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ORIGINAL RESEARCH

Effects of the Application Local Zoledronic Acid On Different Dental Implants in Rats On Osseointegration

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Objective: Recently, a lot of research has been done around the world to popularize the osseointegration of dental implants. In this study, it was investigated the effect of local zoledronic acid application on implants with machined (MAC), resorbable blast materials (RBM), sandblasted and acid-etched (SLA) surface implants integrated in rat tibias.

Methodology: A total of 60 female Wistar rats weighing between 270 and 300 g were used in the study. The rats were passing divided into six classes: controls; MAC (n = 10), RBM (n = 10), SLA (n = 10), and local zoledronic acid (LZA) applied groups; LZA-MAC (n = 10), LZA-RBM (n=10) and LZA-SLA (n = 10) and implants were surgically placement into rat tibias in general anesthesia. After a four-week experimental period, the biomechanical bone implant connection level was determined with reverse torque analysis.

Results: Osseointegration levels were detected highly in SLA and RBM surface compared with the machined surfaced implants in both control and treatment groups ($p < 0.05$). Additionally, local application of zoledronic acid in both three groups; implants increased the biomechanic osseointegration level compared with the controls ($p < 0.05$).

Conclusion: In this research, we observe that the local application of the zoledronic acid could increase the osseointegration, and RBM and SLA surface could be better than machined surfaced implants in terms of bone implant connection. In addition, local application of zoledronic acid may be a safer method than systemic application.

Keywords: zoledronic acid, local application, osseointegration, bone implant linkage, bone implant contact, implant plane

Introduction

The term osseointegration is defined as a direct structural and functional linkage between living bone tissue and the implant surface that is under loading without fibrous tissue. Osseointegrated dental implant-supported prostheses have become a scientifically agreeable and frequently used choice in the treatment of complete and partial edentulism involving the restoration of lost teeth.[1,2]

In addition to place parameters of dental implant material, bone tissue quality and quantity are very significant agents for accomplished osseointegration. The length of time between surgery and loading and the nominal clinical success percentage in poor quality bone tissues are the most challenging problems in dental implant treatments.[3,4]

In order to prevent inadequate bone tissue quality and amount, various techniques for dental implant treatment have been used to improve bone tissue creation and osseointegration. For example, tissue growth factors, melatonin hormone and antiosteoclastic drugs, and bisphosphonates have been used to improve the bone integration of titanium implants.[5,6]

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Success in dental implants depends on osseointegration. Accordingly, research on osseointegration in implants has lately intensified on the additional use of drugs known to affect bone turnover.[7] In particular, in animal fracture models and clinical studies, bisphosphonate class drugs have been successfully applied to improve healing and osseointegration.[8]

Bisphosphonates are drugs that have a high affinity for bone hydroxyapatite. Therefore, its pharmacological effects on bone play a role in bone reconstruction or destruction. We can group bisphosphonates as first generation nitrogen-free (clodronate, etidronate and tiludronate drugs) and second and third generation nitrogen-containing (alendronate, risedronate, ibandronate and zoledronate drugs). Thanks to oral bisphosphonates are poorly absorbed, the percentage bioavailability is lower than intravenous bisphosphonates. Oral bisphosphonates contain alendronate, risedronate, etidronate, and tiludronate. Pamidronate and zoledronate are administered only intravenously, while ibandronate and clodronate are administered by both routes.[9]

Bisphosphonates, widely used in the prevention of metastatic bone cancers, Paget's disease, osteoporosis, multiple myeloma, hypercalcemia, osteogenesis imperfecta and other metabolic diseases of the bone, work by suppressing osteoclast cells that destroy bone. In particular, zoledronic acid (ZOL), the most clinically potent bisphosphonate, is frequently used in the theraphy of osteoporosis disease. Bisphosphonates have been reported to increase the differentiation, proliferation and maturation of osteoblasts.[10] It has been reported that bisphosphonates have antiosteoclastic and proosteoblastic effects on the bone tissue repair system. Although diverse speculations have been proposed, the system of interaction between bisphosphonates and bone tissue has not yet been completely illuminated. According to past studies, bisphosphonates immediately limit the activation of osteoclast cells and may induce mineralized bone formation through osteoblast cells and thus reduce bone loss.[4,11,12]

