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The Influence of Systemic Medicationson Osseointegration of Dental Implants – A Review

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ABSTRACT: This paper appraises current literature regarding the feasible effect of systemic medications on osseointegration of dental implants.In-vitro studies regarding the consequences of drugs on growth factors and bone generating cells have been conducted.It is concluded that some of these drugs have direct effect on osseointegration and some have negative influence on osseointegration of dental implant.

KEYWORDS: Implant, Osseointegration, Studies, Treatment, Mechanism

I. INTRODUCTION

Dental implants are accustomed treat customarily and inevitable partial and complete edentulism in dentistry over 3 decades .The clinical accomplishment of implant rely on osseointegration ,defined by Branemark as "a direct connection between living bone and a load-carrying Endosseous implant at the light microscope level."Clinical research in implantology has recognized peri-surgical acute infection ,clinician naive , paucity of initial implant vulnerability, paucity of patient's obedient , uncontrolled parafunction, smoking, poor oral hygiene, uncontrolled diabetes andhead and neck radiation as determinant provides fail in osseointegration.(1)

In devising for implant placement, it's foremost to meticulously analyze patients from a clinical and radiographic stand-point. There are supplemental elements, yet it might be accountable for clinician to become more experience in reviewing medical record , furthermost the medications, the patients are using for the treatment of systemic diseases. because the worldwide population expands and ages, many patients visit to dentist for routine treatment are on numerous medications for various conditions .Polypharmacy which is defined as concurrent use of multiple medications by the patients for one or more conditions.Patient who seek dentist are generally taking several medications a number of which can become hindrance with osseointegration of dental implants .This is substantially noteworthy within the elderly population. Therefore, cautious evaluation of medication use and comprehension of how vary medications influence osseointegration are inevitable for accomplishment of implant placement. (2)

In this paper we appraisal the literature on the influence of assorted drugs on osseointegration explicitly on cyclosporine, glucocorticords, alcohol, selective serotonin inhibitors, non-steroidal anti-inflammatory drug , bisphosphonates, proton pump inhibitors, anti- hypertensive and chemotherapeutic agents .These don't constitute a broad catalog of chronically prescribed medications but preferably they represents those most often used chronic medications with reported physiological,biological and pharmacological outcome on bone metabolism that will influence the bone-to-implant interface and consequently osseointegration (1)

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TABLE 1:

CYCLOSPORINE:		
STUDIES	MECHANISM	TREATMENT
Movsowitz and El Hadary et.al.,[3,4] have shown that CsA regime accelerates the bone turn-over , contributing to an variation in bone resorption and formation resulting in osteopenia and increase bone . In relation to implants, several reports have shown that the negative effect of CsA on osseointegration. Sakakura and coworkers [5] manifested that long term administration of CsA negatively impact the bone healing around dental implants in rabbits. Durate.et.al[6] also showed improved bone remodeling and specified bone loss in rabbits that are exposed to CsA: the authors concluded that administration of CsA may negatively influence the bone healing around titanium implants,contrarily a preclinical study and a clinical study reveals that the use of cyclosporine A did not adversely influence the process of osseointegration but studies have shown that patients receiving CsA after transplant surgery may encounter with increased occurrence of osteoporosis.	This drug has a mechanism of action that is based on the deterrent of calcineurin formation which is an intracellular protein that take part in the initiation of differentiation and proliferation of T-lymphocytes, but the use of cyclosporine A is also been related to the depletion of expression of protein associated with the formation and maturation of bone tissue, depletion of Vitamin-D quantity, depletion of osteoblastic differentiation and activity and rise in number of osteoclast[7]. Cyclosporine A have as an mechanism of action the repression of calcineurin pathway due to specify blockage of nuclear factor of activated T-Cells (NFAT) that is an active transcriptional complexes in the nucleus which is crucial for driving osteoblast differentiation due to the final expression of the osterix G .	Solid organ transplantation is the alternative method for the treatment of fatal disease that can lead to demise of the host .To successfully transplant organ, particular impediment of the immune system is requisited to avoid rejection of the transplanted organ. Patients undergoing CsA therapy may not be perfect candidate for implant therapy because of compromised general health. Further considering the consequence of CsA on bone turn-over the utilization of this immunosuppressive agents before and through implant therapy must be diligently consider , because the prognosis of the implant – supported prosthesis is directly associated to bone density around the implant (1).

