

Bisphosphonates from a medical perspective: survey through questionnaire

Bisfosfonatos sob uma perspectiva médica: pesquisa por meio de questionário

Bisfosfonatos desde una perspectiva médica: encuesta a través de cuestionario

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Abstract

There is some controversy about the safety of invasive dental treatments in patients on bisphosphonates. The objective of this research was to verify, through the application of a questionnaire, the degree of knowledge that specialist physicians in Geriatrics, Rheumatology, Orthopedics, Gynecology and Oncology have about the interrelationship between the use of bisphosphonates and their effect on the bones of the maxilla and mandible. 100 health professionals were selected, uniformly distributed in five specialties. All were submitted to a questionnaire and the answers were tabulated. The highest indication of bisphosphonates was for osteoporosis 94%, followed by bone metastasis, Paget's disease, hypercalcemia, lytic lesion and bone fracture. As for the class of bisphosphonates, 50% of gynecologists, 78% of orthopedists, 94% of geriatricians and 100% of oncologists and rheumatologists answered that they prescribe the nitrogen class. Regarding the route of administration, geriatricians, gynecologists, orthopedists and rheumatologists prefer the oral route and only oncologists reported a preference for the parenteral route. The risk of osteonecrosis of the jaw related to the use of bisphosphonates is accepted by most physicians interviewed. All respondents refer all patients who have complications in the oral cavity resulting from the use of bisphosphonates to the dentist, however, they still do not indicate regular visits to the dentist before the onset of complications. We consider that there should be greater communication between the doctor and the dentist in cases where the patient uses bisphosphonates before and during treatment to minimize the severity of injuries involving the maxilla and mandible bones.

Keywords: Bisphosphonates; Osteonecrosis; Physicians; Dentists.

Resumo

Existe alguma controvérsia sobre a segurança de tratamentos odontológicos invasivos em pacientes em uso de bisfosfonatos. O objetivo desta pesquisa foi verificar, por meio da aplicação de um questionário, o grau de conhecimento que médicos especialistas em Geriatria, Reumatologia, Ortopedia, Ginecologia e Oncologia possuem sobre a inter-relação entre o uso de bisfosfonatos e seus efeitos nos ossos do corpo maxilar e mandíbula. Foram selecionados 100 profissionais de saúde, distribuídos uniformemente em cinco especialidades. Todos foram submetidos a um questionário e as respostas tabuladas. A maior indicação de bisfosfonatos foi para osteoporose 94%, seguida de metástase óssea, doença de Paget, hipercalcemia, lesão lítica e fratura óssea. Quanto à classe dos bisfosfonatos, 50% dos ginecologistas, 78% dos ortopedistas, 94% dos geriatras e 100% dos oncologistas e reumatologistas responderam que prescrevem a classe do nitrogênio. Quanto à via de administração, geriatras, ginecologistas, ortopedistas e reumatologistas preferem a via oral e apenas oncologistas relataram preferência pela via parenteral. O risco de osteonecrose da mandíbula relacionado ao uso de bisfosfonatos é aceito pela maioria dos médicos entrevistados. Todos os entrevistados encaminham ao dentista todos os pacientes que apresentam complicações na cavidade oral decorrentes do uso de bisfosfonatos, porém, ainda não indicam visitas regulares ao dentista antes do surgimento das complicações. Consideramos que deve haver maior comunicação entre o médico e o

dentista nos casos em que o paciente faz uso de bisfosfonatos antes e durante o tratamento para minimizar a gravidade das lesões envolvendo os ossos maxilar e mandibular.

Palavras-chave: Bisfosfonatos; Osteonecrose; Médicos; Dentistas.