Surface features of dental implant material are among the significant parameters affecting bone implant linkage. In clinical research in which implant surfaces were evaluated in terms of bone implant fusion, it was observed that no implant surface system was completely superior to any other.[13,14]

The reason why dental implants can be considered successful in the long term lies in the surface features of the implants. While the surface features of dental implants were machine turned surfaces of pure titanium in the 1970s, they have now changed to a microroughened surface. Although the techniques we have just mentioned are used in the surface treatment of dental implants, there is currently the development of new biomedical surfaces. After the 1990s, nano touch for the regulation of dental implant surfaces has been examined. Additionally, surface nanotopography and chemistry have been reported to influence protein adsorption, osteogenic cell behavior, and bone implant interaction.[15]

In order for changes on dental implant surfaces to be positive, the nature of osseointegration must be understood. The term osseointegration is thought to be a type of bone healing accompanied by an inflammatory response.[16] In order to improve osseointegration, the nanotopography, surface chemistry and surface energy of the dental implants have been changed. However, these changes also altered in vitro cellular behavior and in vivo bone physiology.[17,18]

In our study, we aimed to examine the healing physiology of zoledronic acid application and the interactions between bone and dental implants by including dental implant surface modifications designed to improve the healing between the bone and the implant surface. The purpose of our research was to mechanically appraise the effect of local ZOL application on implant bone fusion in implants with different surface properties.

Material and Methods

Animals and Study Design

Approval for the designed experimental setup and study was granted by the Firat University Animal Experiments Local Ethics Committee (02.02.2021, approval no.: 2021/02-449). Rats were provided by the Firat University Experimental Research Center (Elazığ, Türkiye). This study was conducted in Elazığ, Turkey, within the scope of the animal experiment protocol of the Ministry of Agriculture of the Republic of Turkey, led by the recommendations of the European Declaration of Helsinki. In the studies conducted, the experiments were carried out without causing any pain to the animals, and all ethical rules were followed. Hole animals used in the experimental stage were obtained from the same center. Advice in the Helsinki Declaration regarding the protection of laboratory experimental animals was followed.

The experimental setup was conducted using 60 female Sprague Dawley rats aged 6–12 months. At the beginning of the empirical study, the average body weight of the female rats was determined as 270–300 g. The rats were housed in special rooms where the temperature was continuously controlled and fed ad libitum, with a 12 hour light and 12 hour dark cycle. As a result of the statistical analyses made before the experiments, it was determined that the number of rats in each group should be at least eight. Considering that rats might die during surgical procedures and experimental setup, the study started with 10 rats in each group. A vaginal smear was taken for standardization, and all rats were in the same oestrus period. Sixty (60) female rats were randomly divided into six equal parts.

Machine-surfaced control group (MAC-C) (n = 10): Machine-surfaced titanium implants were placed into the corticocancellous bone of the right tibias of the rats. After a four-week healing period, the rats were sacrificed.

Resorbable blast media (RBM) surfaced control group (RBM-CNT) (n = 10): RBM-surfaced titanium implants (average roughness (Ra): 1–2) were placed into the corticocancellous bone of the right tibias of the rats. After a four-week healing period, the rats were sacrificed.

Sandblasted, large grit, acid etched (SLA) surfaced control group (SLA-CNT) (n = 10): SLA- surfaced titanium implants (average roughness (Ra): 1–2) were placed into the corticocancellous bone of right tibias of the rats. After a four-week healing process, the rats were sacrificed.

Machine-surfaced local ZOL group (MAC-LZA) (n = 10): The machine-surfaced titanium implants were placed into the corticocancellous bone of the right tibias of the rats by local application of 4 mg/5 ML of zoledronic acid to the implant socket, and, after a four-week healing process, the rats were sacrificed.