It is concluded that use of cyclosporine A diminish the bone formation in critical –sized calvaria defects (CSD) filled with coagulum(COA) and retards the healing of CSD filled with deprotenized bovine bone (DBB) and hydroxyapatite /beta phosphate tricalcium (TCP) and this effect may be associated with reduced expression levels of the proteins related to bone Turn-over [7].

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TABLE 2:

GLUCOCORTICOID:		
STUDIES	EFFECTS	TREATMENT
Bencharit.et.al.(8) substantiated that once osseointegration as happened; the long term prognosis for the implant is successful, despite the use of glucocorticoids. Using male rabbit tibia, Werner and co-workers (9)substantiated has no remarkable change in osseointegration between a group that was injected with dexamethasone and the control group. • Fujimoto et al (10) analyzes the effects of steroid administration on the osseointegration of dental implants with the rabbit tibia and mandible. The authors described 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 may need less effect on osseointegration of titanium implants within the mandible than within the skeletal bone.	Glucocorticoids have detrimental effects on bone remodeling and turnover, as they stimulate osteoblast apoptosis and favor the differentiation of bone marrow cells into adipocytes.Together these differences result in decreased bone formation, consequently alter the balance toward bone loss. Unfortunately, the precise effect of those changes in bone metabolism on successful long-term osseointegration of dental implants in humans has not been determined in high-quality clinical studies. (1)	Glucocorticoids are broadly used to repress inflammation in chronic diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune condition [(1)], like systemic lupus erythematous (SLE) and organ transplantation [(11)]. This occurs due to imbalance in osteoclast and osteoblast function in the commencing phase of glucocorticoid administration. When the patient has given glucocorticoid for longtime, impaired bone modeling is chiefly a consequence of impaired osteoblastogenesis. [(11)]

TABLE 3:

SELECTIVE SEROTONIN INHIBITORS:		
STUDIES	MECHANISM	TREATMENT
Wu et al [(12)] conducted a retrospective cohort study on patients treated with dental implants. The result exhibited that treatment with SSRIs is related with a rise in failure risk of osseointegrated implants. In bone metabolism, SSRI's obstruct serotonin transporters (5-HTTs) on bone cells, producing in a direct negative effect on bone formation and metabolism by surging osteoclast differentiations and	Precisely, these drugs inhibit serotonin reuptake from the synaptic cleft into presynaptic nerve terminals, surging the concentration of serotonin in the synaptic cleft and improving serotonin neurotransmission. The association between depression,	SSRIs are among the most commonly prescribed drugs that are used to treat major depressive disorder and several other psychiatric conditions, including Post Traumatic Stress disorder(PTSD) ; generalized anxiety disorder; panic disorder; premenstrual dysphoric disorder; and some non-psychiatric conditions, such as chronic pain, fibromyalgia, and postmenopausal vasomotor symptoms [(14)]

impeding osteoblast proliferation. As a result, SSRI's decrease bone mass and bone mineral density at an annual reduction rate of 0.60–0.93% surging the risk of osteoporosis.	bone loss and bone disease is well documented.[1].SSRI's have been reported to decrease bone formation and increase the risk of bone fractures [13]. Moreover, SSRIs, but not tricyclic antidepressants, another broadly used medication for the treatment of depression, were related with lower bone mineral density. It has been recommended that serotonin receptors found in osteocytes, osteoblasts and osteoclasts can be activated by SSRI's and, thus, alter their function [1].	SSRI have been used successfully to treat depression. SSRI's have many advantages, such as ease of dosing and safe drug. rate. [1]

The key stone leading to implant failure was problems with mechanical loading of the implants. They emphasize that it was, in part, consequence of the fact that serotonin played a significant role in the anabolic response of bone to mechanical loading and culminate that SSRIs may lead to bone loss by impede the bone-remodeling processes accelerated by mechanical loading. Based on their outcome, the authors propose careful surgical treatment planning for patients taking SSRIs [1].

