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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Dental implants osseointegration in patients with osteoporosis

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Abstract. The successful use of surgical and medical methods of jaw bone tissue restoration has been convincingly confirmed in clinical practice. At the same time, technologies are being developed to improve the osseointegration of dental implants in patients with osteoporosis. The use of various implant coatings, as well as systemic therapy, demonstrate the emergence of new directions in the treatment of patients with partial or complete secondary edentulism with concomitant osteoporosis. This trend is relevant in modern medicine. Information was obtained from the PubMed database, using the keywords «osteoporosis» and «osseointegration» and «dental implantation» and «zoledronic acid» from 2016 to 2022. Articles were selected based on experimental work. Numerous studies have shown that bone tissue is an effective indicator of osteoporotic changes. The main changes in bone tissue in osteoporosis are emphasized — a decrease in bone volume, deterioration of the microarchitecture of the trabecular bone and processes that prevent osseointegration — loss of bone mass, a significant decrease in the percentage of contact in the implant-bone complex. Methods of dealing with the negative impact on the operation of dental implantation have been identified. In a review of studies on the systemic administration of drugs based on bisphosphonates, an increase in the osseointegration of dental implants was revealed, the systemic administration of zoledronic acid preparations significantly increased the formation of new bone, which in turn contributed to the elimination of such a negative effect of osteoporosis as bone resorption. In addition to the systemic administration of bisphosphonates, experimental studies describe the topical application of bisphosphonates in the form of various implant coatings. Topical application of bisphosphonates also contributed to increased osseointegration. Microstructured coated implants showed less marginal bone loss compared to uncoated implants. *Conclusion.* The use of dental implants with modified macro- and microrelief, as well as systemic drug therapy, remains the main direction of scientific research that contributes to the optimization of osseointegration of dental implants.

Key words: osteoporosis, osseointegration, dental implant surgery, zoledronic acid

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Introduction

Bone diseases constitute a large group of common diseases, including osteoporosis, which affects a large number of people, especially the elderly [1]. Osteoporosis is defined as low bone mineral density caused by changes in microstructure that ultimately predisposes patients to low — impact, brittle fractures. Osteoporotic fractures lead to a significant decrease in the quality of life, an increase in morbidity, mortality and disability [2]. Bone remodeling is tightly controlled by osteoclast — mediated bone resorption and osteoblast — mediated bone formation. Fine tuning of the osteoclast — osteoblast balance leads to a strict synchronization of bone resorption and formation, which maintains the structural integrity and homeostasis of bone tissue. Conversely, dysregulation of bone remodeling can cause pathological osteolysis, in which inflammation plays a vital role in promoting bone destruction [3]. Osseointegration is a direct structural and functional connection between an ordered living bone and the surface of a load — bearing implant [4]. Implant osseointegration is an important biological basis of dental implantology [5]. Osteoporosis contributes to impaired osseointegration due to an imbalance in the activity of osteoblasts and osteoclasts. Subsequently, there is a delay in the formation of bone around the implant after dental implant surgery. This leads to an increase in the rehabilitation period and reduces the quality of life in patients with partial/complete secondary loss of teeth [6].

Bone remodeling occurs at the endosseous surfaces where osteoclasts and osteoblasts are located. The bone tissue of the upper and lower jaws is one of the first indicators of osteoporotic changes in the body. There is a strong relationship between hormones, osteoporosis, and aging that affect the alveolar process and skeletal bones in the same way, but it is important to consider the differences in load between loaded, partially loaded, and unloaded bones. Bone mass is redistributed from one place to another where strength is required. Infrequent trabeculation in the region of mandibular premolars — large intertrabecular spaces and thin trabeculae — is a reliable sign of osteopenia and a high risk of skeletal fracture [7].