Resumen

Existe cierta controversia sobre la seguridad de los tratamientos dentales invasivos en pacientes que toman bisfosfonatos. El objetivo de esta investigación fue verificar, mediante la aplicación de un cuestionario, el grado de conocimiento que tienen los médicos especialistas en Geriátrica, Reumatología, Ortopedia, Ginecología y Oncología sobre la interrelación entre el uso de bisfosfonatos y su efecto sobre los huesos de la maxilar y mandíbula. Se seleccionaron 100 profesionales de la salud, distribuidos uniformemente en cinco especialidades. Todos fueron sometidos a un cuestionario y las respuestas fueron tabuladas. La indicación más alta de bisfosfonatos fue para osteoporosis 94%, seguida de metástasis óseas, enfermedad de Paget, hipercalcemia, lesión lítica y fractura ósea. En cuanto a la clase de bisfosfonatos, el 50% de los ginecólogos, el 78% de los ortopedistas, el 94% de los geriatras y el 100% de los oncólogos y reumatólogos respondieron que recetan la clase nitrogenada. En cuanto a la vía de administración, los geriatras, ginecólogos, ortopedistas y reumatólogos prefieren la vía oral y solo los oncólogos reportaron preferencia por la vía parenteral. El riesgo de osteonecrosis de los maxilares relacionado con el uso de bisfosfonatos es aceptado por la mayoría de los médicos entrevistados. Todos los encuestados derivan al odontólogo a todos los pacientes que presentan complicaciones en la cavidad bucal producto del uso de bisfosfonatos, sin embargo, aún no indican visitas periódicas al odontólogo antes de la aparición de las complicaciones. Consideramos que debe haber una mayor comunicación entre el médico y el odontólogo en los casos en que el paciente utilice bisfosfonatos antes y durante el tratamiento para minimizar la gravedad de las lesiones que involucran los huesos maxilares y mandibulares.

Palabras clave: Bisfosfonatos; Osteonecrosis; Médicos; Dentistas.

1. Introduction

Bisphosphonates are used to control the bone remodeling cycle in individuals with malignant neoplasms and in cases of individuals with osteoporosis, Paget's disease, osteogenesis imperfecta among other benign bone disorders (Ribeiro de Freitas et al., 2016). These drugs can be divided according to their mechanism of action into nitrogen, among which we find alendronate, risedronate, ibandronate, pamidronate and zoledronic acid and non-nitrogenous ones such as etidronate, clodronate and tiludronate (Silva et al., 2016). There are two ways of administering bisphosphonates. Oral bisphosphonates have a low absorption rate being deposited in the bone of 20 to 80% of the substance (Holzinger et al., 2014), whereas intravenous bisphosphonates may take more than 10 years to be metabolized and excreted (Fung et al., 2015). Bisphosphonates are anti-resorptive drugs used to treat many diseases and conditions of increased bone resorption and are considered the main drugs associated with drug-associated jaw osteonecrosis (MRONJ) (Alonzo-Rodriguez et al., 2019). Some studies report hypotheses about the pathophysiology of osteonecrosis, which are the pharmacological inhibition of bone remodeling and angiogenesis, presence of trauma, inflammation, infection, soft tissue bisphosphonate toxicity and innate or acquired immune dysfunction (Ruggiero et al., 2014; Aghaloo et al., 2015). The purpose of this research was to determine, through the application of a questionnaire, the degree of knowledge that the specialists in geriatrics, rheumatology, orthopedics, gynecology and oncology have about the interrelationship between bisphosphonate use and its effect on bone jaw.

2. Methodology

The research project was submitted to the Research Ethics Committee of the School of Dentistry and Institute and Center for Dental Research São Leopoldo Mandic - Campinas / SP and approved under No. 1,303,782, in a meeting held on 10/30/15.

The study was an exploratory field research. This type of study delimits a field of work, seeking to gather information about a given problem. In this way, the manifestation conditions are mapped, aiming at explanatory research (Severino, 2018).

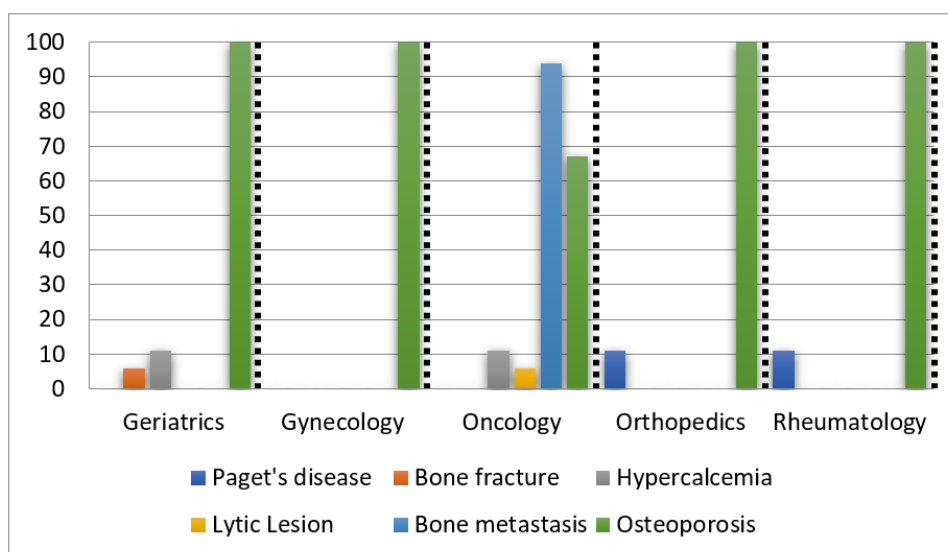
The sample consisted of 100 health professionals, evenly distributed in five specialties, without delimitation of

