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Evaluation of the effects of the systemic proton pump inhibitor-omeprazole on periimplant bone regeneration and osseointegration: An experimental study

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ABSTRACT

Objective: Investigations of the effects of proton pump inhibitors (PPIs) on bone healing have revealed that they affect bone regeneration negatively. The exact mechanism by which this adverse effect on bone tissue is not known. The aim of this study is to biomechanic and biochemical investigation of the effects of the PPIs on guided periimplant bone regeneration.

Material & methods: Spraque dawley rats were divided controls (n = 8): there is no treatment during 8 week experimental period, PPI- Dosage 1 (n = 8) and Dosage 2 (n = 8): 5 mg/kg and 10 mg/kg omeprazol applied 3 times in a week with oral gavage during 8 weeks respectfully. Bone defects created half of the implant length circumferencial after implant insertion and defects filled with bone grafts. After experimental period the rats sacrified and implants with surrounding bone tissues were removed to reverse torque analysis (Newton), blood samples collected to biochemical analysis (glucose, AST, ALT, ALP, urea, creatinin, calcium, P).

Results: Biomechanic reverse torque values did not revealed any statistical differences between the groups (P > 0,05).

Conclusion: According the biomechanical and biochemical parameters PPIs does not effect the periimplant guided bone regeneration.

1. Introduction

Endosseous dental implants are among the most important innovations in the field of dentistry.[1] They are used as a reliable treatment option in patients with complete or local edentulism, as they are functional and aesthetic, stable, and easy to use.[1,2]

The success of dental implants depends not only on the structural and functional properties of the implants themselves but also on osseointegration, which is the connection with bone. Therefore, bone formation and bone regeneration mechanism play an important role. Abnormal situations that occur in the bone metabolism will negatively affect the bone tissue and the mechanism that occurs in a dental implant, potentially causing the failure of the implant.[3]

Certain factors adversely impact osseointegration because of their effects on the bone mechanism. In addition to factors such as the age and gender of the patient, the physical properties of the implant, and the patient's smoking habit, the use of systemic drugs such as proton pump inhibitors (PPIs) may also impair osseointegration between the bone and the dental implant.[4–6]

PPIs are a drug group that has become the third most prescribed pharmaceutical product worldwide.[7] PPIs target and inhibit a proton pump complex (H + + -ATPase) in gastric parietal cells in the stomach. They are often used as the first step in the treatment of gastro-esophageal reflux and stress gastritis, to reduce the negative effects of non-steroidal anti-inflammatory drugs (NSAIDs), and to eradicate Helicobacter pylori infection.[8–10]

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NSAIDs are generally used to reduce the pain of patients after surgical procedures. However, since these drugs may induce gastric disorders, PPIs are used to bind the proton pump complex and limit gastric acidity after surgical procedures.[11] Investigations of the effects of PPIs on bone healing have revealed that they affect osseointegration negatively by reducing the number of the large multinucleated cells that break down bone tissue, known as osteoclasts. Although the exact mechanism by which this adverse effect on osseointegration occurs is not known, it is thought to be the result of reduced gene expression caused by the PPIs.[5]

Bone grafts are generally used during dental implant applications.[12,13] There are synthetic, allogeneic, autogenic, and xenological graft types. They are typically used in block bone graft, lateral sinus lift, bone graft osteotome, and guided bone generation (GBR) techniques. In GBR, membrane and bone grafts are normally used together. One or more bone grafts may be used in surgery.[14]

The literature contains few studies on the effects of PPIs on bone metabolism in dental implant treatment, suggesting the need for studies examining the relationship between bone metabolism and implant fusion and PPIs. In the present study, dental implant osseointegration was evaluated in rats that were grafted and given PPIs (Omeprazole).