In the study by M. Chatterjee et al. (2021) determined microarchitectural changes in the jawbone in response to oophorectomy. 47 rats were ovariectomized and treated prophylactically for osteoporosis for eight weeks with bisphosphonates. Bone-morphometric parameters of the spongy bone of the jaws were assessed using microcomputed tomography. In the region of the upper jaw, trifurcation bone tissue was examined in the region of the second molar and the tubercle of the upper jaw, as well as the region of the lower jaw

in the three regions of the molars and condyles. In the upper jaw, after ovariectomy, the volume of bone in the interradicular septum of the second molar decreased. Treatment with bisphosphonates helped prevent jaw bone loss. At the site of the condylar process of the mandible, the microarchitecture of the trabecular bone significantly deteriorated, while prophylactic treatment with bisphosphonates showed a positive effect in this area of the trabecular bone. Thus, the results of this study showed that osteoporosis caused by ovariectomy manifests itself locally in certain areas of the jaws, and treatment with bisphosphonates can prevent negative changes [8].

In the work of T. Alam et al. (2020) studied postmenopausal women. The subjects were divided into two groups. The osteoporosis group included 30 patients, as well as the group without osteoporosis. A panoramic radiograph was taken followed by two direct digital intraoral periapical radiographs of the premolars and mandibular molars. A statistically significant difference was found in the shape index of the mandibular cortical bone between the two groups. However, there were no statistically significant differences between the two groups in cortical width, mandibular panoramic index, degree of mandibular alveolar bone resorption, fractal dimension, and mean number of teeth. A statistically significant difference was observed in mean age between groups with osteoporosis and groups without osteoporosis. The results of the cortical index of the mandible on a panoramic radiograph are effective indicators of bone changes in postmenopausal osteoporosis. These results further demonstrate the effect of osteoporotic processes on the jaw bones due to reduced estrogen production [9].

A study by Xi Chen et al. (2021) aimed to evaluate the effect of estrogen deficiency and mechanical stress on the bone around osseointegrated dental implants in a rat jaw model. In 36 rats, the first molars in the first segment were extracted. After one week, the rats were divided into the unloaded group and the loaded group, short head implants and long head implants were inserted, respectively. Nine weeks after implantation, the rats underwent an additional oophorectomy or sham operation. Euthanasia was performed 21 weeks after oophorectomy. Bone tissue samples were studied by microcomputed tomography, histological and histomorphometric evaluation was carried out. Systemic bone mineral density (BMD) and bone volume decreased in groups of ovariectomized rats compared with controls. In a histomorphometric study of ovariectomized rats, it was shown that the osseointegration of dental implants was significantly impaired in the group without loading, there was a loss of bone mass compared to the group with loaded implants. Both BMD and the percentage of implant—bone contact were lower in ovariectomized rat groups than in controls, although mechanical loading increased bone—to—implant contact and BMD. The percentage of «sclerostin—positive» osteocytes was lower under exercise compared with unloaded conditions in both the ovariectomized and control groups. The results indicate that estrogen deficiency may be a risk factor for the long—term stability of osseointegrated implants, while mechanical loading may reduce the negative impact of estrogen deficiency on bone formation and osseointegration [10].

In the work of K. Anderson et al. (2020) demonstrated the negative impact of osteoporosis on bone tissue in several ways, in addition to the loss of bone volume, the ability to repair bone tissue, deterioration of the architecture and quality of the bone matrix also decreased. The results obtained in vivo and in clinical studies indicate promising results for the use of osteoporosis drugs to improve implant osseointegration. These results demonstrate that implant osseointegration in osteoporotic bone proceeds more adequately under the influence of drugs for the treatment of osteoporosis [11].

Osteoporosis as an aggravating factor in osseointegration

Oral health is an important component of a person's overall health and quality of life [12]. Elderly patients are now increasingly seeking dental treatment and, in particular, the replacement of missing teeth with dental implants [13]. Therefore, the impact of aging on alveolar bone is of increasing importance with the growth of the

elderly population, especially since increasing age is associated with an increase in the prevalence of systemic diseases such as osteoporosis [14].

Numerous safe and effective drugs are now available for the treatment of osteoporosis, including postmenopausal osteoporosis [15].

Dental implantation is a widely used treatment for patients with missing or defective teeth [16, 17]. Sufficient bone volume (BV) and bone mineral density (BMD) are the two most important factors for predicting the long—term success of dental implant osseointegration. However, osteoporosis, which has a high prevalence in elderly patients, reduces bone density and increases the risk of failed osseointegration and loss of implants [18, 19].

