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Effects of Medications on Dental Implant Failure: A Review

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ABSTRACT

Several studies have shown that some commonly prescribed drugs, including bisphosphonates (BP), proton pump inhibitors (PPI), selective serotonin reuptake inhibitors (SSRI), and non-steroidal anti-inflammatory drugs (NSAID), can affect peri-implant bone healing, remodeling, and osseointegration. In order to ensure successful osseointegration of dental implants, it is important to investigate the effects of systemic diseases and regularly used medications on osseointegration. Therefore, the aim of this review is to investigate the association between the intake of medications that may affect bone metabolism and implant outcomes.

Keywords: Anti-inflammatory drugs, Bisphosphonates, Drugs-related, Implant Failure, Proton Pump Inhibitors, Selective serotonin reuptake inhibitors

Abbreviations: PPI: Proton Pump Inhibitors; SSRI: Selective Serotonin Reuptake Inhibitors; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; BP: Bisphosphonates; HR: Hazard Ratio; CI: Confidence Interval; OR: Odds Ratio

INTRODUCTION

Human life expectancy has been increased by developments in technology and medical science. As a result of developments in technology and health, people's expectation of look younger, to eat better and their social welfare are increasing for all these reasons the tendency to implant surgeries has increased. Dental implants have been preferred for many years as they provide a predictable and effective solution for the treatment of total or partial edentulism by providing aesthetics, comfort, function and stability [1]. Dental implant treatment is a reliable choice and a long-term successful treatment for patients with complete or partial edentulism. Bone formation is extremely important for the osseointegration of dental implants because osseointegration is a physiological process similar to bone fracture healing and strongly influenced by bone metabolic activity [2,3].

OSSEOINTEGRATION

Osseointegration or osseointegration refers to a direct bone-to-metal union without the intervening of non-osseous tissue. This concept is defined by Branemark as “direct contact between living bone tissue and a titanium implant surface, observed with magnification at the light microscope level” [4].

To optimize the healing of a dental implant, peri-implant osteogenesis, uninterrupted and optimal bone healing in the early stages of the osseointegration process are crucial to the success of the dental implant. Many factors affecting osseointegration and peri-implant bone healing are well supported by scientific evidence. These include surgical technique, systemic health, and the quality and quantity of bone present. In particular, certain medical conditions and systemic medications can also affect the quality and quantity of bone present [5-8].

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The World Health Organization estimates that more than 350 million people worldwide suffer from depression [9]. Among the drugs commonly prescribed today are selective serotonin reuptake inhibitors (SSRIs). SSRIs are a class of drugs typically used as antidepressants in the treatment of major depressive and anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs), the most commonly used drugs in the treatment of depression, have been reported to reduce bone formation and increase the risk of bone fracture.

Studies have shown that antidepressant use predicts

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decreased bone mineral density in women, and both depression and antidepressant use have been suggested as possible risk factors for osteoporosis in men [10,11]. It shows that treatment with antidepressants is associated with an increased risk of failure of osseointegrated implants, especially in the case of dental implants[5,12].

In a study by Wu [13], it was shown that implant failure was increased in patients using SSRIs (hazard ratio: 6.28; 95% confidence interval: 1.25-31.61; p = .03). In addition, it should also be considered that the higher risk of implant failures may is influenced as well by the psychological condition of the patient rather than by the intake of SSRI [13].

Chrcanovic [5] in a retrospective study reported SSRI as associated with a 12.5% implant failure rate versus 3.3% in non-users. In this study, Kaplan-Meier survival analysis showed a significantly (P<.001) lower proportion of implants survived over time in SSRI users as compared to non-users. They also noted that SSRI use was higher in older age groups and in women. However, after adjusting for confounding variables in a multivariate model, no significant association between SSRI use and implant failure was found, and the authors concluded that SSRI intake did not affect implant failure [5].