2. Materials and methods

The study was conducted at Firat University Experimental Research Center, having been approved by the Firat University (Elazig, Turkiye) Animal Experiments Local Ethics Committee (2019/146), and the rules of the Helsinki Declaration were fully complied with during the experiment. The rats used in the experiment were provided by Firat University Experimental Research Center. A total of 24 Sprague Dawley rats were used, divided into three groups of eight rats each. The rats were kept in a room with 55% humidity and a controlled temperature of 22 ± 2 °C, in a 12 h light and 12 h dark cycle. The rats were put in standard cages in pairs and were fed ad libitum with a normal diet and water. Female rats were selected in same eustrus period to standartisation.

Control graft group (n = 8): The corticocancellous bone in the metaphyseal parts of the right tibial bones of the subjects was opened. Titanium implants with a diameter of 2.5 mm and a length of 4 mm were placed in the cavities, and a bone graft was placed in the bone defect, corresponding to 2 mm of the implant length in the neck region. No additional treatment was applied during the eight-week experimental setup.

Omeprazole dose 1 graft group (n = 8): The corticocancellous bone in the metaphyseal parts of the right tibia bones of the subjects was opened. Titanium implants with a diameter of 2.5 mm and a length of 4 mm were placed in the cavities, and a bone graft was placed in the bone defect, corresponding to 2 mm of the implant length in the neck region. During the eight-week experimental setup, 5 mg/kg omeprazole was administered with oral gavage three days a week.[5]

Omeprazole dose 2 graft group (n = 8): Cavities were opened in the corticocancellous bone in the metaphyseal parts of the right tibia bones of the subjects. Titanium implants with a diameter of 2.5 mm and a length of 4 mm were placed in the cavities, and a bone graft was placed in the bone defect in the neck region, corresponding to 2 mm of the implant length. During the eight-week experimental setup, 10 mg/kg omeprazole was administered with oral gavage three days a week.[5]

At the end of the eight-week experimental setup, all rats in the groups were sacrificed. Implants and surrounding bone tissue were removed and subjected to biomechanical and biochemical tests that were not decalcified.

2.1. Surgical procedures

All surgical procedures were performed in a sterile environment and with general anesthesia. The rats were given no food for 8 h beforehand. For the general anesthesia, xylazine hydrochloride (Rompun®, Bayer, Germany) and ketamine hydrochloride (Ketasol®, Richter Pharma, Austria) were administered intramuscularly with an insulin injector. Mepivacaine hydrochloride (0.3 ml/kg, 2% with scandicaine epinephrine 1:100,000; Septodont, France) was also infiltrated to reduce hemostasis in the wound area. The area to be surgically treated was cleaned with povidone iodine after being shaved to ensure sterilization. After a 1.5 cm incision was made over the tibial crest with a No. 15 scalpel, the proximal part of the tibia was reached with a periost elevator. Cavities were opened in the corticocancellous bone in the metaphyseal parts of the right tibial bones of the subjects (Fig. 1 A). Titanium implants (Implance Dental Implant System, AGS Medical Corporation, Istanbul, Turkiye) with a diameter of 2.5 mm and a length of 4 mm were placed in these cavities-3.5 mm diameter in 2 mm dept and 2.5 mm diameter in 2 mm-half of implant length- and a bone graft was placed in the bone defect, corresponding to 2 mm of the implant length in the neck region (Fig. 1 B). No additional treatment was applied during the eight-week experimental setup. After the implants were placed, the flaps were closed using absorbable threads (4/0 vicryl; Ethicon, Inc., Somerville, NJ, USA) for soft tissues and monofilament suture (nylon 4.0; Ethicon, Inc.) for skin. After the surgical procedure, the rats were observed daily for signs of pain, dehiscence, infection, restricted movement, anorexia, and weight loss. Antibiotics (50 mg/kg penicillin) and analgesics (0.1 mg/kg tramadol hydrochloride) were given intramuscularly every 24 h for three days. All subjects were sacrificed after an eight-week recovery period. The implants were taken for biomechanical analysis with surrounding bone tissues.