gender, age and social profile. The criteria adopted for the inclusion of these health professionals were: (1) Graduated Medical Professionals, (2) CE Resident Professionals, (3) CREMEC / CE Registered Professionals, (4) Specialized Professionals in at least one of the following specialties: Orthopedics, Geriatrics, Oncology, Rheumatology and Gynecology, (5) Professionals who accepted to participate in the research, (6) Professionals who correctly signed the informed consent form. A questionnaire was applied directly to the medical profession by a single examiner who impartially clarified the questions that arose throughout the questions. This questionnaire had 20 questions prepared by the examiner himself regarding the subject that was addressed. All results were released in data sheets. Each doctor was given a number just as each quiz question was listed. The alternatives for each proposition were divided into letters, varying according to the number of alternatives.

3. Results and Discussion

After applying the questionnaire, twenty professionals from each specialty resulted: Orthopedics, Geriatrics, Oncology, Rheumatology and Gynecology. As for bisphosphonate prescription, 70% of gynecologists, 90% of geriatricians, oncologists, orthopedists and 100% of rheumatologists answered that they prescribe bisphosphonates. The main indication for bisphosphonate was for osteoporosis, with 94%, followed by bone metastasis with 19%. Also mentioned were Paget's disease with 5%, hypercalcemia with 5%, lytic lesion with 1% and bone fractures with 1%. Geriatricians usually indicate osteoporosis treatment (100%), but hypercalcemia (11%) and atypical bone fractures (6%) were also mentioned for this specialty. Gynecologists, in turn, prescribe drug therapy for osteoporosis (100%). Oncologists, for the most part, prescribe for the treatment of bone metastasis (94%), but still indicate as drug therapy for osteoporosis (67%), hypercalcemia (11%) and lytic lesion (5%). Orthopedists prescribe for the treatment of osteoporosis (100%), but Paget's disease (11%) was also cited by this specialty. Rheumatologists indicate as a drug therapy for osteoporosis (100%), but still indicate for the treatment of Paget's disease (11%) (Figure1).

Figure 1 - Indication according to specialty.



Source: Author's Database.

In this figure it is visually perceptible that all specialists indicate bisphosphonates mainly in patients with osteoporosis.

Regarding the bisphosphonate class, 9% of prescribing physicians indicate the chlorinated class, while 91% opt for

the nitrogen group, being gynecologists (50%), orthopedists (78%), geriatricians (94%), oncologists and rheumatologists (100%). The most commonly used route of administration was oral (82%), followed by the parenteral route (18%). The oral route was more indicated by geriatricians, gynecologists, orthopedists and rheumatologists (100%). The parenteral route was more indicated by oncologists (89%). Regarding the duration of therapy, 52% of all physicians indicate for a period longer than three years, the other 48% for a period of less than three years, all independent of the route of administration.

