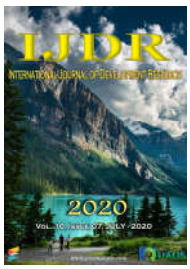
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 10, Issue, 07, pp. 38351-38356, July, 2020
https://doi.org/10.37118/ijdr.19246.07.2020



RESEARCH ARTICLE OPEN ACCESS

MAJOR CONSIDERATIONS OF THE USE OF BISPHOSPHONATE IN IMPLANTOLOGY: A SYSTEMATIC REVIEW

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ARTICLE INFO

Article History:
Received 18th April, 2020
Received in revised form
06th May, 2020
Accepted 20th June, 2020
Published online 30th July, 2020

Key Words:
Bisphosphonate,
Osseointegration,
Dental implant.
Osteoporosis,
Complications.

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ABSTRACT

Introduction: It is estimated that the number of dental implants used in the United States increased more than 10 times between 1983 and 2002 and another five times between 2000 and 2005. More than one million dental implants are performed each year. In this sense, one of the main causes of osteopenia in women over 60 years of age is an estrogen deficiency. Thus, bisphosphonates has been the best drug associated with a significant improvement in the quality of life of patients with bone diseases, such as Paget's disease, bone metastases, imperfect osteogenesis, hypercalcemia, and even severe osteoporosis. **Objective:** to review, through a systematic literature review, the use of bisphosphonate-associated with dentistry. Methods: Experimental and clinical studies were included (case reports, retrospective, prospective and randomized studies) with qualitative and/or quantitative analysis. For greater specifications, the description "bone necrosis" for refinement was added during the research, following the rules of systematic review-PRISMA. 155 articles were found involving implantology and biomaterial. A total of 45 articles were evaluated in full and 37 were included and discussed in this study. **Major findings:** Bisphosphonate coating of dental implants is a promising tool for surface modification, with the aim of improving the osseointegration process and the clinical outcome. The biological effects of bisphosphonates arethought to be mainly associated with the inhibition of osteoclasts, while their effects on osteoblast function are unclear. Thus, surfaces coated with bisphosphonates to stimulate osteoblast differentiation have been investigated by several in vitro studies with contradictory results. **Conclusion:** Osteoporosis is a metabolic condition that affects alveolar bone density, but does not present problems for the installation of osseointegrated implants, as long as there is sufficient bone mass in the region where the tooth will be implanted. Alendronate sodium is used to decrease bone resorption and should be considered as an adjunct therapeutic agent for the treatment of osteoporosis.

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Citation: ***Rogério Luiz de Araújo Vian, Idiberto José Zotarelli Filho and Elias Naim Kassis.*** "Major considerations of the use of bisphosphonate in implantology: a systematic review*", International Journal of Development Research*, 10, (07), 38351-38356.

INTRODUCTION

The scope of Modern Dentistry is to restore the patient's normal comfort, function, aesthetics, phonation, and health. What makes implantology unique is the ability to achieve this goal. However, the more teeth a patient loses, the more challenging the task becomes (Jahan, 2013). It is estimated that the number of dental implants used in the United States increased more than 10 times between 1983 and 2002 and another five times between 2000 and 2005 (Rawal, 2019). More than one million dental implants are performed each year (Touyz, 2017). The high need and use of treatments related to implants result from the combined effect of several factors and the most important is the aging of the population with the longest life expectancy and age-related tooth loss (Touyz, 2017). In this sense, one of the main causes of osteopenia in women over 60 years of age is an estrogen deficiency. This deficiency associated with aging causes an osteoporotic condition. Hormone replacement is necessary for an adequate treatment of menopausal symptoms and to prevent possible osteoporosis (Pogrel, 2017). There are some drugs that help in the treatment of postmenopausal osteoporosis. They are calcitonin, Bisphosphonate (BP), and selective estrogen receptor modulators (Pogrel, 2017). Thus, BP has been the best drug associated with a significant improvement in the quality of life of patients with bone diseases, such as Paget's disease, bone metastases, imperfect osteogenesis, hypercalcemia, and

