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Atrophic maxilla and osseointegrated implants: a systematic review

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Abstract

Introduction: In the scenario of the dental implants, what makes implantology unique is the ability to achieve this goal, however, the more teeth a patient loses the more challenging the task becomes. Osteoporosis may be a risk factor for the use of implants. Alternative approaches such as guided surgery and placement of short implants are progressively supplanting more invasive bone regeneration procedures. There are some drugs that help in the treatment of postmenopausal osteoporosis, they are calcitonin, bisphosphonates and the selective modulators of estrogen receptors. **Objective:** Foi realizar uma revisão sistemática sobre as principais considerações e desfechos clínicos da maxila atrófica no cenário dos implantes dentários osseointegrados, osteoporose e o uso dos bifosfonatos. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from October 2022 to January 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles from 2005 to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 225 articles were found, and 65 articles were evaluated in full and 31 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 45 studies with a high risk of bias and 90 studies that did not meet GRADE. In the scenario of atrophic maxilla issues, it was concluded that osteoporosis is a metabolic condition that affects alveolar bone density, but does not present problems for the installation of osseointegrated implants, provided there is enough bone mass in the region where the tooth will be implanted. The rehabilitation of atrophic maxilla through dental implants is still challenging, however, alternatives such as guided surgery and the installation of short implants are progressively supplanting the more invasive bone regeneration procedures. Some drugs that help in the treatment of postmenopausal osteoporosis, are calcitonin, bisphosphonates, and the selective modulators of estrogen receptors. Bisphosphonates have been the best drug associated with significant improvement in the quality of life of patients with bone diseases such as Paget's disease, bone metastases, osteogenesis imperfecta, hypercalcemia, and even severe osteoporosis.

Keywords: Atrophic maxilla. Dental implant. Bisphosphonate. Osseointegration. Osteoporosis.

Introduction

In the scenario of the dental implants, what makes implantology unique is the ability to achieve this goal, however, the more teeth a patient loses the more challenging the task becomes [1,2]. It is estimated that the number of dental implants used in the United States increased by more than 10 times in the last 10 years [3]. More than one million dental implants are performed each year. The high need and use of treatments related to implants result from the combined effect of several factors and the most important are aging population with longer life expectancy, and age-related dental loss [4].

In this sense, osteoporosis may be a risk factor for the use of implants [5,6]. Osteoporotic patients often

require bone regeneration techniques because they do not fulfill ideal conditions for implant placement due to diminished bone structure and rapid resorption of alveolar bone. [7]. Still, the rehabilitation of atrophic maxilla through dental implants is challenging. However, alternative approaches such as guided surgery and placement of short implants are progressively supplanting more invasive bone regeneration procedures. A V-4 technique described in 2016 facilitates the placement of dental implants in patients with an atrophic maxilla; however, their authors recommend incision, opening of the flap and elevation of the anterior region of the maxillary sinuses [8].

In this sense, one of the major causes of osteopenia in women over 60 years of age is estrogen deficiency. This deficiency associated with aging causes an osteoporotic picture. A hormone replacement is necessary for an adequate treatment of the symptoms of menopause and to prevent possible osteoporosis [5,6]. There are some drugs that help in the treatment of postmenopausal osteoporosis, they are calcitonin, bisphosphonates (BP) and the selective modulators of estrogen receptors [6]. Thus, BP has been the best drug associated with significant improvement in the quality of life of patients with bone diseases such as Paget's disease, bone metastases, osteogenesis imperfecta, hypercalcemia and even severe osteoporosis [6].

In this context, these drugs are used worldwide in cancer patients and are given intravenously as zoledronic acid (Zometa®) [7-12]. They can also be administered orally, such as alendronate (Fosamax®) and risedronate (Actonel®) for the treatment of postmenopausal osteoporosis [13]. In 2003, a side effect associated with the use of BP with oral manifestation called Osteonecrosis Associated with BP was described for the first time [10].