Influencing the osseointegration of implants in patients with osteoporosis is a necessity, since implantation in these patients often fails [20, 21]. Currently, in clinical practice, there are several methods for the prevention and treatment of osteoporosis, the main of which are bisphosphonates. Bisphosphonates are a group of drugs commonly used to treat osteoporosis based on zoledronic acid. Zoledronic acid (ZOL) is a potent bisphosphonate that prevents bone resorption by blocking osteoclast—mediated bone resorption [22]. There are both local application of preparations based on modified coatings and systemic drug therapy [23].

Methods to promote osteointegration

Systemic use of bisphosphonates

In the study by N. Sokmen et al. (2021) studied the effect of systemic application of ZOL on the osseointegration of titanium implants with and without primary stability. Male Sprague Dawley rats were divided into 2 main groups: with primary stabilization (PS +) and without it (PS -). These main groups were divided into a control group and 0.1 mg/kg systemic administration of ZOL. All subjects were euthanized after a 4—week recovery period. The connection of the bone implant and the filling of the threads of the samples were analyzed according to the method of histological analysis without decalcification. Regarding the percentage of thread filling and bone implant connection, statistically significant differences were found between groups with and without PS. The overall effect of the use of ZOL and PS on the percentage of bone graft connection was found to be statistically significant. Within the framework of this study, it can be concluded that the systemic administration of zoledronic acid can enhance the osseointegration of the implant [24].

M. Oliveira et al. (2015) evaluated the effect of intravenous bisphosphonates in combination with or without dexamethasone on the osseointegration of titanium implants placed in an animal model. 27 male Wistar rats were divided into 3 groups: group 1 was treated exclusively with zoledronic acid, group 2 was treated with zoledronic acid and dexamethasone, and group 3 received saline injections only. Two intraosseous implants were placed in each tibia. Three animals from each group were euthanized at postoperative days of 7, 14 and 28 days. Non—decalcified sections were observed by light microscopy for histological and histomorphometric analyses. Histomorphometric analysis using animals and implants as the unit of measure did not reveal a statistically significant difference in bone—to—implant contact and bone density between the three groups. Histological observation showed that animals treated with zoledronic acid in combination with or without dexamethasone showed markedly lower bone remodeling activity 14 and 28 days after implant placement compared to controls. The studied bisphosphonate regimens did not interfere with implant osseointegration, cortical or bone deposition, but the possible lack of bone remodeling of the original cortical bone may affect long—term osseointegration [25,26].

M. Lotz et al. (2019) evaluated the effect of bisphosphonates on the osseointegration of titanium implants with microstructure surfaces, which have been shown to support osteoblast differentiation in vitro and rapid osseointegration in vivo. 40 Sprague Dawley rats were subjected to ovariectomy (OV) or sham surgery (SS). After 5 weeks, animals were injected subcutaneously with bisphosphonate (BP) or phosphate buffered saline (PBS) every 25 days. One week after the initial injection, the micro-relief implants were transcortically placed in the distal

metaphysis of each femur, resulting in four groups being divided: 1) SS + PBS; 2) SS + BP; 3) OV + PBS and 4) OV + BP. After 28 days, the qualitative characteristics of bone and implant osseointegration were assessed using microcomputed tomography, calcified histomorphometry, and a torque test during removal. Micro — CT revealed a decrease in bone volume in ovariectomized rats, which was retarded by treatment with bisphosphonates. The reduction in bone — to — implant contact was evident with OV + PBS compared to SS + PBS. In OV + BP compared to OV + PBS, bisphosphonate treatment did not reduce bone — to — implant contact. The torque test showed a higher result, torsional stiffness and torsional energy in SS compared to OV without any effects associated with bisphosphonate treatment. The results show that osseointegration is reduced in osteoporotic animals. Bisphosphonates stop the progression of osteoporosis but do not enhance osseointegration [27].

N. Mardas et al. (2017) evaluated new bone formation in osteoporotic rats treated with zoledronic acid (ZOL). The study included 48 Wistar rats, of which 32 had osteoporosis caused by oophorectomy. Of these, half of the rats received a single dose of ZOL, while the other half received no treatment. The remaining 16 rats were sham — operated and used as healthy controls. New bone formation was assessed by qualitative and quantitative histological analysis. Hierarchical analysis of variance showed that treatment with ZOL significantly increased new bone formation, while the presence of osteoporosis could reduce new bone formation. Thus, the study proves once again that the treatment of ZOL can improve the formation of new bone in rats with osteoporosis and promote bone healing in rats [28].