A retrospective review by Carr [14], was conducted of all patients who received at least 1 dental implant from January 1, 1995, through December 31, 2014, assessing their history of SSRI use, active SSRI use, and SSRI use during follow-up with implant failure. During the study period, 5456 patients received their first implant (median age, 53 years). The median duration of follow-up was 5.3 years (interquartile range, 2.3-10.2 years) for the 4927 patients who did not have implant failure. For the 529 patients who had implant failure, it occurred at a median of 0.5 years. After adjusting for age, sex, and era of implant, history of use of the SSRI sertraline was associated with an increased risk of implant failure among all patients (hazard ratio [HR], 1.60; 95% CI, 1.15-2.23; p = 0.006) and among the subset of patients with a history of SSRI use (HR, 1.64; 95% CI, 1.07-2.52; p = 0.02). Active SSRI use was not significantly associated with implant failure for any of the SSRIs evaluated, whether the comparison group was all patients or SSRI users only. In this study, it shows that no significant association between SSRI use during follow-up and implant failure. In the population reviewed, a history of sertraline use was associated with a 60% greater risk of implant failure than patients with no history of sertraline use [14].

A retrospective cohort study by Altay [15] was conducted, including a total of 2055 Osseo integrated dental implants in 631 patients (109 implants in 36 SSRI \users and 1946 in 595 nonusers). The odds of implant failure were 3.123 times greater for SSRI users compared with nonusers. Patients using SSRIs were found to be 3.005 times more likely to experience early implant failure than nonusers. The results of this study suggested that SSRIs may lead to increase in the rate of osseointegration failure, although not reaching statistical significance [15].

Mujawar [16] conducted a 5-year retrospective study on 352 patients of both sexes with 680 dental implants. History of depression and SSRI medication was retrieved. Patients were divided into two groups. Group I (110 patients, 230 dental implants) patients were on SSRI, while group II (242 patients, 450 dental implants) patients were non-SSRI. They found that 24% implant failure was seen in patients >50 years of age and 7.2% <50 years of age in patients on SSRIs as compared with 7.4 and 3.5% on non-SSRI group respectively. This suggests that group I had higher implant failure rate, especially in patients above 50 years of age [16].

In a retrospective study by Chandra [17] consisted of 410 patients (720 dental implants). The study consists of two groups. Group I (SSRI users) consisted of 128 patients (245 dental implants) patients, whereas Group II (non-SSRI users) was formed by 282 patients (475 dental implants). In their study, patients on SSRI showed an implant failure rate of 12% compared to healthy individuals at 5.8%. When Groups I and II were compared for different parameters such as age, sex, and smoking, it was observed that the chances of implant failure were more in Group I [17].

Overall, after evaluating the included studies it can be concluded that patients taking the SSRI group of drugs for any neurological disorders had a higher chance of implant failures due to its adverse effect on peri-implant bone remodeling and metabolism.

BISPHOSPHONATES

Osteoporosis is a skeletal disorder characterized by reduction of the bone mass per unit of volume [18]. This condition is characterized by an increased susceptibility to bone fracture. Osteoporosis can be classified as either primary or secondary. Primary osteoporosis can affect both genders at all ages. It more frequently occurs after menopause in women or during late age in men. Secondary osteoporosis results from the use of medications, or from other conditions or diseases [18]. It is preventable through different modalities, including adequate calcium and vitamin D intake, physical activity, hormone replacement therapy, selective estrogen receptor modulators, and bisphosphonates [18-20].

Bisphosphonates (BP) inhibit osteoclast action and thereby bone resorption. It can be administered via oral or intravenous routes. According to the American Society of Clinical Oncology, the use of intravenous bisphosphonates for the reduction of bone pain, hypercalcemia of malignancy, and skeletal complications in patients with multiple myeloma, lung, breast and other cancers is the current standard of care [21-23]. Oral bisphosphonates are used to treat osteoporosis, Paget's disease, and osteogenesis imperfecta [24,25].

Evidence in the literature of an association between the use of systemic bisphosphonates and osteonecrosis of the jaw (ONJ) has led to the recommendation that these patients not undergo any surgical procedure, including placement of dental implants [26,27]. However, several reports have demonstrated successful implant placement in patients receiving BP [28-30]. The relationship between osteoporosis and dental implant failure also has been investigated by many authors [31-36].

