this paper we review the literature on the influence of several agents on osseointegration, specifically, cyclosporine, glucocorticoids, alcohol, selective serotonin reuptake inhibitors, non-steroidal anti-inflammatory drugs, bisphosphonates and chemotherapeutic agents. These do not represent a comprehensive list of chronically prescribed medications. Rather they represent some of those most commonly used chronic medications with reported physiological, biological and pharmacological effects on bone metabolism that may affect the bone-to-implant interface and, thus, osseointegration.

Cyclosporine

Cyclosporine A (CsA) is an immunosuppressive drug prescribed to prevent transplant rejection and to treat immunologic diseases. Although the exact mechanism of action of CsA is unclear, it has been shown to have anti-anabolic effects on osteoblasts and to suppresses and inhibit the critical role of T-lymphocytes in bone remodeling.¹⁰ Animal studies have shown that CsA administration leads to high bone turnover, resulting in an imbalance between bone resorption and formation, leading to osteopenia and enhanced bone loss.^{11,12} Furthermore, several studies have reported that this agent may increase the incidence of bone fracture and may be associated with bone mineral loss.¹³⁻¹⁵

In relation to implants, several reports have demonstrated the negative effect of CsA on osseointegration. Sakakura and co-workers^{10,16} showed that long-term administration of CsA negatively influences bone healing around dental implants in rabbits. Durate et al.¹⁷ also showed increased bone remodeling and significant bone loss in rabbits that were exposed to CsA; the authors concluded that the administration of CsA may negatively influence bone healing around titanium implants. Sakakura and co-workers¹⁸ also investigated the effects of CsA on bone around successfully osseointegrated implants in rabbits. The authors noted that the administration of CsA in rabbits with previously integrated dental implants impaired mechanical retention.

There is a lack of clinical evidence of the effects of CsA on osseointegration of dental implants in humans. However, studies have shown that patients receiving CsA after transplant surgery may experience an increased incidence of osteoporosis.¹⁴ The exact mechanism of action of CsA around bone tissue is not clearly understood. It has been suggested that CsA-induced alteration of bone metabolism may be related to its immunosuppressive mechanisms mediated by cytokines.¹⁰ Patients undergoing CsA therapy may not be ideal candidates for implant therapy because of compromised general health. Further, considering the effects of CsA on bone

turnover, the use of this immunosuppressive agent before and during implant therapy must be carefully considered, as the prognosis of the implant-supported prosthesis is directly related to bone density around the implant.¹⁹

Glucocorticoids

Glucocorticoids are widely used to suppress inflammation in chronic diseases, such as asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune diseases.²⁰ Bone loss is one of the most common and debilitating side effects associated with prolonged high-dose glucocorticoid therapy, and this may negatively affect implant osseointegration.²¹ Studies have shown that glucocorticoids reduce bone formation and increase bone resorption,²² and several have reported a loss of osseointegration associated with their chronic use.^{23,24} Moreover, chronic use of glucocorticoids has been cited as an absolute contraindication²⁵ or relative contraindication in the placement of implants in the jaws.²⁶

However, we found conflicting evidence regarding the effects of glucocorticoids on osseointegration and implant healing. For instance, Bencharit et al.²⁷ demonstrated that once osseointegration has occurred, the long-term prognosis for the implant is favourable, despite the use of glucocorticoids. Using male rabbit tibia, Werner and co-workers²⁸ demonstrated no significant difference in osseointegration between a group that was injected with dexamethasone and the control group. Another study²⁶ examined the effects of steroid administration on the osseointegration of dental implants with the rabbit tibia and mandible. The authors reported that the "removal torque" of implants placed in the tibia was reduced with steroid administration, but this did not apply to implants placed in the mandible. They concluded that steroid administration might have less effect on osseointegration of titanium implants in the mandible than in the skeletal bone.

Glucocorticoids have deleterious effects on bone remodeling and turnover, as they promote osteoblast apoptosis and favour the differentiation of bone marrow cells into adipocytes.²¹ Together these changes lead to decreased bone formation, thus shifting the balance toward bone loss. Unfortunately, the exact effect of these changes in bone metabolism on successful long-term osseointegration of dental implants in humans has not been determined in high-quality clinical studies.