TABLE 4:

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
STUDIES	MECHANISM	TREATMENT
Ribera and co-workers [15] proclaimed a negative effect of meloxicam on the osseointegration of titanium implants in rats. They exhibited depletion in the degree of bone-to-implant contact within both cortical and cancellous bone. In addition, Chikazuet.al [16] 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 culminated that minimal new bone was formed around the implants in the COX-2 knockout mice, proving that COX-2 is necessary for proper osseointegration of dental implants. 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	There are three isoforms of cyclooxygenase: COX-1, COX- 2, and COX-3. COX-2 is crucial for differentiation of mesenchymal stem cells into osteoblasts and also work as a main source of PGE2 that trigger osteoblast to increase bone formation, bone mass, and strength. NSAIDs and COX-2	Non-steroidal anti-inflammatory drugs have anti-inflammatory and analgesic properties and they are often prescribed in dentistry. This group of drug is constantly used by many patients for the management of chronic inflammatory condition such as arthritis [1], also for coexisting cardiovascular diseases and muscular disorder [17]. The foremost biologic influence of these anti-inflammatory drugs is the repression of cyclooxygenase enzymes that is reliable to make Prostaglandins products [17]. Prostaglandins play an important role in normal bone healing and orthoclastic activity, bone formation and angiogenesis [1].

pain and edema immediately before or after implant placement[1].	inhibitors directly affect the bone healing process via repression of the COX-2 enzyme, which will decrease the amount of Prostaglandins, differentiation and activation of osteoblast in the early phases of bone healing [17].	

Further randomized clinical trials with longer follow-up period are required since it remains unclear in what potency the exposure to these medications is harmful to dental implant osseointegration. The current literature reviews indicate that NSAIDs in concrescence with implant placement in long term gives a greater risk for implant loss. Examining the available studies, we concluded that dental implants are safe and foreseeable procedures for rehabilitation in patients under NSAIDs .Short period does not differ from the survival rate in healthy patients not using NSAIDs or using placebo [18].

TABLE 5:

BISPHOSPHANATES:		
STUDIES	MECHANISM	TREATMENT
Tardast.et.al.[19] Discovered that patients who previously developed BRONJ where on corticosteroid therapy have decreased rate of healing than patient who does not use corticosteroid .Post-operative care is the key factor as mentioned in an article published by Freiberger.et.al[20] Stipulated that hyperbaric oxygen therapy gained patients with highest tissue healing rate. Ruggiero.et.al.[21] proposed that implant placement should be ignored in patients who are on intravenous bisphophonates therapy or treatment for cancer.	These compounds are equivalent of naturally-occurring inorganic pyrophosphonate in which the oxygen atom is taken by a carbon atom. When bone resorption occurs, bisphosphonates are released from the hydroxyapatite crystal and are taken up by osteoclasts. Bisphosphonates also Because bone resorption is combined to osteoblastic bone formation for remodeling, bone turnover (i.e., resorption and deposition) becomes crucially repressed .Still, the bone continues to mineralize and could become fragile and less pliant [22].	Bisphosphonates are a group of drugs used for the treatment of metabolic bone diseases, including osteoporosis, Paget's disease and other conditions like tumor-associated osteolysis and hypercalcemia. Although bisphosphonates substantially improved the standard of life of patients, there is a possibility that bisphosphonates related osteonecrosis of the jaw (BRONJ) may occur. Risk factors promoting BRONG are periodontal surgery, implant placement, tooth extraction, mechanical trauma of jaw bone .And also, systemic diseases , consumptions of other medications ,smoking and alcohol have great incidence on bisphosphonates related osteonecrois.

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In conclusion, forethought of implantation procedure with good and post-operative method as important [23]. There are inadequate data to indicate that implant placement should be refrained in patients receiving bisphosphonates. However, dentist who place implant ought to be knowledgeable about the risk of healing patients who are taking bisphosphonates either oral or intravenous [1].

TABLE 6:

PROTON PUMP INHIBITOR		
STUDIES	EFFECTS	TREATMENT
Chrcanovicet.al[24]there is no dissociation of success rate , based on variable factor such as age , gender, use of other medications such as NSAID's, antibiotics , parafunctional habits such as bruxism , implant length, diameter , position quality of bone , bone augmentation and lifestyle changes such as smoking and type of prosthesis . Because of this methodological constraint, the outcome of the study is mysterious to expound and apply clinically	The detrimental effects of PPIs on bone metabolism are interpreted through many possible mechanisms. PPI induced hypochlorhydria gives rise to the malabsorption of calcium in the small intestine The prolonged use of PPIs may impede collagen cross-linking and weaken the bone structure by creating an increase in homocysteine concentration and parathyroid hormone levels [25]. Although detrimental effects of PPI on bone have been widely studied, the detrimental consequence on bone related clinical conditions such as osseointegration of dental implants has been hardly studied[26].	Proton Pump Inhibitor(PPI) have been broadly used in gastroenterology for the treatment of several disorders like gastro-esophageal reflex disease(GERD) , peptic ulcer , dyspepsia , Helicobacter Pylori infections ,stress gastritis and eosinophilic esophagitis . PPI unalterably impede the proton pump in the acid secreting parietal cells of the stomach and repress the gastric acidity [25]. These days, there is noticeable increase in the usage of PPI; many individuals are using PPI as continuous or long term therapy[26]