even severe osteoporosis (Chrcanovic, 2016). These drugs are used worldwide in cancer patients and are administered intravenously as zoledronic acid (Zometa®). They can also be administered orally, such as alendronate (Fosamax®) and risedronate (Actonel®) for the treatment of postmenopausal osteoporosis (Duarte, Nociti, (2004). In 2003, an associated side effect was first described to the use of BP with oral manifestation called Osteonecrosis Associated with BP (Basso, 2018). In this context, osteoporosis is a global bone disease prevalent in human aging (Gelazius, 2018). BPs are commonly used as therapy because they influence the calcium metabolism of hard and soft tissues. Ulceration of the mucosa and dermis with exposure of the underlying bone results from incomplete epithelial recovery due to reduced desmosome formation due to a lack of available calcium. However, pathological conditions, such as osteonecrosis of the jaw related to blood pressure, have been described (Camargo, 2017). This hypothesis states that other situations that require intact functional desmosomes, such as skin healing over chronic pressure points that lead 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 confirmed by the decreased modulation of calcium ions due to blood pressure and its effect on the formation of the intercellular communicating junction (Jahan, 2019).

In addition, an article reported a type of localized osteonecrosis that can occur in patients who have had a successful osseointegrated implant for many years and then started anti-resorptive therapy. Eleven female patients who successfully implanted, but underwent anti-resorptive therapy (BP or denosumab), several years later and developed osteonecrosis around the implants. In each case, osteonecrosis occurred only around the implants and not around the patient's remaining teeth. The implants of eight patients were removed with bone sequestration firmly attached to the implant. This is different from the normal implant failure pattern. Implant failure can occur when patients with successfully integrated implants are subsequently placed on anti-resorption therapy, and osteonecrosis takes on a specific form, in which sequestration is formed that remains adherent to the implant. Why the remaining adjacent teeth are not affected is unclear (Rawal, 2019). As it is a possible alternative for reducing losses and increasing bone density, as well as for the possibility of osteonecrosis, which requires therapeutic and preventive measures in the involvement of invasive practices, such as dental implants, the present study aimed to review through of a systematic literature review the use of bisphosphonate-associated with dentistry.

METHODS

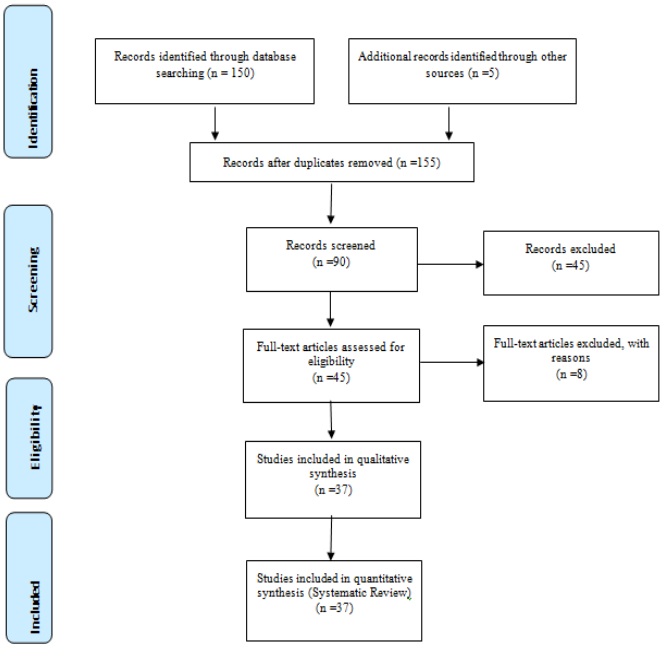
Experimental and clinical studies were included (case reports, retrospective, prospective and randomized studies) with qualitative and/or quantitative analysis. Initially, keywords were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and then verified and validated by the MeSHSystem (Medical Subject Headings, the US National Library of Medicine) to achieve a consistent search.

MeSH Terms: The main descriptors (Mesh Terms) used *were "Bisphosphonate. Osseointegration. Dental implant. Osteoporosis. Complications".*

For further specifications, the description" bone necrosis "for refinement was added during the research, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http: //www.prisma-statement.org /). The bibliographic search was carried out through online databases: PubMed, Periodicos.com, and Google Scholar. The deadline and related research were set, covering all available literature on virtual libraries.