S. Dikicier et al. (2017) evaluated the effect of systemic intravenous administration of zoledronic acid (ZOL) on implant osseointegration and surrounding bone mineral density (BMD) in ovariectomized rats. 36 rats were divided into three groups: control (C), ovariectomized (OV), and ovariectomy — zoledronic acid (OV/ZOL). Rats in the C group underwent sham surgery, while rats in the OV and OV/ZOL groups underwent oophorectomy. After 12 weeks, OV/ZOL rats were injected with 0.04 mg/kg ZOL intravenously once a week for 6 weeks. Rats of groups K and OB were injected with 0.9 % NaCl. The implants were placed into the bone. After 8 weeks, the rats were euthanized and the bone was removed for radiodensitometric study. The results showed that there were statistically significant differences between all groups. While the highest mean BMD values were observed in the OV/ZOL group, the lowest were in the OV group. Systemic use of ZOL increased bone density around implants placed in rat osteoporotic bone [29].

Topical application of bisphosphonates

The problem of improving the effectiveness of implant treatment of patients with osteoporosis remains relevant today due to the high incidence of postoperative complications. Among the main factors influencing the success of dental implant treatment, the nature of the implant surface is important. For patients with adentia osteoporosis, the use of dental implants with an optimized surface, a conditioned component that affects bone remodeling is especially important [30]. Osteoblast adhesion is an important step in the osseointegration of dental implants and can be affected by modification of the implant surface or the addition of bioactive substances [31].

Osseointegration of dental implants can be facilitated by modification of the implant surface using bisphosphonate coatings. In addition, there is clinical interest in promoting bone formation around the implant and restoring bone structure in patients with low bone mass. The combination of an antiresorptive coating of an implant with zoledronic acid (ZOL) and a systemically applied anti — sclerostin antibody compared with treatment with a single anti-sclerostin antibody or a coating of the ZOL implant was evaluated by P. Korn et al. (2019) in a rat osteoporosis model. Uncoated control surface implants and ZOL coated implants were placed in the proximal tibia of old osteoporotic rats three months after oophorectomy. 32 rats in each group received anti — sclerostin antibody therapy once a week. Osseointegration was assessed 2 and 4 weeks after implantation using histological and biomechanical testing. The overall

implant survival was 97 %. Histomorphology revealed pronounced bone formation along the entire length of the ZOL—coated implant. At 4 weeks post—implant placement, bone—to—implant contact, cancellous bone mineral density, and bone/tissue volume were significantly increased for the combination of ZOL and anti—sclerostin antibody compared to either anti—sclerostin antibody or only ZOL—coated implant. Removal time was also significantly increased in the combination therapy group compared to animals treated with anti—sclerostin antibodies alone or with ZOL—coated implants. In a rat model with osteoporosis, the combination of anti—resorptive coating of the ZOL implant and systemically applied antibodies to sclerostin resulted in a significant increase in bone formation around the implant. Therefore, the combination of ZOL and an antibody to osteoanabolic sclerostin was more effective than either agent alone [32].

S. Kellesarian et al. (2017) also evaluated the effect of topical zoledronate (ZOL) supplementation, topically or as an implant surface coating, on osseointegration. In 18 studies, ZOL was applied to implant surfaces as a coating, and in five studies, ZOL was applied topically into bone cavities. As a result, 87 % of the studies have shown that topical application of ZOL is effective in enhancing osseointegration or new bone formation around implants. Thus, another study proves that local administration of ZOL enhances osseointegration in animals [33].