In this context, osteoporosis is a prevalent global bone disease in human aging. BPs are commonly used as therapy because they influence calcium metabolism of hard and soft tissues. Mucosal and dermal ulceration with exposure of the underlying bone results from incomplete epithelial recovery due to reduced desmosome formation due to lack of available calcium. However, pathological situations, such as BP-related jaw osteonecrosis, have been described. This hypothesis states other situations that require intact functional desmosomes such as skin healing over chronic pressure points leading to pressure ulcers and hemidesmosomes such as epithelial seals in contact with titanium surfaces will have a higher prevalence of collapse among patients treated with BP. This can be proven by the decreased modulation of calcium ions due to BP and its effect on intercellular communicating junction formation [4].

Also, as yet another example of literary support, one paper reported a type of localized osteonecrosis that can occur in patients who had successfully osseointegrated implants for many years and then started anti-resorptive therapy. Eleven female patients who successfully implanted but were placed on anti-resorptive therapy (BPs or denosumab) several years later and developed osteonecrosis around the implants were identified. In each case, osteonecrosis occurred only around the implants and not around the patient's remaining teeth. Implants from eight patients were removed with bone sequestration firmly attached to the implant. This is different from the normal pattern of implant failure. Implant failure can occur when patients with successfully integrated implants are subsequently placed on anti-resorption therapy, and osteonecrosis takes on a particular form where a sequestration forms that remain adherent to the implant. Why the remaining adjacent teeth are not affected is unclear [5].

In view of this, the present study aimed to carry out a systematic review of the main considerations and clinical outcomes of the atrophic maxilla in the setting of osseointegrated dental implants, osteoporosis and the use of bisphosphonates.

Methods

Study Design

This was followed by a systematic literature review model on the main clinical findings of mandible fractures, according to the PRISMA rules (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/).

Data sources, MeSH Terms and research strategy

The literary search process was carried out from October 2022 to January 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2005 to 2022, using the descriptors (MeSH Terms): “Atrophic maxilla. Dental implant. Bisphosphonate. Osseointegration. Osteoporosis", and using the Booleans "and" between the descriptors (MeSH Terms) and "or" between the historical findings.

Study quality and risk of bias

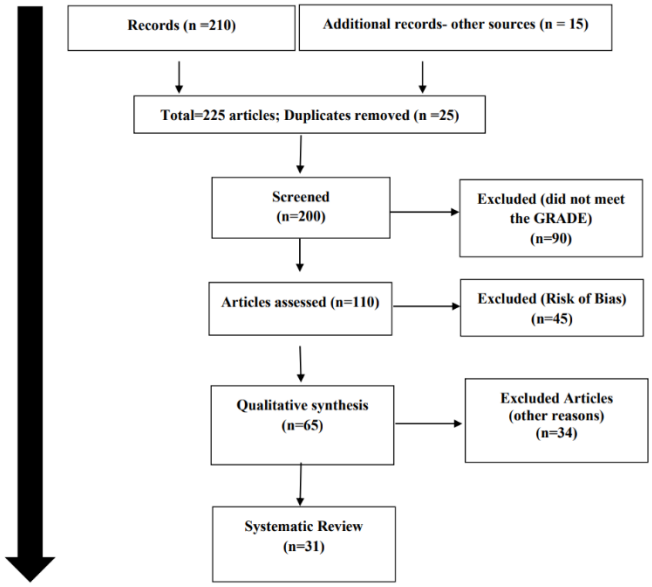
The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Literary Findings

A total of 225 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 202 articles. A total of 65 articles were evaluated in full and 31 were included and developed in this systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 45 studies with a high risk of bias and 90 studies that did not meet GRADE.

Figure 1. Selection of studies.



Major Findings

Based on the studies, osteoporosis is defined as a systemic skeletal disorder, associated with aging, characterized by loss of bone mass, which makes the bone more fragile and more prone to fractures [14]. The osteoporosis represents as a level of bone mineral density greater than 2.5 standard deviations below the average of normal young women [16-20]. After 60 years of age, a third of the population has this disorder, it occurs twice more in women than in men and its diagnosis is made with greater prevalence from the third decade of life [2,3].

In this sense, osteoporosis is one of the dysfunctions commonly found by implant dentists [21-24]. Osteoporosis acts by modifying the metabolism of the bone tissues, disorganizing the trabecular architecture of the cortical and alveolar bone, which are responsible for tooth support. It is estimated that 1.3 million of all fractures and 133,000 hip fractures occur each year as a result of osteoporosis [25].