RBM-surfaced local ZOL group (RBM-LZA) (n = 10): The RBM-surfaced titanium implants (average roughness (Ra): 1–2) were placed into the corticocancellous bone of the right tibias of the rats by local application of 4 mg/5 ML of zoledronic acid to the implant socket, and, after a four week healing process, the rats were sacrificed.

SLA-surfaced local ZOL group (SLA-LZA) (n = 10): The SLA-surfaced titanium implants (average roughness (Ra): 1–2) were placed into the corticocancellous bone of the right tibias of the rats by local application of 4 mg/5 ML of ZOL to the implant socket, and, after a four-week healing process, the rats were sacrificed.

Surgical Procedures

Hole surgical interventions were performed under general anaesthesia in sterile conditions. General anaesthetics (10 mg/kg xylazine and 40 mg/kg ketamine) were administered intraperitoneally to the rats. After the surgical area was shaved, it was cleaned with povidone-iodine solution. During the surgical placement of the implants, a 2 cm incision was made over the right tibia bones of the rats with a scalpel (no. 15), and the metaphyseal part of the bone was reached. The surgical area was cleaned with sterile saline solution to prevent heating while the implant sockets were opened. After 4 mm long and 2.5 mm diameter implants (TiAl6V4, Implance Dental Implant Systems, AGS Medikal Corporation, Istanbul, Turkey) were placed into the corticocancellous bone in the right tibias of the rats, the soft tissues were sutured with 4–0 absorbable sutures (polyglactin) (Figure 1). After the completion of all surgical procedures, antibiotics (40 mg/kg cephalosporin) and analgesics (0.1 mg/kg tramadol hydrochloride) were administered intramuscularly for three days to prevent infection and pain. The rats were sacrificed at the end of the four-week experimental period following the surgical interventions. Titanium implants were collected along with the surrounding bone tissue and fixed in formaldehyde solution. A biomechanical test device analysed the osseointegration of the obtained implant samples by applying reverse torque (Mark 10, NY, USA). Data are recorded as force (N/cm) (Figure 2).

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis of the data in the study. In this evaluation, the conformity of the parameters to the normal distribution was evaluated with the Kolmogorov–Smirnov test. In addition, the Kruskal–Wallis test was used to compare the non-normally distributed parameters between groups, and the Mann–Whitney *U*-test was used to determine the group that caused the difference. Significance was evaluated at the $p < 0.05$ level.

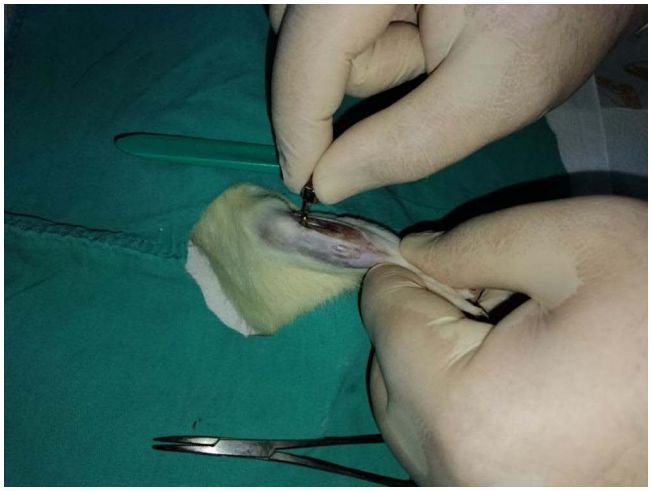

Figure 1 Surgical placement of the implants in the corticocancellous bones of the metaphyseal parts of the right tibias of rats.

Figure 2 Biomechanical; reverse torque analysis, of the implants (Mark-10 Cap Torque Tester, Model TT01-12, NY, USA).