Alcohol

Alcohol is one of the most widely used drugs in the world, with reported rates of alcoholism as high as 10% in the North American population.²⁹ Alcohol is a central nervous system depressant with wide-ranging and detrimental

systemic effects.³⁰ It has been shown to affect the central nervous system, gastrointestinal tract, immune system, liver and cardiovascular system.³⁰ Alcohol also inhibits osteoclast activity, reduces bone quality and delays fracture repairs.^{31,32} Alcohol consumption is a risk factor for osteoporosis,³³ with reductions in cortical bone area and trabecular volume reported in alcoholic animal models.³⁴

A recent study³⁵ examining bone-to-implant contact as well as bone formation around titanium implants in rabbits that were fed an alcoholic diet found that alcoholic rabbits had significantly less bone density and reduced direct bone-to-implant contact.³⁵ De Deco et al.³² found similar results in a rat model system. In a retrospective study,³⁶ more than half of the patients lost their implants because of alcohol addiction. A matched case-control analysis³⁷ found that implant failures clustered in patients classified as heavy drinkers (more than 5 units a day) as opposed to light drinkers (less than 5 units a day) and those who denied alcohol consumption.

Although the exact mechanism by which alcohol alters bone metabolism is still unclear, it has been suggested that alcohol intake may alter the ongoing balance between erosion and remodeling of bone tissue.³⁸ Patients with routine and excessive alcohol consumption may be at higher risk of implant failure. These patients have been shown to display delayed healing following the induction of a surgical wound as a result of alcohol-induced deficiencies in the complement system (part of the immune system), suppression of T-lymphocytes and impairment in the mobility, adhesion and phagocytic capabilities of the innate immune system.³⁹

Selective Serotonin Reuptake Inhibitors

Depression, a globally prevalent disorder,⁴⁰ is a complex mental illness that is associated with significant disability and reduced quality of life. Low levels of serotonin have been implicated as the cause of depression,⁴¹ and, in the last 3 decades, selective serotonin reuptake inhibitors (SSRIs) have been used successfully to treat depression. SSRIs have many advantages, such as ease of dosing and low toxicity in overdose. Moreover, they have been widely used because their adverse-effect profile is less prominent than that of some other antidepressant agents. Also, in contrast with other antidepressants (e.g., tricyclic antidepressants and monoamine oxidase inhibitors), these agents do not appear to affect blood pressure or heart rate. SSRIs have been recommended as first-line antidepressant medications and this recommendation is supported by the 2011 American Psychiatric Association (APA) guidelines.⁴²⁻⁴⁶

Specifically, these drugs inhibit serotonin reuptake from the synaptic cleft into presynaptic nerve terminals, thereby increasing the concentration of serotonin in the synaptic

cleft and enhancing serotonin neurotransmission.⁴⁷ The association between depression, bone loss and bone disease is well documented.⁴⁸ Depression has been linked to low bone mass, and SSRIs have been linked to falls, bone loss and fractures.⁴⁹ A recent meta-analysis found SSRI use to be associated with a significantly greater risk of fractures.⁵⁰ Moreover, SSRIs, but not tricyclic antidepressants, another widely used medication for the treatment of depression, were associated with lower bone mineral density.⁵¹ It has been suggested that serotonin receptors found in osteocytes, osteoblasts and osteoclasts can be activated by SSRIs and, thus, alter their function.⁴⁴

Taking all these factors into consideration, Wu et al.⁵² postulated that treatment with SSRIs may have a negative effect on dental implant osseointegration. In a retrospective cohort study of 916 implants in 490 patients, their data demonstrate that treatment with SSRIs was associated with an increased risk of failure of osseointegrated implants. The authors propose that the main factor contributing to implant failure was problems with mechanical loading of the implants. They add that this was, in part, a result of the fact that serotonin played an important role in the anabolic response of bone to mechanical loading and conclude that SSRIs may cause bone loss by inhibiting the bone-remodeling processes triggered by mechanical loading.⁵² Based on their results, the authors propose careful surgical treatment planning for patients taking SSRIs.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory and analgesic properties and, thus, are commonly prescribed in the dental setting. This group of drugs is also routinely used by many patients for the management of chronic inflammatory conditions, such as arthritis. A number of NSAIDs, including ibuprofen, naproxen, flurbiprofen, diflunisal and ketorolac, have been shown to be effective for dental pain. These agents are also routinely prescribed as analgesics and anti-inflammatory agents following dental implant surgery.