Also, osteoporosis can be classified as type I and type II. Type I (postmenopausal) occurs when there is loss of trabecular bone mass, resulting in fractures of the vertebrae and wrists, which may be more evident in the mandible and the alveolar bone, is associated with the aging and plasma decrease of estrogen in the menopause, affecting mainly women; And Type II (senile), occurs when there is loss of trabecular bone mass that can affect both cortical and spongy bone, resulting in hip fractures, which can affect both sexes and in ages over 70 years [17-22].

There is a higher prevalence of the development of osteoporosis in women, and there are some risk factors that may explain this difference, such as early menopause, artificial menopause, nulliparous, and estrogen replacement [26-29]. For men, reduced testicular function (male hypogonadism) can be cited as a risk factor. Several other risk factors may predispose to both sexes: heredity, tobacco, alcohol, caffeine, obesity, absence of physical activity, ethnicity, changes in calcium levels, malnutrition, decreased levels of vitamin D, elevated Levels of parathyroid hormone and other hormones, all these factors may manifest in both men and women with osteoporosis [22].

The recommended intake of calcium is 800 mg day-1, in women who have already gone through menopause, 1.5 g may be required to maintain a positive calcium balance [30,31]. For patients with established osteoporosis, there are drugs that, in general, act directly in the process of bone remodeling, seeking to reduce bone resorption, among them, is bisphosphonates (BP), which are drugs of proven efficacy that act in the prevention and treatment of several Bone diseases [31].

In this sense, dental implants are defined as supports or structures of titanium metal, which through surgeries are fixed in the maxillary bone replacing the dental roots, thus allowing the artificial teeth to fit the metal. Dentistry uses several rehabilitation techniques for masticatory functions, and osseointegrated implants are considered safe, provided they are implanted in areas of good quantity and bone quality. However, some systemic conditions may interfere with implant stability, such as osteoporosis. Implantology has shown increasing success rates when it presents a harmonious bone/implant relationship (osseointegration) [17].

The discovery of osseointegration occurred through studies of microcirculation in the bone marrow performed on the rabbit fibula, developed by Per-Ingvar Branemark. He verified in Branemark's studies that a titanium implant when inserted into the medullary space, under certain conditions, and remaining immobile without mechanical trauma during the period of bone repair, end up full of compact bone without the interference of other tissues [18-20].

In this context, osteoporosis is a factor that retards the regeneration of maxillary bone in patients who have undergone implant surgery, prolonging the normal recovery time of maxillary bone which can vary from three to six months [30]. Therefore, it is necessary that people affected by this disease who will receive dental implants need a longer time for bone repair. Due to the increase in life expectancy, rehabilitation with implants in people over 60 years old is the most common age group in which there is a higher probability of metabolic pathologies [31].

Thus, to obtain osseointegration of the implant, which is the direct and structural unit of the bone tissue to the titanium and function, it is necessary to respect several principles, among them, those related to the surgical technique, respecting tissue physiology [29]. Thus, it is necessary to control the traumatogenic factors during surgery such as intensity, frequency, and duration of the milling (osteotomies), which can generate excessive trauma to the bone tissue, impairing the bone repair potential of the injured area. Facing situations where the traumatic stimulus exceeds its physiological limit, the implant may be involved by fibrous connective tissues, leading to the formation of a bone or fibrous per implant interface, without osseointegration [29].

For the success of osseointegrate implants other factors must also be considered, not only related to the professional (surgical technique), but also the industry and the patient himself. In addition to performing the appropriate surgical technique, it is up to the professional to select the patient, evaluating it as a whole, from his complaint, including his expectation regarding the treatment, mainly comprising his pre-operative systemic and local conditions [30,31]. At the moment of preparation of the receptor bone bed for the subsequent installation of the osseointegrated implant, bone necrosis occurs, which will be replaced by new bone tissue. When there is osteoporosis, the process of bone remodeling can be compromised, preventing or delaying osseointegration [31].