Fugazzatto and co-workers found that a history of oral bisphosphonates for 3 years did not lead to ONJ after implant placement [28]. Similarly, in a parallel-group controlled trial involving patients who had undergone surgical placement of dental implants, Jeffcoat concluded that there was no significant difference between the incidence of ONJ among patients taking bisphosphonates and the control group [29]. Also, Grant et al. 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 [30]. Finally, after a systematic review, Madrid and Sanz concluded that a patient receiving oral bisphosphonates for less than 5 years is "safe" to undergo dental procedures, specifically dental implants [37].

Starck and Epker reported in a study that in a patient who placed 5 implants in the lower incisor region and subsequently had successful osseointegration, all 5 implants were replaced after 5 months of oral etidronate disodium for osteoporosis [38]. Wang [39] reported the development of bisphosphonate-induced ONJ in a patient who had been taking oral bisphosphonates for more than 10 years [39].

In an animal study conducted by Yu [40] on 21 rabbit models, it was observed that zoledronic acid may have a negative effect on the osseointegration of the dental implant in the short term, but this effect tends to decrease in the long term [40]. A case report published by Rawal [41] described a patient who underwent long-term oral BP therapy with spontaneous exfoliation of implant-supported bone for osteonecrosis [41].

In conclusion, there is insufficient data in the literature to recommend that implant placement should be avoided in patients receiving bisphosphonates. However, dentists should be aware of the risk of implant treatment in patients receiving oral or intravenous bisphosphonate therapy.

PROTON PUMP INHIBITORS

Proton pump inhibitors are effective in both the prevention and treatment of conditions such as peptic ulcer, gastroesophageal reflux disease, dyspepsia, helicobacter pylori infections, eosinophilic esophagitis, gastrinomas, and stress gastritis. Chemicals such as Omeprazole, Lansoprazole, Pantoprazole, Dexlansoprazole, Esomeprazole, Rabeprazole, which are widely prescribed worldwide, are from this drug group, and their use has increased considerably, especially in recent years and in elderly individuals. Millions of people use PPIs continuously or long-term [42,43].

PPIs suppress stomach acidity by inhibiting the functions of the proton pump (H+/K+ATPase), which can also be found in bones. Proton pump inhibition of osteoclasts can reduce their activity. Therefore, the relationship between PPI administration and bone metabolism has been accepted by the US Food and Drug Administration (FDA), and it is reported that PPIs reduce bone mineral density (BMD) by affecting calcium homeostasis and impairing calcium absorption. In addition, several observational studies have shown an association between PPI use and a higher risk of bone loss and bone fractures [44-46].

Despite the known adverse effects of PPIs on the skeleton, few studies have investigated the effect of these drugs in many important clinical situations involving bone, including osseointegrated dental implants [47-49].

Wu [50] conducted a study on the risks of PPI use to implant osseointegration. This retrospective cohort study included a total of 1,773 osseointegrated dental implants in 799 patients (133 implants in 58 PPIs users and 1,640 in 741 non-users). The failure rates were 6.8% for people using PPIs compared to 3.2% for non-users. Subjects using PPIs had a higher risk of dental implant failure (HR = 2.73; 95% CI = 1.10–6.78) compared to those who did not use the drugs [50].

In a retrospective study by Ursomanno [47], a total of 1,480 implants from 635 patients were used. Mean crestal bone loss of 1.60 mm was noted at implants from PPI patients, in contrast to 1.01 mm of crestal implant bone loss at implants from the non-PPI group (group difference = 0.59 mm, 58.40% increase, P = .024, CI [95%] = 0.08 to 1.09 mm). Greater crestal implant bone loss was associated with patients with a history of PPI medication use [47].

A retrospective cohort study by Altay [48] involving 1,918 dental implants in 592 patients (69 implants in 24 PPI users and 1,849 implants in 568 nonusers, respectively) was conducted. The odds of implant failure were 4.60 times greater among PPI users versus nonusers. Dental implants that were placed in patients using PPIs were found to be 4.30 times more likely to fail prior to loading [48].

