

Influence of pharmacological groups on osseointegration failure in dental implant

Influencia de grupos farmacológicos en la falla de la oseointegración en implantología dental

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ABSTRACT

Introduction: Osseointegration is the phase in which the dental implant is firmly attached to the surrounding bone. This process is essential for the long-term success of dental implants. However, osseointegration may be compromised by the medications the patient receives to treat underlying pathologies. Therefore, depending on the medications prescribed to the patient, it is important for the clinician to recognize which pharmacological groups affect osseointegration and consequently implant failure, in order to evaluate each particular case.

Objective: The aim of this study is to provide information on the pharmacological

groups that may affect osseointegration of dental implants and cause their failure.

Methods: A search of the available literature (clinical cases, epidemiological studies and reviews) was performed in clinical reference databases (Pubmed-Medline, Elsevier-Clinical key) using MESH descriptors related with implants and drugs in a publication period from 2019 to 2023.

Results: A total of 116 articles were included, identifying several pharmacological groups commonly used in medicine that have a significant effect on osseointegration due to their mechanism of action, including bisphosphonates, anticoagulants, analgesics, proton pump inhibitors, among others.

Conclusions: This review compels the most common drugs that can affect the osseointegration process, including their pharmacological groups. It is important to identify in the medical history of the patients the use of these drugs in order to know the potential complications which may occur during the osseointegration process and to take measures to avoid failure during this dental procedure.

Keyword: osseointegration; pharmaceutical preparations, dental implants; pharmacologic actions; tooth loss.

RESUMEN

Introducción: La osteointegración es la fase en la que el implante dental se fija firmemente al hueso circundante. Proceso esencial para el éxito a largo plazo de los implantes dentales. Sin embargo, la osteointegración puede verse comprometida por medicamentos que recibe el paciente para tratar enfermedades subyacentes. En función de los medicamentos prescritos al paciente, es importante que el clínico reconozca qué grupos farmacológicos afectan a la osteointegración y el posterior fracaso del implante para evaluar cada caso concreto.

Objetivo: Exponer información sobre los grupos farmacológicos que pueden afectar a la osteointegración de implantes dentales y provocar su fracaso.

Métodos: Se realizó una búsqueda de la literatura disponible (casos clínicos, estudios epidemiológicos y revisiones) en bases de datos clínicas de referencia (Pubmed-Medline, Elsevier-Clinical Key) utilizando descriptores MESH relacionados

con implantes y fármacos en un periodo de publicación de 2019 a 2023.

Resultados: Se incluyeron un total de 116 artículos, en los que se identificaron varios grupos farmacológicos de uso común en medicina que tienen un efecto significativo sobre la osteointegración, debido a su mecanismo de acción, como bifosfonatos, anticoagulantes, analgésicos e inhibidores de la bomba de protones, entre otros.

Conclusiones: La revisión recoge los fármacos más comunes que pueden afectar al proceso de osteointegración, incluyendo sus grupos farmacológicos. Por lo que es importante identificar en la historia clínica de los pacientes, el uso de estos fármacos para conocer las posibles complicaciones que puedan ocurrir durante el proceso de osteointegración y tomar medidas para evitar el fracaso durante este procedimiento dental.

Palabras clave: oseointegración; preparaciones farmacéuticas, implantes dentales; acciones farmacológicas, pérdida de diente.

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Introduction

Oral implantology is the integrated application of several procedures aimed at restoring function, esthetics and facial harmony through the placement of implants in partially and fully edentulous patients to achieve optimal occlusion and function, through proper diagnosis and correct planning and execution of treatment.^(1,2,3)

It is possible to place dental implants in partially and fully edentulous patients and to achieve sufficient osseointegration with their functional prosthodontic load, with very high survival rates and excellent results after an average clinical follow-up of many years.^(4,5) However, several factors exist that may influence the achievement of favorable outcome, such as the medical condition of the patient, materials used to manufacture the implant in terms of macroscopic design and surface, the

different surgical techniques used to place it, among others.⁽⁶⁾ Medical conditions that may alter the implantation process include those that may also affect osseointegration, which is the direct functional and structural assembly between living bone and the surface of a loaded implant.^(3,7) This process is considered successful when there is complete integration 3 months after the implant has been placed. For this to occur, the bone must be healthy with an adequate mineralization and the mechanisms of response to damage, such as the immune system, it must be in optimal conditions to promote healing, prevention of infection and restoration of homeostasis of the tissue in which the implant has been placed.⁽⁴⁾ Some pharmacological treatments interfere with these biological processes, leading to the implant failure, depending on their mechanism of action.⁽⁸⁾

The literature review was conducted in clinically relevant databases using MESH descriptors and a range of publication years between 2018-2023 to investigate the major pharmacological groups that affect bone quality, immune system, and healing process/conditions that may lead to implant failure.