Also, the authors Ourique et al. [22] have already reported on the importance of knowledge of systemic alterations so that necessary measures are taken to minimize or prevent eventual damages caused by osteoporosis in the anatomical, physiological, and functional integrity of the alveolar bone. All care is necessary for the success of this process since the immediate benefit of the rehabilitative treatment with implants is observed in the improvement of the capacity to crush the food, and in the physical and psychological well-being of the patient. Ishii et al. [17] state that although osteoporosis is a significant factor that can interfere with bone volume and density, it cannot be considered an absolute contraindication for implant installation. It is essential that during the anamnesis, all patients are questioned about their state of health, reporting the use of medications and the type of medical treatment they are undertaking so that a safe and effective treatment plan is drawn up for each case.

In this context, BP is a widely used drug group for various bone disorders and has been approved by the U.S. Food and Drug Administration for the treatment of osteoporosis, metastatic bone cancer, and Paget's disease [29]. They were first used for industrial purposes in the 19th century to prevent corrosion in the textile, fertilizer, and oil industries. In 1968, the first paper describing the use of BP in medicine was published, however, in 2002 serious side effects of these medications were reported following dental surgery procedures. This includes osteonecrosis, avascular necrosis, osteomyelitis, osteochimionecrosis, and maxillary BissPhossy [29].

At the moment there are two main types of BP, those containing nitrogen (oral:

alendronate and risedronate, intravenous: pamidronate and zoledronate) and those that do not contain (etidronate, clodronate, and tiludronate). BP act by suppressing and reducing bone resorption by osteoclasts, directly preventing the recruitment and function of osteoclasts, and indirectly stimulating osteoblasts to produce inhibitors of osteoclast formation [30].

Besides, BP are drugs derived from inorganic pyrophosphate, which are present in the body and physiologically regulate calcification and bone resorption. Pyrophosphate also provides greater resistance to chemical and enzymatic hydrolysis [20]. Camargo, Minosso, and Lopes, (2007) [11] report that treatment should always combine an anti-resorptive agent with a non-pharmacological measure such as physical exercise and consumption of calcium and vitamin D by diet. Antireabsorption agents are described by Ishii (2009) [17] as estrogen replacement therapy, selective estrogen receptor modulators, BP, and calcitonin, and also describe bone formation stimulating agents such as a parathyroid hormone.

Moreover, the authors Ourique et al. [22] have shown in their studies that calcium intake is associated with hormone replacement (estrogen), which leads to an increase in trabecular bone mass. Calcium when ingested alone is not able to definitively prevent the onset of osteoporosis. The authors also report that in addition to osteoporosis, age, sex, race, hormonal pattern, decreased vitamin D synthesis, inhibition of calcium absorption, parathormone increase, nicotine, fragile physical structure, renal deficiency, menopause, alcohol and low Consumption of calcium may jeopardize

the success of an implant.

Further, according Ferreira Junior et al. [15] stated that BP can contain bone loss, increase bone density, and reduce the risk of fractures resulting from progressive loss of bone mass. In the BP group, alendronate is the most potent because it has an affinity for bone tissue. Another indication to prevent osteoporosis is calcitonin, which is a peptide derived from parafollicular thyroid cells, aiding bone resistance. Alendronate, for osteoporotic patients, can be administered orally at 10.0 mg/day or 70.0 mg / weekly, and cannot be exceeded because it causes gastrointestinal changes such as erosive esophagitis. It is necessary to use this medicine in fasting, for being little absorbed in the intestine, and to wait 40 to 60 minutes to feed. It is a drug that deposits about 40-60% rapidly into the bone and the rest is released through the urine. The plasma half-life of BP is very short, ranging from thirty minutes to two hours, so after these medications are absorbed by the bone tissue, they may persist for more than 10 years in skeletal tissues.

A review study with Meta-Analysis included clinical human studies, randomized or not. A total of 18 publications were included in the review. Regarding implant failure, the metaanalysis found a risk ratio of 1.73 (95% confidence interval [CI] 1.21-2.48, p = 0.003) for BP patients when compared to patients who did not take the medicine. The probability of an implant failure in patients receiving BP was estimated at 1.5% (0.015, 95% CI 0.006-0.023, standard error [SE] 0.004, p<0.001). BP cannot be suggested to affect marginal bone loss from dental implants due to a limited number of studies reporting this result. Due to a lack of sufficient information, the meta-analysis for the outcome of "postoperative infection" was not performed. The results of the present study cannot suggest that dental implant insertion in patients taking BP affects implant failure rates due to a limited number of published studies, all characterized by a low level of specificity, and most of them dealing with a limited number of cases without an adequate control group. Therefore, the real effect of BP on osseointegration and survival of dental implants is not yet well established [8].