The aim of the clinical study by J. Abtahi et al. (2019) was to evaluate the effect of a bisphosphonate coating on a titanium implant on the implant stability coefficient (CS) and the radiographic level of marginal bone on implants. In a randomized, double—blind, internal control study, 16 patients underwent dental implant surgery with zoledronic acid—coated implants and one patient received an uncoated implant as a control. The coated and uncoated implants, which were visually indistinguishable, were titanium implants with a moderately rough surface. CS values were obtained at administration and after 2, 4, 6 and 8 weeks. Radiographs were taken at insertion and 8 weeks later. The primary outcome was the difference in CS values between coated implants and control implants at 4 and 6 weeks, adjusted for setting values. The secondary outcome was marginal bone loss from implantation to 8 weeks. CS values remained virtually constant over 8 weeks and there was no significant difference between coated and uncoated implants at any given time. Marginal bone loss was 0.12 mm for control implants and 0.04 mm for coated implants. No statistically significant differences in CS values between coated and uncoated implants were observed during early healing, but less marginal bone loss was observed on coated implants [34].

In another work, A. Ghanem et al. (2017) evaluated the role of osteogenic coatings, the deposition of a thin film of organic and inorganic osteoinductive and osteoproliferative materials on implant surfaces in enhancing bone—implant (BI) contact in osteoporotic bone. Six animal studies were included in which osteoporosis was induced by bilateral oophorectomy. In all studies, implant surface roughness was increased by various osteogenic surface coatings, including alumina, hydroxyapatite, calcium phosphate, and zoledronic acid. Five studies have shown that bone volume and BI are significantly higher in implants with coated surfaces than in uncoated implants. Research shows that osteogenic coatings are effective in improving BI [35, 36].

Conclusion

Based on the results of the analysis of the literature, it can be considered proven that hormonal imbalance, as one of the factors in the development of osteoporosis, not only affects the microarchitectural changes in the jawbone, but also the osseointegration of dental implants. The impact of osteoporosis on implant treatment is still a matter of debate in the scientific community, as it may lead to a higher failure rate. Despite the fact that long—term use of bisphosphonates does not contribute to accelerated bone healing; their use does not develop complications. However, the use of bisphosphonates, both locally and systemically, contributed not only to the osseointegration of implants, but also to the improvement of bone tissue and the absence of progression of osteoporosis.

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Остеоинтеграция дентальных имплантатов у пациентов с остеопорозом

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Аннотация. *Актуальность.* Успешное применение хирургических и медикаментозных методов восстановления костной ткани челюстей убедительно подтверждено в клинической практике. Вместе с тем продолжаются развиваться технологии по улучшению остеоинтеграции дентальных имплантатов у пациентов с остеопорозом. Применение различных покрытий имплантатов, а также системная терапия демонстрируют появление новых направлений в лечении пациентов с частичной или полной вторичной адентией с сопутствующим остеопорозом. Это направление является актуальным в современной медицине. *Материалы и методы.* Поиск информации проводили на основе базы данных PubMed по ключевым словам: «osteoporosis» and «osteointegration» and «dental implantation» and «zoledronic acid» с 2016 г. до 2022 г. Были отобраны статьи на основе экспериментальных работ. По результатам многочисленных исследований доказано, что костная ткань является эффективным индикатором остеопорозных изменений. Подчеркнуты основные изменения костной ткани при остеопорозе — уменьшение объема кости, ухудшение микроархитектоники трабекулярной кости и процессы, препятствующие остеоинтеграции — потеря костной массы, значительное снижение процента контакта в комплексе имплантат — кость. Выявлены методы борьбы с отрицательным влиянием на операцию дентальной имплантации. В обзоре исследований по системному введению препаратов на основе бисфосфонатов выявлено усиление остеоинтеграции дентальных имплантатов, системное введение препаратов золедроной кислоты значительно увеличивала образование новой кости, что в свою очередь способствовало устранению такого негативного эффекта остеопороза, как резорбция костной ткани. Помимо системного введения бисфосфонатов в экспериментальных исследованиях описывается местное применение бисфосфонатов в виде различных покрытий имплантата. Местное применение бисфосфонатов также способствовало усилению остеоинтеграции. У имплантатов с микроструктурированным покрытием наблюдалась меньшая потеря маргинальной кости в сравнении с имплантатами без покрытия. *Выводы.* Использование дентальных имплантатов с модифицированным макро- и микрорельефом, а также системная медикаментозная терапия — остается основным направлением научных исследований, способствующим оптимизации остеоинтеграции дентальных имплантатов.

Ключевые слова: остеопороз, остеоинтеграция, операция дентальной имплантации, золедроновая кислота

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