Results

Data analysis showed that the biomechanical bone implant fusion values of the MAC-LZA, SLA and RBM groups were higher than those of the MAC-C group ($p < 0.05$). The biomechanical bone implant fusion values of the RBM-LZA and SLA-LZA groups were higher than those of the SLA group ($p < 0.05$). The biomechanical bone implant fusion values of SLA and RBM surfaces treated with LZA were higher than those of the RBM group ($p < 0.05$). When the groups with LZA were evaluated, it was observed that the biomechanical bone implant fusion values of the implants with SLA and RBM surfaces were higher than those of the machined group ($p < 0.05$). When the control groups were evaluated, osseointegration levels were detected highly in SLA and RBM surface compared with the machined surfaced implants ($p < 0.05$). In the control and experimental groups, it was observed that implants with RBM and SLA surfaces did not exhibit a statistical difference in terms of biomechanical bone implant fusion ($p > 0.05$) (Table 1).

Discussion

Research has shown that the success of dental implants is linked to a patient's medical history. While there is an increase in the number of implants applied to the elderly population, osteoporosis is commonly observed among these patients.[19] Studies have reported the negative effects of osteoporosis on the jawbone. It is reported that bisphosphonates are commonly used in the treatment of osteoporosis.[20–22]

Table 1 Biomechanical Bone Implant Connection (N/Cm) Levels of the Groups

Groups	N	Mean (N/cm^2)	Minimum	Maximum	P*
Machined	8	5.6	4.2	8.4	0.000
SLA[a1]	8	10.23	6.7	18	
RBM[a2]	8	14.01	7.5	22.6	
Local ZA Machined[a3]	8	12.3	9	18.8	
Local ZA RBM[a4,b1,c1,d1]	8	25.83	12.9	31.1	
Local ZA SLA[a5,b2,c2,d2]	8	27.59	19.2	36.5	

Notes: *Kruskal-Wallis Test. A Statistically different compared with Machined group, Mann–Whitney U. [a1]0.002, [a2]0.001, [a3]0.001, [a4]0.001, [a5]0.001. bStatistically different compared with SLA group, Mann–Whitney U. [b1]0.002, [b2]0.001. cStatistically different compared with RBM group, Mann–Whitney U. [c1]0.005, [c2]0.002 dStatistically different compared with Local ZA Machined group, Mann–Whitney U. [d1]0.002, [d2]0.001.

In in vivo studies, bone implant fusion has been emphasized in the use of bisphosphonate locally in treatments. Local use of bisphosphonates in bone implant fusion has been reported to have favourable results.[23–26]

In this research, the effect of bisphosphonates used in the therapy of osteoporosis on bone implant fusion was evaluated. Similar results were obtained, and it was found that bisphosphonate use positively affected implant osteointegration.

In their study, Im et al applied implants with RBM and SLA surface properties to the canine region of the maxilla. They obtained positive results in early stability measurements with a periotest in both implant types. However, in the measurements performed at the 12th week, better results were obtained in implants with RBM surface properties compared to implants with SLA surface properties. In the statistical analyses, torque values and bone implant fusion rates were evaluated and no statistically significant difference was found. As a result, good results were obtained in osteointegration in both implant surface types, and it has been reported that both implant surface types show healing properties compatible with bone.[27]

In studies that compared SLA surface and RBM surface implants with machine-formed surfaces, more favourable results were obtained in osteoblast activity and bone–implant contact in implants with SLA and RBM surface properties.[28,29]

In a study comparing implants with SLA, RBM and RBM acid-etching surface properties, no significant difference was found in reverse torque and implant-bone fusion, although the surface area of implants with an SLA surface was higher.[30]

In the present research, the osteointegration values of implants with machined, SLA and RBM surfaces were evaluated by measuring the reverse torque. Significant differences in reverse torque values were obtained in implants with SLA and RBM surface properties compared to machined-surface implants. As in other studies, no significant difference was obtained between SLA and RBM surfaces.