Besides, the authors state that patients who use BP may have impaired healing of the damaged dental implant as it impedes bone remodeling and may lead to a condition called osteonecrosis, which is considered a side effect of this drug [1,3]. Although there are much data on the beneficial effects of BP in the treatment of advanced osseous diseases, numerous reports have documented the ability of these medications to cause local lesions of bone osteonecrosis mainly in the jaw [30]. Osteonecrosis may remain asymptomatic for weeks and possibly months, and lesions usually develop around tapered areas and prior surgical sites, including extractions, retrograde apical tetanus, periodontal surgery, and dental implant surgery. Symptoms include pain, soft tissue edema, infection, tooth loss, and drainage. Radiographically, osteolytic changes are observed and tissue biopsy shows the presence of actinomyces [31].

In the dental procedures, the most common BP that the implant is exposed to is the oral ones that contain nitrogen, such as risedronate, ibandronate, and alendronate. Comprehensive anamnesis is essential before the initiation of any elective treatment, the risk versus benefits of dental treatment should be discussed in detail with the patient [29].

In this context, another study using the BP analyzed the factors related to obtaining effective mechanical and immunological adhesion, viability, epidermal collagen growth factor, and immunoglobulin synthesis were evaluated. The presence of BP culminated in lower cell adhesion to titanium discs, particularly for sodium alendronate (SA) at 5 μM (40%) and zoledronic acid (ZA) at all concentrations (30 to 50% according to increased concentrations). Reduced cell viability occurred after an exposure of these cells to ZA (40%); however, only 5 μM of SA-treated cells had decreased viability (30%). Reduced synthesis of growth factors and collagen was observed when cells were treated with ZA (20 and 40%, respectively), while about 70% of IgG synthesis was increased. BPs negatively affected the adhesion and metabolism of oral mucosal cells, and this effect was related to BP type as well as concentration and treatment period. The negative effects of BPs on oral mucosa cells may hinder the formation of an effective biological seal in osseointegrated implants [9].

Also, a review study aimed to study the purpose of dental implant placement in patients who have been treated or are undergoing treatment with BP medication. Outcome measures included implant failure or implant-related jaw osteonecrosis. In total, 32 literature sources were reviewed, and 9 of the most relevant articles that fit the criteria were selected. Heterogeneity between studies was found and no meta-analysis could be performed. Five studies looked at intra-oral BP medication for implant placement, three studies looked at intravenous BP medication for implant placement, and one study evaluated the two types of medication administered for implant placement. Patients with intraoral therapy appeared to have better implant survival (5 implants failed 423) rate of 98.8% versus intravenously treated patients (6 implants failed 68) by 91%; The control group compared with the intraoral BP group appeared with 97% success in implant survival rate (27 implants failed in 842), showing no significant

difference in implant placement success. Patients treated with intravenous BP appear to have a greater chance of developing implant-related jaw osteonecrosis. The intraorally treated group of patients appeared to have more successful results. Implant placement in intraorally treated patients can be considered safe with precautions [10].

Conclusion

In the scenario of atrophic maxilla issues, it was concluded that osteoporosis is a metabolic condition that affects alveolar bone density, but does not present problems for the installation of osseointegrated implants, provided there is enough bone mass in the region where the tooth will be implanted. The rehabilitation of atrophic maxilla through dental implants is still challenging, however, alternatives such as guided surgery and the installation of short implants are progressively supplanting the more invasive bone regeneration procedures. Some drugs that help in the treatment of postmenopausal osteoporosis, are calcitonin, bisphosphonates, and the selective modulators of estrogen receptors. Bisphosphonates have been the best drug associated with significant improvement in the quality of life of patients with bone diseases such as Paget's disease, bone metastases, osteogenesis imperfecta, hypercalcemia, and even severe osteoporosis.

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Conflict of interest
The authors declare no conflict of interest.

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It was applied by Ithenticate@.

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