2.2. Biomechanical analysis

For biomechanical analysis, a reverse torque test was performed on the sacrificed rats. The tibia block piece with implants was prepared for the tests. Samples were kept in a liquid solution with 10% buffered formalin. Immediate evaluation was made to prevent dehydration. All of the implants were placed in polymethylmethacrylate blocks. To measure the torque of the implants, a turning apparatus was placed, and, using a digital torque tool (Tonichi STC400CN, Buffalo Grove, IL, USA) a counterclockwise extraction force was applied manually, slowly and increasingly. The procedure was terminated immediately with the return of the dental implant into the bone socket. At the time of the break-first rotation of the implant in the socket, the highest torque force (Ncm) obtained by the digital torque device was automatically recorded (Fig. 1C).

2.3. Biochemical analysis

Biochemical analyses were performed in the central biochemistry laboratory of Firat University Faculty of Medicine. Blood samples from the rats were obtained under deep anesthesia. Glucose, AST (aspartate aminotransferase), ALT (alanine aminotransferase), urea, creatinine, calcium (Ca), phosphorus (P), and serum alkaline phosphatase (ALP) values were analyzed with blood samples taken by cardiac puncture without anticoagulant. The biochemical data were measured individually in rats.

3. Results

As shown in Supplemental Table 1 and Supplemental Table 3 when performing the experimental reverse torque analysis, samples that were not placed properly were not included in the study. No statistically significant difference was observed in the biomechanical reverse torque analysis of the titanium implants of the groups ($P > 0.05$). As shown in Supplemental Table 1 although osseointegration was lower in the Omeprazole dose 2 graft group compared to the control group, no statistically significant difference was found ($P > 0.05$).

As shown in Supplemental Table 2; the biochemical analysis also revealed no significant difference in glucose, ALT, ALP, urea, Ca, and P

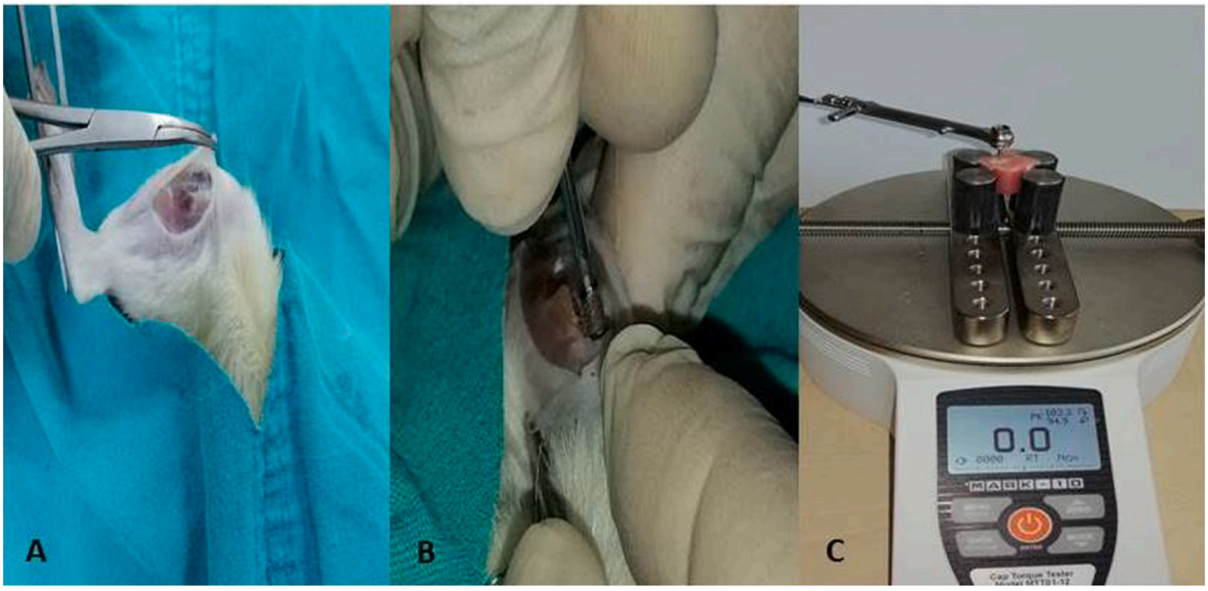

Fig. 1. A. Surgical approach of the metaphyseal part of the right tibial bone after crestal incision and dissection of the soft tissues. Fig. 1 B. Creation bone cavities and insertion the titanium implants and after this graft application. Fig. 1C. Reverse torque analysis of the samples (Tonichi STC400CN, Buffalo Grove, IL, USA).

values among the groups. A statistically significant difference was observed in levels of AST and creatinin. AST level detected lower compared with the controls ($P < 0,05$) and creatinin level in Dosage 1 and 2 group lower compared with the control animals ($P < 0,05$).