TABLE 7:

ANTI-HYPERTENSIVE:		
STUDIES	DRUGS	TREATMENT
Van Steenbergheet.al[27], showed that, the implant survival rate was remarkably higher	Beta –blockers: Apart from their cardiovascular outcome, beta-blockers inhibit the beta-2 receptors responsible for bone resorption	Hypertension may be a long-term medical condition during which the blood pressure within the arteries is increased. Antihypertensive medications, such as beta-blockers, thiazide diuretics, angiotensin-converting-enzyme (ACE)

when patients were under antihypertensive medication. It demonstrated that treatment with antihypertensive drugs may be correlated with an increased survival rate of osseointegrated implants.	producing in increasing bone augmentation. So, beta-blockers have been exhibited to have favorable outcome on bone structure, metabolism, and healing. Thiazide diuretics: Thiazide diuretics enhance calcium uptake. Reduced urinary calcium excretion causes rise in serum calcium levels that could sequentially lead to decreased parathyroid hormone levels and consequently decreased bone turnover producing positive outcome on bone mineral density (BMD). ACE Inhibitors and ARB's: ACE inhibitors and ARBs Impede the activity of ACE and then influence bone metabolism.	inhibitors, and the angiotensin II receptor blockers (ARBs), are the most often advised drugs for people suffering from high blood pressure. Furthermore, these antihypertensive drugs also have an effect on bone, especially in bone formation, metabolism, and healing. Bone metabolism is controlled at three levels: by osteoblast-osteoclast interaction, by the immune system, and by the central nervous system. Although antihypertensive drugs seem to be favorable in preventing osteoporosis and bone fractures, the influence of these drugs has hardly been studied in other bone-related clinical conditions such as osseointegrated medical devices, including dental implants (28) .

TABLE 9:

CHEMOTHERAPEUTIC AGENTS:		
STUDIES	EFFECTS	TREATMENT
Young et al(29) examined the implications of chemotherapy on bone formation around femoral prostheses by giving cisplatin to dogs pre- or postoperatively: postoperative chemotherapy provoked minimum bone formation, while preoperative chemotherapy did not reform the formation of new bone. Concerning to dental implants, Kovacs et.al^(30) revealed successful osseointegration and functional stability in patients with a history of chemotherapy when implants were placed at least 6 months after therapy . However, chemotherapy is one of many anti-cancer therapies and, as other treatment modalities may lead to adverse outcomes in the oral cavity, these must be taken into account at the time of implant treatment planning (1).	The adverse sequelae of chemotherapy on bone have been debated for decades, and the chemotherapeutic agent's methotrexate and doxorubicin have been involved in the retardation of bone healing. Moreover, chemotherapy is known to detrimentally influence patients, nutritional status, and there is statement that poor nutrition can damage osseointegration and fracture healing [(1)].	Chemotherapy is the medications (cytostatic or cytotoxic agents) that impede the growth of cancer cells and, eventually, can induce their eradication. The major drawback of most chemotherapeutic agents and antineoplastic drugs is their paucity of selectivity. Furthermost, focusing fast-growing neoplastic cells, these agents also act on normal cells that have a hastened cell cycle, such as bone marrow cells, hair follicle cells and the epithelial cells of the gastrointestinal tract.

II. CONCLUSION:

The bone remodeling, repair and healing process in the implant is similar to that of primary bone healing in the initial stages of osseointegration. Factors that affect the bone healing may impede osseointegration thus resulting in implant failure. Some studies have clearly shown the direct outcome on osseointegration and the implant survival. But many of the studies are done invitro or animal study on the influence of various drugs explicitly on cyclosporine, glucocorticords, alcohol, selective serotonin inhibitors, non-steroidalanti-inflammatory drugs, bisphosphonates; proton pump inhibitors, anti- hypertensive and chemotherapeutic agents affect the osseointegration.Future studies on humans and Randomized Controlled Clinical Trial (RCT) are necessary to validate and to prove the outcome of these drugsin the success of an implant osseointegration.

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