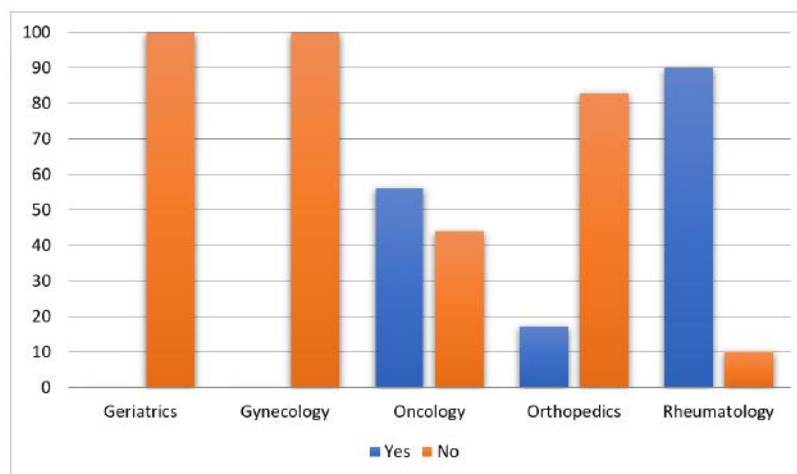
Most geriatricians (72%) prescribe for less than three years, regardless of the route of administration employed, while only 28% prescribe for more than three years. About 71% of gynecologists prescribe for a period of less than three years, regardless of the route of administration used, while 29% indicate for more than three years. Most oncologists (67%) prescribe for a period of less than three years, regardless of the route of administration employed, while only 33% prescribe for more than three years. About 28% of orthopedists prescribe for a period of less than three years, regardless of the route of administration employed, in contrast the majority (72%) indicate for more than three years; Approximately 10% of rheumatologists prescribe for less than three years, regardless of the route of administration employed, while the majority (90%) prescribe for more than three years. Regarding the interruption of treatment, due to the need for surgical intervention, 65% of physicians would agree to suspend the use of bisphosphonate for a period of one year. Specifically, 56% of geriatricians, 86% of gynecologists, 61% of oncologists, 67% of orthopedists, and 60% of rheumatologists responded that they would agree to discontinue bisphosphonate use for a period of one year because of the need for surgical intervention. However, 35% did not agree with this interruption.

Regarding jaw osteonecrosis, 78% of physicians agreed on the possibility of triggering this complication after any intraoral surgical treatment in patients using bisphosphonate. Already 22% say they are unaware of such risks. Specifically, 72% of geriatricians, 57% of gynecologists, 100% of oncologists, 72% of orthopedists and 65% of rheumatologists replied that they agreed on the possibility of triggering this complication in bisphosphonate patients. In addition, it was also examined whether patients were clear about the risk of developing jaw osteonecrosis with bisphosphonate after any invasive dental surgery, where 87% of experts responded advising patients about this possible adverse effect and only 13 % said no. Specifically, 85% of geriatricians, 67% of gynecologists, 100% of oncologists, 77% of orthopedists, and 88% of rheumatologists responded that they clarified patients with regard to the risk of developing jaw osteonecrosis after bisphosphonate use. invasive dental surgery. Regarding the case series of osteonecrosis in the jaws, related to the use of bisphosphonates, in the clinical practice of physicians who responded prescribing this drug, the presence of this disease was not observed by most of them (83%). Only 17% reported a history of jaw osteonecrosis in their offices after using this medication. Specifically, 56% of oncologists, 17% of orthopedists and 90% of rheumatologists reported a history of jaw osteonecrosis in their offices after bisphosphonate use. There was no presence of this disease in the clinical practice of geriatricians and gynecologists (Figure 2).

Regarding the bisphosphonate route of administration, in clinical cases of jaw osteonecrosis, 73% of the cases were parenterally administered bisphosphonates and only 27% were administered orally. It can be evidenced that in all cases of jaw osteonecrosis reported by oncologists, parenteral bisphosphonates were used; Already in 67% of the cases reported by orthopedists and in all cases reported by rheumatologists were administered orally. No osteonecrosis was observed in the jaws in the clinical practice of geriatricians and gynecologists. Among the patients with osteonecrosis in the jaws involving bisphosphonate use, 60% had concomitant bone cancer, 27% had osteoporosis, while 13% had no other disease. Of the cases reported by oncologists, 60% had concomitant bone cancer, 20% had osteoporosis, the other 20% were healthy; In the cases reported by orthopedists, 33% concomitantly had cancer, while 67% had osteoporosis. All cases reported by the rheumatologists had concomitant bone cancer. No osteonecrosis was observed in the jaws in the clinical practice of

geriatricians and gynecologists.

Figure 2 - Casuistry of osteonecrosis in the jaws related to the use of bisphosphonates.