In a study by Charcovic [51], a total of 3,559 implants were placed in 999 patients, with 178 implants were reported as failures. The implant failure rates were 12.0% (30/250) for PPI users and 4.5% (148/3,309) for nonusers. The intake of PPIs was shown to have a statistically significant negative effect for implant survival rate (HR 2.811; 95% CI: 1.139 to 6.937; P = .025) [51].

A retrospective cohort study by Rogoszinski [49] contained 933 implants placed in 284 patients. A total of 323 (32.6%) implants were placed in patients with ongoing PPI use. The use of PPI was observed to be insignificant after controlling

for confounding factors and was not an independent predictor of implant failure (odds ratio [OR], 0.801; 95% confidence interval [CI], 0.56-1.15; P = .24) or peri-implantitis (OR, 0.801; 95% CI, 0.56-1.15; P = .24) [49].

Based on the included retrospective studies, there seems to be an association between PPI and implant failure and theoretically may influence the success of a dental implant.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

NSAIDs exert their effects through inhibition of the cyclooxygenase (COX) enzyme, therefore they interfere with the synthesis of prostaglandins (PG) and thromboxanes; PGs and thromboxanes are inflammatory mediators responsible for pain [52].

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].

Altered PG levels as a result of COX inhibition may have an adverse effect on the role of PG in bone tissue, potentially causing a shift in progenitor cell movement towards bone resorption [56]. Marquez-Lara [57] highlighted the large variability regarding the effect of NSAIDs on bone healing and highlighted the lack of consensus on the effect of NSAIDs following orthopedic procedures [57].

The largest and long-term study analyzing failing osseointegration of 197 implants revealed that patients using NSAIDs peri-operatively experienced 44% implant failure, while 38% implant failure rate was occurred in patients, who did not take NSAID peri-operatively. Moreover, the NSAIDs cohort experienced 3.2 times more cases of radiographic bone loss >30% of the overall height and 1.9 times more cases of cluster failures [58]. Accordingly, it might be speculated that the intake of peri-operative NSAIDs may inhibit the inflammatory bone metabolism, especially in vulnerable populations while having minimal clinical effect in healthy patient populations [58].

In an animal study by Cai [59] in rabbits, a 7-day regimen of appropriate doses of diclofenac sodium and parecoxib did not adversely affect osseointegration of dental implants and bone healing in calvaria, neither short nor long term (12 weeks) [59].

Ribeiro and co-workers 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 [60]. Meloxicam also negatively affects bone area and bone density when administered subcutaneously to male rats [61].

Alissa [62] conducted a double-blinded randomized control trial with (human) patients receiving NSAIDs (ibuprofen) and placebos post implant placement for a 1 week duration [62]. The implants were submerged and undistributed for a three-to-six-month duration following which they were loaded with a prosthesis. This study radiographically measured marginal bone levels at 3 and 6 months (with respect to baseline at 2 weeks) and did not find any significant differences [62,63].

A similar non-randomized study was conducted by Sakka and Hanuneh [64] whereby patients were allocated to a NSAID (Ibuprofen) or non-NSAID group. Similarly, NSAID use were continued for 1 week [64]. Their study was similar to Alissa [62] where marginal bone levels were compared and no significant differences found at three-monthly and six-monthly intervals [62-64].

In conclusion, this review shows that there is insufficient evidence to draw conclusions about the effect of NSAIDs on dental implant osseointegration and bone healing due to the lack of consensus in the literature.

CONCLUSION

Based on the results from the present review, it was shown that proton pump inhibitors and selective serotonin reuptake inhibitors may be associated with implant failure. Due to the lack of consensus in the literature, there is insufficient evidence to draw conclusions about the effect of NSAIDs on dental implant osseointegration and bone healing and that implant placement should be avoided in patients receiving bisphosphonates. Therefore, the effect of these drugs as risk factors should be further investigated in future studies for implant outcomes.

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