As shown in Supplemental Table 4 ALP levels detected higher ccpmpared with the controls ($P < 0,05$). In addition to this creatinin levels lower in test groups compared with the controls ($P < 0,05$). Athor parameters revealed no statistical difference ($P > 0.05$).

4. Discussion

The negative effects on bone healing of PPIs, which are one of the most widely prescribed groups of drugs worldwide, have been extensively studied.[15] However, studies on the negative effects of dental implants in bone-related clinical conditions such as osseointegration are limited.[16–19] Bone metabolism plays a very important role in the osseointegration of the dental implant, which is a structural and functional connection between living bone and the dental implant surface. Bone formation and remodeling are crucial to the success of the implant. Any systemic medication that has an effect on bone homeostasis can positively or negatively affect the osseointegration of the implant.

It has been reported that omeprazole, which is used as a PPI, has negative effects on bone healing by decreasing the expression of BMP-2 and BMP-4 growth factors, decreasing the number and activity of granulocytes, decreasing osteoclast activity, and depressing calcium absorption.[20–25] These finding are also supported in our study, which showed a reduction in the calcium level in both dose 1 and dose 2 groups compared to the control group, although no statistical difference was found.

Xixi et al. evaluated the risk factors of PPI use in association with dental implants.[26] They observed an increase in the dental implant failure rate in patients using PPIs compared to those who did not, suggesting that the drugs may be the cause of the failure. They emphasized that the findings of their study are consistent with the well-known deleterious effect of PPIs on bone metabolism.[27,28] In a previous study, they reported a higher risk of bone fracture after the use of PPIs, owing to their adverse effect on bone homeostasis.[29] Similarly, the FDA emphasized the increased risk of bone fracture associated with the use of PPIs. It has also been reported that systemic administration of omeprazole may adversely affect bone healing and implant osseointegration in rats.[26]

In previous studies, rats exposed to four-week omeprazole treatment suffered a decrease in Ca content in the tibial bone.[30] However, a study conducted by Leontiadis and Moayyedi reported that PPI had no effect on calcium absorption.[31] These differences between the two studies may have been due to differences in treatment dose and duration. Therefore, the possible effect of omeprazole on the gastrointestinal absorption of calcium and the bone healing process remains controversial.[5]

In the present study, the Ca level decreased in both doses of omeprazole, although no statistical significance was found. In addition, the control group was compared with the dose 1 and dose 2 groups; lower results-ast, alt, urea, creatinin, calsicum and phosphore were obtained in the test groups, but no significant difference was found.

In a recent study, omeprazole treatment was applied for one month, and a statistically significant increase in serum ALP activity was observed, owing to a decrease in the level of serum Ca. It has been suggested that this was caused by a decrease in the intestinal absorption of Ca. In the same study, no significant change was observed in serum parathyroid hormone (PTH), vitamin D, magnesium (Mg), or phosphate (P) levels.[32,33]

The present study yielded similar results. A statistically significant difference was found in serum ALP levels in the groups to which omeprazole was administered.

5. Conclusion

Omeprazole is frequently used in periodontal surgery to reduce the negative effects of pain medication on the digestive system. In dental implant applications, systemic factors as well as local factors affect implant success in a variety of ways. Therefore, the negative effects of systemic drugs used after surgical procedures should be considered. The present study appears to show that omeprazole has a negative effect on the success of dental implants, but the amount of dose administered limits this effect. Further, more comprehensive studies are required to provide more accurate information.

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Declaration of competing interest

The authors declare there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jobcr.2022.04.006.

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