Methods

A bibliographic search in the databases Medline (Pubmed) and Clinical Key (Elsevier) was performed employing PRISMA guidelines.

The inclusion criteria were:

- Articles published between 2018 and 2023
- English language
- MESH descriptors in the title were Osseointegration and drugs
- Meta-analysis, randomized controlled trials, systematics reviews and clinical trials were included.

The total number of articles included in the initial search was 116, classified as follows:

- Meta-analysis (7)
- Randomized controlled trials (7)
- Systematics' reviews (87)
- Clinical trials (15)

Discussion

In this review, we analyze the key findings related to the drug influence on osseointegration process, which refers to the direct and structural connection between the dental implant and the surrounding bone, which allows the implant to be firmly integrated into the maxilla or mandible. This bone integration provides stability and adequate support for the dental prosthesis to be placed on the implant.⁽⁹⁾

Factors that may influence osseointegration

There are numerous factors that affect the quality and speed of osseointegration. The following are the most important.^(1,10,11)

- Patient health: some patients with underlying pathologies may present poor bone quality and wound healing delayed generated during implant treatment. Diseases that affect bone metabolism such as osteopenia and osteoporosis; diseases related to lipid and carbohydrate metabolism, such as hyperlipidemia and diabetes, promote bone loss and inhibit osseointegration of dental implants.^(5,12)
- Surface and design of the implant: the absence of micromovement between bone and implant is very important since the lack of primary stability leads to the formation of fibrous tissue, which negatively affects the osseointegration process and causes implant failure.⁽¹³⁾ The design of implants in the form of plates or nails is made according to the specific needs of each patient and

their physiological state.^(4,13,14) In a observational study conducted by Penitente et al in 2023 showed that several authors have shown that implant failure also correlates with the length of the implant. In fact, they suggest that the length should be between 10-13 mm, regardless of the diameter, since it has been shown that different measurements can cause failures in a percentage equal to 50%. The maxillary location of the implant also has an influence, multiple authors have reported that most implant failures occur when placed in the upper maxilla.⁽¹³⁾

- Biomechanical factors: Is related to the overloading that implants can suffer and their consequent failure. To avoid this faultiness a good immediate loading protocol should be planned. This protocol should allow control of the rotational forces, take into account the provisional and definitive restorations, and establish a good and adequate occlusion with a touch that reduces the extrinsic muscular forces.^(4,13)
- Influence of certain pharmacological groups: several drugs commonly used in clinical practice can have a positive or negative effect on the osseointegration process and consequently on the success of the implant. This point is discussed in detail in the immediately following subheading.^(10,11)

However, a careful postoperative care and follow-up protocol is necessary to ensure successful osseointegration.

Pharmacological groups that may have an effect on osseointegration

Most of the literature reviewed supports that several pharmacological groups affect bone quality, immune response or healing process. Among the pharmacological groups that interfere in the osseointegration process are:

- Antiresorptive medications (M05B): are drugs commonly used to treat bone diseases such as osteoporosis and bone cancer.^(12,15) These medications work by inhibiting the activity of osteoclasts, the cells responsible for bone

resorption, which helps to increase bone mineral density and reduce the risk of fractures. For example, diphosphonates inhibit bone resorption at the tissue level, modifying its rate towards the formation and increase of bone mass. Three cellular mechanisms have been proposed as the basis of these effects: decreased osteoclastic activity and decreased osteoclast formation. However, it has recently been documented those bisphosphonates can cause loss of the osteoclast cytoskeleton and of actin, a protein necessary for this cell to polarize and form a sealing ring on the bone surface, thus starting bone resorption. This can occur with prolonged use, high doses or intravenous administration. They are therefore associated with a serious side effect known as osteonecrosis of the jaw (ONJ).^(16,17) ONJ is a condition in which death of bone tissue in the mandible or maxilla occurs, and can result in pain, infection and significant bone loss. It has been observed most frequently in patients who have been given intravenous bisphosphonates (cancer), although it has also been reported in patients taking oral bisphosphonates to treat osteoporosis.^(15,18) The relationship between the use of bisphosphonates and osteonecrosis of the jaws has generated concern in the dental community, particularly with regard to the placement of dental implants in patients being treated with these drugs. It has been observed that bisphosphonates may interfere with the healing ability and osseointegration of dental implants, increasing the risk of postoperative complications, such as infection and necrosis of surrounding tissue.^(12,15,18)