Series of Articles and Eligibility: A total of 155 articles were found involving implantology andbisphosphonate. Initially, the existing title was excluded and duplicated according to the interest described in this study. After this process, the abstracts were evaluated and a new exclusion was performed. A total of 45 articles were evaluated in full and 37 were included and discussed in this study.

Flow chart



Development and Discussion: 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 (Carvalho, 2010; Duarte, 2004; Embracher Filh, 2003). The World Health Organization has defined osteoporosis as a level of bone mineral density greater than 2.5 standard deviations below the average for normal young women (Ferreira Júnior, 2007; Gegler, 2006). After the age of 60, one-third of the population has this disorder, it occurs twice as often in women than in men and its diagnosis is made with a greater prevalence from the third decade of life. Among systemic changes, osteoporosis is one of the disorders commonly found by implant dentists (Migliorati, 2006). Osteoporosis acts by modifying the metabolism of bone tissues, disrupting the trabecular architecture of the cortical and alveolar bone, responsible for dental support. It is estimated that 1.3 million of all fractures and 133,000 hip fractures occur each year as a result of osteoporosis (Misch, 2008; Goiato, 2010). Osteoporosis can be classified as type I and type II. Type I (post-menopause) occurs when there is the loss of trabecular bone mass, resulting in fractures of the vertebrae and wrists, which may be more evident in the jaw and alveolar bone, is associated with aging and a decrease in plasma estrogen in the body (menopause), affecting mainly women;

And Type II (senile), occurs when there is the loss of trabecular bone mass that can affect the cortical and spongy bone, resulting in hip fractures, which can affect both sexes and at ages over 70 years old (Goiato, 2010). There is a higher prevalence of the development of osteoporosis in women and there are some risk factors that can explain this difference, such as early menopause, artificial menopause, nulliparous, and estrogen replacement (Chadha, 2013; Mellado-Valero, 2010; López-Cedrún, 2012; Kwon, 2012). For men, reduced testicular function (male hypogonadism) can be cited as a risk factor. There are several other risk factors that can predispose to both sexes: heredity, tobacco, alcohol, caffeine, obesity, lack of physical activity, ethnicity, changes in calcium levels, malnutrition, decreased levels of vitamin D, high levels of hormone parathyroid and other hormones, all of these factors can manifest in men and women with osteoporosis (Yip, 2012). The recommended calcium intake is 800 mg.day-1; in women who have already gone through menopause, 1.5 g may be needed to maintain a positive calcium balance (Yip, 2012; Memon, 2012). For patients with established osteoporosis, there are drugs that, in general, act directly in the bone remodeling process, seeking to reduce bone resorption, including BP, which are proven drugs that work in the prevention and treatment of various bone diseases (Memon, 2012). In this sense, dental implants are defined as supports or structures of titanium metal, which through surgery are fixed on the jaw bone, replacing the dental roots, thus allowing artificial teeth to adjust to the metal. Dentistry uses several rehabilitation techniques for masticatory functions, and osseointegrated implants are considered safe, as long as they are implanted in areas of good quantity and bone quality (Abtahi, 2012).