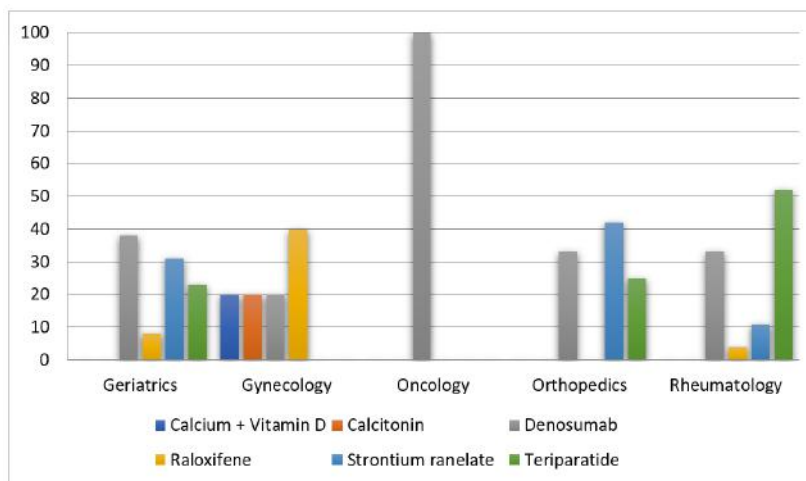
Source: Author's Database.

The figure shows that most individuals who had osteonecrosis of the jaws were identified mainly in rheumatology, oncology, and orthopedics consultations.

Regarding the presence and / or absence of harmful habits to health in cases of characteristic lesions of osteonecrosis in the jaws, related to bisphosphonate use, in 73% of the reported clinical cases, the patient had no bad habits and in 27%, the patients they smoked. Specifically, only 40% of the clinical cases of jaw osteonecrosis related to bisphosphonate use reported by oncologists were smokers. No harmful health habits were noted in the cases reported by orthopedists and rheumatologists. No osteonecrosis was observed in the jaws in the clinical practice of geriatricians and gynecologists. As for the existence of another medication that can replace bisphosphonate effectively and with less adverse effects, 55% of physicians who prescribe bisphosphonate reported knowing other drugs, while 45% would not be able to indicate other pharmacological therapy. Specifically, 72% of geriatricians, 29% of gynecologists, 28% of oncologists, 50% of orthopedists, and 85% of rheumatologists responded that they know of another medication that can replace bisphosphonate effectively and with less adverse effects. In addition, it was asked which other drug could replace bisphosphonate with proven efficacy and fewer adverse effects, where 50% cited denosumab, 42% teriparatide, 27% strontium ranelate, 8% raloxifene, 2% calcitonin and 2% calcium and vitamin D.

Specifically, for drugs that could replace bisphosphonate with proven efficacy and fewer adverse effects, 38% of geriatricians cited denosumab, 8% raloxifene, 31% strontium ranelate and 23% teriparatide. Of the gynecologists 20% cited calcium and vitamin D, 20% calcitonin, 20% denosumab and 40% raloxifene. All oncologists cited denosumab. Of the orthopedists, 33% mentioned denosumab, 42% strontium ranelate and 25% teriparatide. Of the rheumatologists, 33% cited denosumab, 4% raloxifene, 11% strontium ranelate and 52% teriparatide (Figure 3).

Figure 3 - Drugs that could replace bisphosphonate according to doctors.



Source: Author's Database.

In this figure, we observe that most professionals interviewed agreed that Denosumab is the drug that can replace the use of bisphosphonates.

Regarding the importance of a dental pre-assessment before starting bisphosphonate therapy, 58% of physicians considered it relevant, and 42% believed it to be indifferent. Specifically, 19% of geriatricians, 50% of gynecologists, all oncologists, 67% of orthopedists, and 35% of rheumatologists consider a dental pre-assessment important before starting bisphosphonate therapy. The importance of following up with the dentist on bisphosphonate patients was also evaluated, where 53% of physicians who indicated this drug recommend regular visits to the dentist, and 47% do not consider dental follow-up relevant. Specifically, 39% of geriatricians, 64% of gynecologists, 78% of oncologists, 67% of orthopedists and 25% of rheumatologists recommend regular visits to the dentist. Among the doctors who prescribe bisphosphonate, when clinical cases with lesions characteristic of osteonecrosis in the jaws arise related to the use of bisphosphonates, all consider it essential to refer the patient to the dentist. Regarding the presence and / or absence of other adverse effects related to bisphosphonate use, other than jaw osteonecrosis, 78% of physicians prescribing this medication observed other adverse effects. Specifically, 67% of geriatricians, 64% of gynecologists, 89% of oncologists, 83% of orthopedists and 85% of rheumatologists observed the presence of bisphosphonate-related adverse effects in patients in their offices.