- Corticosteroids (H02A): these are drugs that are used to treat a wide variety of inflammatory, autoimmune and allergic conditions due to their anti-inflammatory and immunosuppressive properties. In the context of dental implants, corticosteroids can affect the healing process and osseointegration because they can suppress the immune system's inflammatory response, which can decrease the ability of the body to fight infection and promote proper healing around the dental implant. This may increase the risk of infection and complications during the healing process.

Corticosteroids have also been shown to inhibit the formation of new bone tissue by interfering with the activity of osteoblasts, the cells responsible for the synthesis and deposition of bone matrix, hindering the formation of the bone interface necessary for implant osseointegration and thus delaying wound healing.^(12,13)

- Proton pump inhibitors (A02BC): are a group of chemical compounds that have been used as active ingredients since the 1980s. They are one of the most prescribed groups nowadays, since pathologies related to gastric hypersecretion have been increasing in recent years due to changes in lifestyle, including eating habits. This type of molecules are mostly prodrugs, which means that once the pharmaceutical form in which they are contained is ingested, they need to arrive intact to the site where they will undergo physiological activation and be able to enter the organism and perform their action, which consists of forming a covalent bond with the H⁺/K⁺-ATPase enzyme, also known as the proton pump, inactivating it.⁽¹⁹⁾ Treatment with these drugs produces adverse effects, one of the most interesting of which is the decrease in calcium absorption and reduction of vitamin B12 assimilation, since calcium is one of the most important minerals as it is the most abundant in the organism. Almost all calcium is stored in the bones, giving them structure, hardness and rigidity. Calcium is essential for many functions in the body, (muscle contraction, neurotransmission, among others) we acquire it from the diet and supplements. The gastrointestinal tract regulates Ca absorption; part is absorbed by passive diffusion and part by active transport (regulated by vitamin D). It is most effective in the duodenum, ileum (65%) and jejunum (17%). From the normal diet, 30-40% of calcium is absorbed. In both cereals and supplements, calcium comes in the form of calcium carbonate (oxalates, phytates, urates). These salts need an acidic environment to release the calcium for absorption, and it is for this reason that IPB compromises the absorption of the mineral, as it decreases gastric secretion and therefore the calcium is not released from the salts and

is not absorbed. This causes the body to activate physiological processes that allow the release of calcium necessary for biological functions from the bones, demineralizing them and compromising their structure, hardness and rigidity.^(12,19)

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs-M01A): these drugs act by stereo specifically and competitively inhibiting the cyclooxygenase enzyme (COX), either reversibly or irreversibly, affecting the catalytic capacity of the enzyme. By inhibiting COX, in particular COX-2 isoform, the arachidonic acid to is not be converted into prostaglandins, which are essential in the signaling pathways related to inflammation. They have anti-inflammatory and analgesic action, being used as treatments with different durations, for example in the case of dental conditions they are used for short periods of treatment, while in diseases with chronic inflammation or autoimmune origin, the treatment is for extended periods. Physiologically, in the osseous system COX-2 enzyme stimulus the formation of new bone and the prostaglandins promote the osteoblast differentiation, thus the COX-2 blocking and a declining prostaglandin production increase the bony fractures which would directly compromise osseointegration and implant success¹². However, the studies found are not conclusive on this issue.⁽²⁰⁾
- Selective serotonin reuptake inhibitors (SSRI-N06AB): are a class of medications commonly used to treat disorders such as depression, anxiety, obsessive-compulsive disorder (OCD) and other mood disorders. Within this group are fluoxetine, sertraline, citalopram and paroxetine, among others. Some research has suggested that SSRIs may have effects on osteoblasts, the cells responsible for the formation of new bone tissue, specifically with the ability of osteoblasts to proliferate and differentiate properly, which could negatively affect bone formation around dental implants, thus affecting the biological process of osseointegration due to their potential impact on bone cell function.^(21,22,23)