However, some systemic conditions can interfere with implant stability, such as osteoporosis. Implantology has shown increasing success rates when it presents a harmonious bone/implant relationship (osseointegration) (Abtahi, 2012). The discovery of osseointegration occurred through studies of bone marrow microcirculation carried out in the rabbit fibula, developed by Per-Ingvar Branemark. He found in Branemark's studies that a titanium implant, when inserted in the medullary space, under certain conditions, remained immobile without mechanical trauma during the period of bone repair, ends up full of compact bone without the interference of other tissues (Jacobsen *et al*., 2013). In this context, osteoporosis is a factor that slows down the regeneration of the jaw bone in patients undergoing implant surgery, prolonging the normal recovery time of the jaw bone that can vary from three to six months (Yip, 2012). Therefore, it is necessary that people affected by this disease and who will receive dental implants need more time for bone repair (Yip, 2012). Due to the increase in life expectancy, implant rehabilitation in people over 60 years of age is the most common age group in which there is a greater likelihood of metabolic pathologies (Memon, 20112). To achieve osseointegration of the implant, which is the direct and structural union of bone tissue to titanium and function, it is necessary to respect several principles, including those related to surgical technique, respecting the physiology of the tissue (Kwon, 2012). Thus, it is necessary to control traumatogenic factors during surgery, such as intensity, frequency, and duration of milling (osteotomies), which can generate excessive trauma to bone tissue, impairing the potential for bone repair in the injured area. In the face of situations in which the traumatic stimulus exceeds its physiological limit, the implant may be surrounded by fibrous connective tissues, leading to the formation of a bone interface or fibrous per implant, without osseointegration (Kwon, 2012). For the success of osseointegrated implants, other factors must also be considered, not only related to the professional (surgical technique), but also to 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 him as a whole, based on his complaint, including his expectation regarding the treatment, mainly comprising the systemic and preoperative local conditions (Yip, 2012; Memon *et al*., 2012) When preparing the recipient 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 bone remodeling process can be compromised, preventing or delaying osseointegration (Memon *et al*., 2012). Ishii *et al*. (2009.) 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 anamnesis, all patients are asked about their health status, reporting the use of medications and the type of medical treatment they are undergoing, so that a safe and effective treatment plan for each individual case is developed. Several authors Ourique *et al*. (2005) have already reported the importance of knowledge of systemic changes so that the necessary measures are taken to minimize or prevent any damage caused by osteoporosis in the anatomical, physiological and functional integrity of the alveolar bone. Every care is necessary for the success of this process, as the immediate benefit of the rehabilitation treatment with implants is observed in the improvement of the ability to crush food, in the physical and psychological well-being of the patient.

Bisphosphonate - Main Approaches: Bisphosphonate coating of dental implants is a promising tool for surface modification, with the aim of improving the osseointegration process and the clinical result. The biological effects of BP are thought to be mainly associated with the inhibition of osteoclasts, while their effects on osteoblast function are unclear. Thus, surfaces coated with BP to stimulate osteoblast differentiation have been investigated by several in vitro studies with contradictory results. Therefore, a study of systematic review and meta-analysis evaluated the effect of the surfaces of implants coated with BP on the activity of alkaline phosphatase in osteoblasts. Eleven studies met the inclusion criteria. Meta-analysis showed that coating titanium surfaces with BP increases the activity of alkaline phosphatase in osteoblasts after 3 days (n = 1), 7 (n = 7), 14 (n = 6) and 21 (n = 3) days. (7-day beta coefficient = 1.363, p-value = 0.001; 14-day beta coefficient = 1.325, p-value <0.001; 21-day beta coefficient = 1.152, p-value = 0.159). The meta-analysis suggests that bisphosphonate coatings on the surfaces of titanium implants may have beneficial effects on the osteogenic behavior of osteoblasts cultured on titanium surfaces in vitro. Further studies are needed to assess the extent to which bisphosphonate lining can improve osseointegration in clinical situations (Wehner, 2020). BP is a group of drugs widely used for various bone disorders and has been approved by the US Food and Drug Administration for the treatment of osteoporosis, metastatic bone cancer and Paget's disease (Kwon *et al*., 2012). 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 article was published describing the use of BP in medicine, but in 2002 serious side effects of these drugs were reported after