The mechanism of action of NSAIDs is well known and has been associated with the enzyme cyclooxygenase (COX). Specifically, NSAIDs prevent the conversion of arachidonic acid to prostaglandin. Prostaglandins play an important role in normal bone healing, osteoclastic activity, bone formation and angiogenesis.⁵³ However, conflicting information on the effect of these drugs on bone remodeling has been reported. For instance, several studies show that healing of bony fractures is delayed when NSAIDs are used.^{54,55} Also, Ribeiro and co-workers⁵⁶ reported a negative effect of meloxicam on the osseointegration of titanium implants in rats. They showed a reduction in the degree of bone-to-implant contact within both cortical and

cancellous bone. Meloxicam also negatively affects bone area and bone density when administered subcutaneously to male rats.⁵⁷ Similarly, in vivo studies on a male rat tibia model demonstrated that administration of 1.07 mg/kg of diclofenac twice daily for 5 days delayed peri-implant bone healing.⁵⁸ In addition, Chikazu et al.⁵⁹ examined the effect of COX-2 on bone healing after the placement of implants in the femurs of male wild-type (COX-2(+/+)) and knockout (COX-2(-/-)) mice. They concluded that minimal new bone was formed around the implants in the COX-2 knockout mice, proving that COX-2 is essential for proper osseointegration of dental implants.

With respect to humans, a randomized double-blind control trial demonstrated that oral administration of 600 mg of ibuprofen 4 times daily for 7 days had no significant effect on loss of bone level after 3 or 6 months.⁶⁰ A 2014 retrospective study⁶¹ examining the causes of osseointegration failure noted that disproportionately more failures occurred in the cohort of patients who received NSAID therapy during the period surrounding dental implant surgery. In addition, the NSAID-treated cohort experienced greater perio-implant bone loss and clustered implant failures.⁶¹ All in all, despite the lack of consensus in the literature, it may be advisable to avoid prescribing NSAIDs for the management of post-operative pain and edema immediately before or after implant placement.

Bisphosphonates

Bisphosphonates are antiresorptive agents that specifically inhibit osteoclast activity and are, therefore, commonly used to maintain bone density and strength.⁶² Oral bisphosphonates, which are more commonly prescribed than intravenous forms, are given to patients for the treatment of metabolic bone diseases, particularly osteopenia and osteoporosis.⁶³ Intravenous bisphosphonates are prescribed for patients with life-threatening hypercalcemia caused by multiple myeloma and breast and prostate cancer.⁶⁴

There is evidence of a relation between the use of systemic bisphosphonates and osteonecrosis of the jaw (ONJ), particularly in those receiving high intravenous doses, such as cancer patients.⁶⁵ The risk of bisphosphonate-induced ONJ has led to the recommendation that these patients not be subjected to any surgical procedures, including placement of dental implants.^{64,65}

However, we found conflicting evidence on the effects of bisphosphonates on osseointegration. For instance, Fugazzatto and co-workers⁶⁶ found that a history of oral bisphosphonates for 3 years did not lead to ONJ after implant placement. Similarly, in a parallel-group controlled trial involving patients who had undergone surgical placement of dental implants, Jeffcoat⁶⁷ concluded

that there was no significant difference between the incidence of ONJ among patients taking bisphosphonates and the control group. Also, Grant et al.⁶⁸ found no significant difference in treatment results between patients with and without oral bisphosphonates during implant treatment and no patients developed ONJ after implant treatment. Finally, after a systematic review, Madrid and Sanz⁶⁹ concluded that a patient receiving oral bisphosphonates for less than 5 years is "safe" to undergo dental procedures, specifically dental implants.