- Immunosuppressants (L04): are other drugs that influence the process of implant osseointegration as they are medications used to suppress the body's immune system response. They are commonly prescribed to prevent organ transplant rejection and to treat autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and Crohn's disease. These drugs inhibit the body's immune response, which can decrease inflammation and autoimmune activity, but can also increase the risk of infections and complications related to wound healing.⁽²⁴⁾ Immunosuppressants reduce the ability of immune system to respond to external stimuli, including bacteria that may enter the surgical site during dental implant placement, increasing the risk of infection and complications during the healing process. Patients taking immunosuppressants may have an increased risk of developing postoperative complications such as surgical site infections or prolonged inflammatory processes.⁽²⁵⁾
- Anticoagulants (B02): are drugs used to prevent the formation of blood clots and reduce the risk of thrombotic events, such as heart attacks and strokes. Within this group we can mention warfarin, factor Xa inhibitors (rivaroxaban, apixaban) and direct oral anticoagulants. Anticoagulants can increase the risk of excessive bleeding during surgical procedures, such as dental implant placement, so it is important to carefully assess the risk of bleeding in patients who are taking anticoagulants and consider strategies to minimize this risk, such as temporary discontinuation of the medication prior to the procedure or the use of local hemostatic agents.⁽²¹⁾ While anticoagulants may increase the risk of bleeding during and after dental implant placement, there is no strong evidence that they directly affect wound healing or implant osseointegration. However, it is important to closely monitor healing and provide adequate postoperative care to detect and treat any bleeding or healing-related complications.⁽²²⁾ Considering the balance between the risk of bleeding and the risk of thrombosis, in patients requiring anticoagulants due to underlying medical conditions, any decision to temporarily discontinue

anticoagulation should be carefully evaluated by the medical and dental team, as discontinuing medication may increase the risk of serious thrombotic events, such as stroke or pulmonary embolism.⁽²³⁾

Drugs that can cause implant failure that are approved in Colombia

In Colombia, Resolution 2366 of 2023 establishes the health services and technologies financed with UPC resources, to which all Colombians are entitled, regardless of the regime they belong. Appendix 1 contains the list of pharmaceutical products financed by the UPC. Within this list, a search was made for drugs belonging to the pharmacological groups that affect the osseointegration process, and the results are shown below:

- Antiresorptive medications: alendronic acid, ibandronic acid.
- Corticosteroids: methylprednisolone, prednisolone, prednisone, fludrocortisone, hydrocortisone, beclomethasone, dexamethasone, betamethasone, fluticasone, mometasone.
- Proton pump inhibitors: esomeprazole, pantoprazole, omeprazole.
- Non-Steroidal Anti-Inflammatory Drugs: meloxicam, diclofenac, acetylsalicylic acid, ibuprofen.
- Selective serotonin reuptake inhibitors (SSRI): fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, mirtazapine.
- Immunosuppressants: cyclosporine, colchicine, hydroxychloroquine, sulphadiazine, dapsone, methotrexate, mycophenolate, azathioprine, infliximab, adalimumab, golimumab, etanercept, certolizumab, tocilizumab, rituximab, belimumab, abatacept, secukinumab, ixekizumab, guselkumab, ustekinumab, mepolizumab, benralizumab, dupilumab, omalizumab, tofacitinib, upadacitinib, baricitinib.

- Anticoagulants: heparin, enoxaparin, nadroparin, dalteparin, fondaparinux, protamine, apixaban, rivaroxaban, dabigatran, warfarin, acetylsalicylic acid, dipyridamol, clopidogrel, prasugrel, ticagrelor, tirofiban.

Conclusions

Some pharmacological groups employed to treat pathologies in the patient to be implanted have also an impact on the osseointegration. In this group we find the bisphosphonates, which are used in the treatment of bone diseases and can have a negative effect on the ability of the bone to integrate with the dental implant. Others, such as immunosuppressants, can interfere with the healing process; anticoagulants can cause bleeding and complicate the surgical procedure, proton pump inhibitors that alter the calcium absorption and demineralizing the bone and compromising bone quality. For dental treatment planning and management, especially in patients receiving chronic drug therapy, understanding the influence of these pharmacologic groups on osseointegration is critical. Collaboration between the dentist, the oral surgeon, and the medical specialist is essential to mitigate the risks associated with these medications and to ensure successful outcomes in implant dentistry procedures.

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Conflicts of interest

The authors declare no conflicts of interest.

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