dental surgery procedures. This includes osteonecrosis, avascular necrosis, osteomyelitis, osteocymionecrosis, and maxillary Biss-Phossy (Kwon *et al*., 2012). At the moment, there are two main types of BP, those that contain nitrogen (oral: alendronate and risedronate, intravenous: pamidronate and zoledronate) and those that do not (etidronate, clodronate, and tiludronate). BP works by suppressing and reducing bone resorption by osteoclasts, directly impeding the recruitment and function of osteoclasts and indirectly stimulating osteoblasts to produce inhibitors of osteoclast formation (Hibi, 2020). BP is a medication derived from inorganic pyrophosphate, present in the body and physiologically regulating bone calcification and resorption. Pyrophosphate also provides greater resistance to chemical and enzymatic hydrolysis (Hibi, 2020). Camargo, Minosso, Lopes, (2007) (Camargo, 2007) report that therapeutic treatment should always combine an anti-resorptive agent with a non-pharmacological measure, such as physical exercise and consumption of calcium and vitamin D in the diet. Anti-resorption agents are described by Ishii (2009) as estrogen replacement therapy, selective modulators of estrogen receptors, BP, and calcitonin and also describe bone formation stimulating agents, such as a parathyroid hormone. Ourique *et al*. (2005) demonstrated in their studies that calcium intake is associated with hormone replacement (estrogen), which leads to an increase in trabecular bone mass. Calcium, when taken alone, is not able to definitively prevent the onset of osteoporosis. The authors also report that, in addition to osteoporosis, age, sex, races, hormonal pattern, decreased vitamin D synthesis, inhibition of calcium absorption, increased parathyroid hormone, nicotine, fragile physical structure, kidney failure, menopause, alcohol, and low calcium consumption can compromise the success of an implant. Still, according to Ishii *et al*. (2009), BPs are anti-resorptive agents derived from pyrophosphoric acid that invalidate bone resorption. Ferreira Junior *et al*. (2007) stated that BPcan 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, a peptide derived from parafollicular thyroid cells, aiding bone resistance.

Alendronate, for patients with osteoporosis, can be administered orally at 10.0 mg/day or 70.0 mg/week, and cannot be exceeded because it causes gastrointestinal changes, such as erosive esophagitis. It is necessary to use this medicine on an empty stomach, as it is poorly absorbed in the intestine and wait 40 to 60 minutes to feed. It is a drug that deposits about 40-60% quickly in the bone and the rest is released through the urine. BP plasma half-life is very short, ranging from thirty minutes to two hours; therefore, after the absorption of these drugs by bone tissue, they can persist for more than 10 years in skeletal tissues (Ourique, 2005). In addition, a meta-analysis study included clinical studies in humans, randomized or not. A total of 18 publications were included in the review. Regarding implant failure, the meta-analysis found a risk ratio of 1.73 (95% confidence interval (CI) 1.21-2.48, p = 0.003) for patients with BP when compared to patients who did not take the medicine. The probability of 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). It cannot be suggested that BP affects marginal bone loss from dental implants due to a limited number of studies reporting this result. Due to the lack of sufficient information, the meta-analysis for the outcome "postoperative infection" was not performed. The results of the present study cannot suggest that the insertion of dental implants in patients undergoing 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 still not well established (Chrcanovic, 2016).

Bisphosphonates – Complications: Ishii *et al*. (2009) stated that patients who use BP may have impaired healing of the damaged dental implant, as they prevent bone remodeling and can lead to a condition called osteonecrosis, considered a side effect of this drug. Although there is much data on the beneficial effects of BP in the treatment of advanced bone diseases, several reports have documented the ability of these drugs to cause local lesions of bone osteonecrosis mainly in the mandible (Abtahi, 2012). In this sense, osteonecrosis can remain asymptomatic for weeks and possibly months, and the lesions usually develop around conical areas and previous surgical sites, including extractions, retrograde apical tetanus, periodontal surgery, and dental implant surgery. Symptoms include pain, soft tissue swelling, infection, tooth loss, and drainage. Radiographically, osteolytic changes are observed and tissue biopsy shows the presence of actinomyces (Jacobsen, 2013). In the dental office, the most common BPs exposed to the implant are oral ones containing nitrogen, such as risedronate, ibandronate, and alendronate. Comprehensive anamnesis is essential before starting any elective treatment, the risk versus benefits of dental treatment should be discussed in detail with the patient (Memon, 2012). In this context, another study using BP analyzed the factors related to obtaining effective mechanical and immunological adhesion, viability, epidermal collagen growth factor, and immunoglobulin synthesis. The presence of BP culminated in less cell adhesion to the titanium discs, mainly for sodium alendronate (SA) at 5 μM (40%) and zoledronic acid (ZA) in all concentrations (30 to 50% according to the increase in concentrations). The reduced cell viability occurred after the exposure of these cells to ZA (40%); however, only 5 μM of cells treated with AS 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. The BPs negatively affected the adhesion and metabolism of the oral mucosa cells, and this effect was related to the type of BP, as well as to the concentration and treatment period. The negative effects of BP on oral mucosa cells can prevent the formation of an effective biological seal in osseointegrated implants (Basso, 2018).