Then, what were the possible opposite actions? 33% of professionals found esophagitis, 32% gastric dysfunction, 28% musculoskeletal pain, 25% renal dysfunction, 23% atypical bone fracture, 5% hypocalcemia and 5% fever. Geriatricians observed gastric dysfunction (36%), skeletal muscle pain (14%), esophagitis (43%), atypical bone fracture (7%). Gynecologists observed gastric dysfunction (42%), skeletal muscle pain (25%), esophagitis (25%), atypical bone fracture (8%). Oncologists noted gastric dysfunction (4%), renal dysfunction (50%), skeletal muscle pain (25%), fever (8%), hypocalcemia (13%). Orthopedists observed gastric dysfunction (20%), skeletal muscle pain (13%), esophagitis (7%), atypical bone fracture (60%). Rheumatologists observed gastric dysfunction (19%), renal dysfunction (10%), skeletal muscle pain (14%), esophagitis (43%), fever (5%), atypical bone fracture (10%).

In the present study, in relation to the bisphosphonate prescription, 88% of experts answered that they prescribe this medication, while only 12% reported not having contact with this drug, confirming the literal data that points the bisphosphonates as a class of first choice drugs. for the treatment of diseases that include excessive osteoclastic action. This preference is related to the significant improvement in the quality of life of users of this drug, thus, they have been prescribed on a large scale (Ghoneima et al., 2010; Agrillo et al., 2012; MCClung et al., 2013).

As for bisphosphonate indications, according to professionals who reported prescribing the drug, we have: 94% for osteoporosis, 19% for metastasis, 5% for Paget's disease, 5% for hypercalcemia, 1% for lytic lesion, and 1% for bone fractures. In addition to these possibilities, bisphosphonates can literally be clinically used to treat various other osteodegenerative diseases. All based on its mechanism of action, due to its ability to selectively inhibit osteoclastic cells and also their antitumor property (Ghoneima et al., 2010; Agrillo et al., 2012; MCClung et al., 2013; Russel, 2011).

Among the professionals who reported prescribing this medication, if surgical intervention is required, 65% agreed to discontinue use of the medication for a period of one year, regardless of the route of administration. However, 35% did not accept discontinuation of bisphosphonate therapy. At this point, there is still controversy about the positive effect of pausing bisphosphonate therapy. Some researchers believe that the patient will benefit from stabilizing osteonecrosis lesions in the jaws, reducing the risk of new injuries, decreasing symptoms related to osteonecrosis in the jaws and some adverse effects (Dimopoulos et al., 2009; Papapetrou, 2009; Ruggiero et al., 2009).

On the other hand, other scholars state that even if bisphosphonate use is discontinued prior to surgery, the risks of complication would not be reduced, and bone pain, lytic lesions, bone metastases and some adverse effects may recur, that these drugs may influence bone metabolism, due to their negative charge and chemical structure, up to ten years after drug therapy has been discontinued (Papapetrou, 2009; Yip et al., 2012).

Knowledge about the theme of jaw osteonecrosis after intraoral surgical treatment was evaluated in this study. Seventy-eight percent of the interviewed physicians answered that they are aware of the risk of jaw osteonecrosis after dental surgery in bisphosphonate patients, 22% say unaware of such risks. Numerous cases of jaw osteonecrosis related to bisphosphonate use have been reported in the literature, based on a combination of several factors, such as the complex interaction in bone remodeling, inhibiting osteoclastic action, inducing an overly hard bone; the constant local trauma, resulting in the accumulation of numerous microlesions; the need for bone repair far above the capacity of hypodynamic maxillary bone renewal; the presence of infection; osteocyte apoptosis and hypovascularization, which will compromise bone nutrition (Goss et al., 2010; Shin et al., 2010; Vescovi et al., 2011; Sebestyen et al., 2012; Vestergaard et al., 2012).