Several cases report bisphosphonate-induced ONJ following implant placement.⁷⁰⁻⁷⁴ For instance, Starck and Epker⁷⁰ describe a patient who had 5 implants placed in the lower incisor region followed by successful osseointegration; subsequent use of oral etidronate disodium for osteoporosis resulted in the displacement of all 5 implants after 5 months. Wang et al.⁷¹ reported the development of bisphosphonate-induced ONJ in a patient who had been taking oral bisphosphonates for over 10 years.

Recently, the American Association of Oral and Maxillofacial Surgeons released a position paper⁷⁵ advocating the use of the term medication-related ONJ instead of bisphosphonate-induced ONJ in light of evidence suggesting that other antiresorptive agents, such as antibodies against receptor activator of nuclear factor κ B ligand, as well as antiangiogenic medications can have effects similar to those of bisphosphonates. They concluded that the rate of medication-related ONJ in patients taking oral antiresorptive medications for more than 3 years can be as high 0.5% following dental extractions. The position paper does not comment on the risk of developing medication-related ONJ following placement of dental implants.

In summary, there are insufficient data to suggest that implant placement should be avoided in patients receiving bisphosphonates. Nonetheless, dental practitioners who place implants must be aware of the risk of treating patients who are under bisphosphonate therapy, oral or intravenous.

Chemotherapeutic Agents

Chemotherapy is the use of medications (cytostatic or cytotoxic agents) that prevent the proliferation of cancer cells and, ultimately, can cause their destruction.^{76,77} The main disadvantage of most chemotherapeutic agents and antineoplastic drugs is their lack of selectivity. In addition to targeting fast-growing cancer cells, these agents also act on normal cells that have an accelerated cell cycle, such as bone marrow cells, hair follicle cells and the epithelial cells of the gastrointestinal tract.⁷⁷ The detrimental effect of chemotherapy on bone has been suspected for many years,⁷⁸ and the chemotherapeu-

tic agents methotrexate and doxorubicin have been implicated in the delay of bone healing.⁷⁹ Moreover, chemotherapy is known to adversely affect patients' nutritional status, and there is evidence that poor nutrition can impair osseointegration and fracture healing.⁷⁸

Young et al.⁸⁰ examined the effects of chemotherapy on bone formation around femoral prostheses by administering cisplatin to dogs pre- or postoperatively: postoperative chemotherapy caused less bone formation, while preoperative chemotherapy did not alter the formation of new bone. With regard to dental implants, Kovacs⁸¹ demonstrated successful osseointegration and functional stability in patients with a history of chemotherapy when implants were inserted at least 6 months after therapy. Similarly, a retrospective study by the same investigator concluded that chemotherapy with cisplatin or carboplatin and 5-fluorouracil was not detrimental to the survival and success of dental implants in the mandible.⁸² Other case reports also show that chemotherapy appears to have no detrimental effects on implant osseointegration or survival.^{83,84} Thus, it seems that there is no substantial evidence in the literature to prevent a patient who has received chemotherapy from having a dental implant surgically placed in the mandible or maxilla. Nonetheless, chemotherapy is one of many anti-cancer therapies and, as other treatment modalities may cause detrimental effects in the oral cavity, these must be considered at the time of implant treatment planning.

Conclusion

Implants have been used in dentistry with much success in the last 3 decades. Optimal bone remodeling, repair and healing in the early stages of osseointegration are essential for the ultimate success of these devices. Many factors that affect bone healing may affect osseointegration and, thus, may contribute to implant failure. Several drugs have been shown to impede bone healing. We have described the effects of CsA, glucocorticoids, alcohol, SSRIs, NSAIDs, antiresorptives and chemotherapeutic agents on osseointegration. Although some studies clearly show direct effects on osseointegration and thus implant success, many of these are in vitro or animal studies and, thus, cannot be applied to humans. We, therefore, recommend that clinicians be aware of the potential issues outlined in this paper. Further human studies are needed.

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