In addition, a review study aimed to study the purpose of placing dental implants in patients who have been treated or are being treated with BP medication. Outcome measures included implant failure or implant-related mandibular osteonecrosis. In total, 32 sources of the literature were reviewed and 9 of the most relevant articles that fit the criteria were selected. Heterogeneity between studies was found and no meta-analysis can be performed. Five studies analyzed BP intraoral medication for implant placement, three studies analyzed BP intravenous medication for implant placement and one study evaluated the two types of drugs administered for implant placement. Patients with intraoral therapy appeared to have better implant survival (5 implants failed 423), a rate of 98.8% versus patients treated intravenously (6 implants

failed 68) by 91%. The control group compared to the intraoral BP group showed a 97% success rate in the implant survival rate (27 implants failed in 842), showing no significant difference in the success of implant placement. Patients treated with intravenous BP appear to have a greater chance of developing implant-related mandibular osteonecrosis. The group of patients treated intraorally appeared to have more successful results. The placement of the implant in patients treated intraorally can be considered safe with precautions (Gelazius, 2018). BP is a synthetic drug analogous to inorganic pyrophosphate, being endogenous regulators of bone mineralization. Its chemical structure presents PO3 phosphate linked to a central carbon and the union of chains called R1 and R2, chains of extreme importance for the effectiveness of these drugs (Abtahi, 2012). The R1 chain is short and is also responsible for having pharmacokinetic and chemical properties of BP (Junior, 2007). However, the R2 chain is long and determinant in relation to the mechanism of action and anti-resorptive power, presenting non-nitrogenous BP and nitrogenous structures, which are incorporated by osteoclasts in bone resorption, resulting in cell death due to apoptosis (Caldas, 2008).

In the chemical structure of BP, which is not nitrogenous, when metabolized by osteoclasts, they will be substrates for the synthesis of cytotoxic analogs of ATP, where cell death will occur (Barrantes, 2016). However, nitrates after being reabsorbed by osteoclasts act to interrupt the mevalonate pathway, responsible for controlling cholesterol synthesis. This interruption will compromise the intracellular vesicular transport, causing cell death, impairing bone resorption (Bernal, 2010). Bone resorption is performed by osteoclasts, which consist of bone mineral dissolution, leading to the formation of cavities and the release of elements from the bone matrix; in bone deposition, osteoblastic matrix synthesis occurs, leading to primary mineralization and an extensive secondary mineralization sequence (Sampaio, 2011). In addition to resorption, bone production is also limited by a decrease in the surface of the new formation. This decrease in bone formation occurs secondary to reduced resorption. The newly formed bones will have less chance of being newly formed, due to the reduced remodeling volume, generating more time for complete mineralization (Andrade, 2014). The prior knowledge of the dental surgeon about the side effects of medications with BP is of paramount importance, as well as the correct planning, management, clinical protocol, prevention and rehabilitation of recurrent changes in the use of this medication. It is up to the professional to carry out previous clinical evaluations and constant monitoring of oral health conditions in patients submitted to the use of these substances, in order to take the best preventive and curative measures for each case.

Conclusion

Osteoporosis is a metabolic condition that affects alveolar bone density, but does not present problems for the installation of osseointegrated implants, as long as there is sufficient bone mass in the region where the tooth will be implanted. It suggests to the dentist the knowledge of the diagnosis so that he can make a careful evaluation, guiding the professional to observe the quality of the bone through routine imaging exams. In addition, sodium alendronate is used to decrease bone resorption and should be considered as an adjunctive therapeutic agent for the treatment of osteoporosis.

Competing interests: The authors no have competing interests.

Acknowledgement

We appreciate greatly the UNIPOS graduate for support, also UNORP of Sao Jose do Rio Preto/SP;Brazil for the support.

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