In the clinical practice of the specialists, no cases of osteonecrosis in the jaws were observed in patients using bisphosphonate by most professionals (83%). Only 17% of physicians reported a history of maxillary osteonecrosis in their offices, whereas it has been reported in the literature that bisphosphonate-related osteonecrosis of the jaws is a rare complication, in absolute numbers, but not statistically significant. It is noteworthy that bisphosphonate-related osteonecrosis in the jaws is a severe complication that can lead to high morbidity in affected individuals, demonstrating a concern of the scientific community and health professionals with its approach, prevention and treatment (Vescovi et al., 2011; Lazarovici et al., 2009; Leung et al., 2009).

On the other hand, among the physicians who reported that they reported a history of jaw osteonecrosis in their offices involving the bisphosphonate, the route of drug administration was evaluated, showing that 73% of the clinical cases were used intravenously, only 27% were orally. According to the literal data, the incidence of triggering of osteonecrosis in the jaws related to the use of orally administered bisphosphonate is minimal, however, possible. However, although there are cases in patients who use orally, the highest percentage remains in users of intravenous bisphosphonate, perhaps because they have a much higher dosage and bioavailability than the oral route and are employed for a much longer period, being more frequent. potent, thus causing an exacerbated reduction of osteoclast action (Vestergaard et al., 2012).

The duration of bisphosphonate therapy was also evaluated, slightly more than half of the doctors interviewed (52%) responded that they prescribed the drug for a period of more than three years, both oral and parenteral, and the remainder (48%) reported that they indicated therapy for less than three years, regardless of the route of administration. Another alarming

fact is that the prolonged and continuous use of bisphosphonates may considerably increase the risk of osteonecrosis in the jaws, since, because they are not metabolized by the body, accumulating and remaining in the bone matrix for long periods of time, the presence of a high concentration of this drug in active bone remodeling sites increases its potency, suppressing bone repair and / or renewal. Thus, the benefits of prolonged bisphosphonate use should be weighed against the potential negative effects of bone metabolism suppression (Russe, 2011; Sebestyen et al., 2012; Dell et al., 2012; Feldstein et al., 2012; Meier et al., 2012; Erviti et al., 2013).

Professionals who observed a history of jaw osteonecrosis in their clinical practice involving the bisphosphonate were asked if the patient had pathogenic comorbidity and what the disease (s) would be. 60% of the reported clinical cases, patients concomitantly had cancer, 27% had osteoporosis, while 13% had no other disease, asserting that the majority of patients with jaw osteonecrosis have an associated health problem, not ruling out the possibility of developing jaw osteonecrosis in concomitant bisphosphonate users (Dodson, 2009; Shane et al., 2010).

According to the results of this study, 58% of the interviewed physicians considered relevant a dental examination before the administration of these drugs, or 42%, who said it was not important. Still, 53% recommend to users regular visits to the dentist, while a large percentage, 47%, do not consider dental follow-up important. Since alveolar bone has up to ten times higher bone turnover rates than other bones in the human body, some dental treatments that require bone repair may be compromised in bisphosphonate users. Thus, for preventive purposes, it is essential that the doctor refer the dentist for an oral evaluation prior to treatment, in order to provide the patient with a good oral adequacy, especially performing invasive procedures before bisphosphonate use, when there is need. In addition to advising the patient, they regularly visit the dental surgeon to monitor their oral health, detecting and treating if caries and periodontal diseases occur even in the early stages (Vestergaard et al., 2012).

In addition to jaw osteonecrosis, in relation to the other negative adverse effects of bisphosphonates, the vast majority of specialists, 78%, observed the presence of other opposite actions, while 22% reported no other effects. In addition, of these 78% of physicians who observed other negative side effects, 33% of these professionals found esophagitis, 32% gastric dysfunction, 28% musculoskeletal pain, 25% renal dysfunction, 23% atypical bone fracture, 5% hypocalcemia and 5 % fever. In addition to these systemic adverse effects, eye disorders, acute phase response, atrial fibrillation, cancer, among others, as well as local effects on the oral cavity were also noted (McClung et al., 2013).

4. Final Considerations

In this study, it was found that the relevance of a multidisciplinary treatment, with interaction between the doctor and the dentist, in the treatment of patients who use bisphosphonates is still unclear.

We believe that there should be greater communication between the doctor and the dentist in cases where the patient uses bisphosphonates before and during treatment to minimize the severity of injuries involving the maxillary and mandibular bones.

As a perspective for future studies subsequent to this work, case-control studies or even cohorts are suggested to evaluate changes in drug prescriptions mainly in patients with osteoporosis and in oncological cases with bone metastasis.

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