In a study by Duarte et al, the ovaries of rats were excised and treated with alendronate and estradiol. The osseointegration of dental implants was then evaluated. Positive results were obtained in implant osseointegration, and it was suggested that the negative effects of oestrogen deficiency after ovariectomy could be eliminated with bisphosphonates.[31]

In a study by Giro et al, bisphosphonate treatment was applied and extraction torque was investigated in subjects with oestrogen deficiency. It was reported that oestrogen deficiency negatively affected the extraction torque, whereas bisphosphonate use reduced this negative effect.[32]

In a study by Astrand et al, ZOL was applied locally to HA-coated implants in ovariectomized rats. During the healing period, no adverse trabecular distribution was observed in the peri-implant tissues. An improvement in fixation was even observed. While resorption occurs in osteoclasts, this was reduced and prevented by bisphosphonate treatment.

Bisphosphonates penetrate the mineral structure in the bone structure and cause inactivation of osteoclasts in the resorption process.[24]

In one study, the use of ZOL as a bisphosphonate was evaluated using histomorphometry and microtomography (micro-CT). Positive effects on trabecular number, thickness and connectivity were observed. An increase in thrust force was observed as a result of ZOL use, and this increase was found to be 8.4 times higher than normal bone.[33] ZOL is reportedly involved in stimulating apoptosis of osteoclasts and macrophages and has effects on osteoclast mediated bone resorption.[34]

Jakobsen et al applied alendronate locally on dogs and evaluated the results for 12 weeks. It was reported that an increase in bone implant fusion occurred in hydroxyapatite-coated titanium implants compared to the control group.[35] Cuaira'n et al applied orthodontic mini implants to dogs, and then 50 mL phosphate buffered solutions containing 16 mg ZOL were applied locally to the implant socket.[36] The researchers reported that ZOL application had a positive effect on bone implant fusion. Titanium implants were applied to rat maxillae by Abtahi et al, and positive effects on bone implant fusion were observed.[37]

In other study, Sokmen et al reported that both local and systemic application of zoledronic acid in implants with RBM surface placed without primary stabilization increased osseointegration levels in implants with and without primary stabilization compared to controls and that local application could be a successful and safe method.[38]

Similarly, in this study, reverse torque values were found to be higher in implants with local ZOL than in those without. The highest osteointegration value was obtained in implants with local SLA surfaces, while the lowest value was obtained in implants with machined surfaces. In the comparison between RBM with local ZOL and SLA surfaces with local ZOL, higher values were obtained in implants with SLA surfaces. This suggests that the use of local ZOL has a positive effect on the osteointegration value as the surface area increases.

In a research conducted by Abtahi et al, they reported that there was no statistical difference between bisphosphonate coated dental implants and non-bisphosphonate coated dental implants in the early healing period, but dental implants not coated with bisphosphonate suffered more marginal bone loss than the other group.[39] Zuffetti et al stated that local application of bisphosphonate drugs positively affects the survival of dental implants.[40]

In their study, where Fiorillo et al evaluated the effects of bisphosphonate drugs on the health dental implants, they argued that it could start recent opportunities in orthopedic surgery through osteoporotic bone and tooth rehabilitation in patient groups using bisphosphonate drugs.[41]

In line with the literature reviewed, although bisphosphonate drug groups make important contributions to various medical and dental treatments, their effects on dental implant procedures require careful evaluation. In addition, local applications of bisphosphonates positively affect the success rates of dental implant osseointegration. Therefore, ongoing study on this topic is extremely important for improving protocols for patients who use bisphosphonates and the success of dental implant applications.

Conclusions

According to the limited results of the study, it can be stated that local application of ZOL may be an effective method to increase osseointegration in machined, RBM and SLA surface implants. In addition, local application of ZOL may be a more reliable method than systemic application. There is a need for further studies examining the local ZOL application and osseointegration mechanism, considering different implant surface structuring methods.

In our study, it was concluded that local ZOL application had a positive impact on the bone around the dental implant. In conclusion, with our study, we can say that local application of ZOL to dental implants is a step forward in better understanding and measuring the basic biological process.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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