Effects of Steroid-Induced Osteoporosis on Osseointegration of Titanium Implants

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The purpose of this study was to clarify the effects of steroid administration on the osseointegration of pure titanium implants. Twelve female New Zealand white rabbits, 8 weeks of age, were divided into two groups: a prednisolone-treated group (Group P) and a control group (Group C). In each rabbit, two implants were placed into the mandible and two into the tibial metaphyses with bone tapping. The six steroid-treated rabbits received three courses of 4 days of prednisolone injections (10 mg/kg per day) before implant placement, 1 month and 2 months after implant placement. The six control rabbits received no administration of prednisolone. Three months after implant placement, all rabbits were sacrificed. Bone density of the femur and removal torque of the implants placed in the tibia were significantly lower in Group P than in Group C. In addition, there were significant correlations between the bone density of the femur and the removal torque of the implants placed in the tibia. There was no significant difference in removal torque of the implants placed in the mandible between Group P and Group C, and there was no significant correlation between the bone density of the femur and the removal torque of the implants placed in the mandible. These results suggest that steroid administration could have less effect on the osseointegration of titanium implants in the mandible than in the skeletal bone.
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Key words: microdensitometry, rabbit, removal torque, steroid-induced osteoporosis, titanium implant

Since the concept of osseointegrated implants was introduced by Brånemark in 1965, high success rates in edentulous or partially edentulous patients have been reported.[1–4] However, there are various risk factors associated with implant therapy, and steroid-induced osteoporosis is one of them. Two studies have reported on loss of osseointegration in patients who had chronic use of corticosteroid.[5,6] Moreover, chronic use of corticosteroid has been cited as an absolute contraindication[7] or relative contraindication[8] for the placement of implants in the jaws. There is no experimental study documenting the effect of corticosteroid on osseointegration.

To evaluate the effects of steroid administration on the osseointegration of titanium implants, removal torque of implants placed in the mandible as well as the tibia of steroid-induced osteoporosis rabbits was measured.

Materials and Methods

Animal Model. Twelve female New Zealand white rabbits, 8 weeks of age and housed in large individual cages, were divided into two groups: a prednisolone-treated group (Group P; 6 animals) and a control group (Group C; 6 animals). Their mandibular incisors were extracted under general anesthesia using pentobarbital (25 mg/kg) and local infiltration of 1% lidocaine with 1:100,000 epinephrine for hemostasis. After tooth extraction, antibiotics (Flomoxef sodium, Shionogi, Osaka, Japan) were administered intramuscularly at 0.2 g per day for

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4 days. The rabbits were fed pellets containing 1.86% calcium and 0.65% phosphorus ad libitum throughout the experimental period. Group P received three courses of 4 days of consecutive daily intramuscular injections of 10 mg/kg prednisolone, ie, 4 days before implant placement and 1 month and 2 months after implant placement. Group C received injections of saline solution in the same manner as Group P. Total body weight of all animals was measured both preoperatively and postoperatively. The animals' serum concentrations of calcium, phosphate, and alkaline phosphatase were also measured. All rabbits were sacrificed 3 months after implant placement.

Implant Type. The implants used in this study (Nagoya Rashi, Seki, Japan) were screw-shaped and manufactured from commercially pure titanium (TW35, JIS). The size and shape of the implants were determined following Johansson's experiments.[9,10] The screw had an outer diameter of 3.7 mm, a pitch of 0.6 mm, and a square top. It had an infraperiosteal length of 6 mm and extended 4 mm supraperiosteally. The implants were cleaned in buthanol and ethanol in ultrasonic baths. The sterilization procedure was completed by autoclaving.

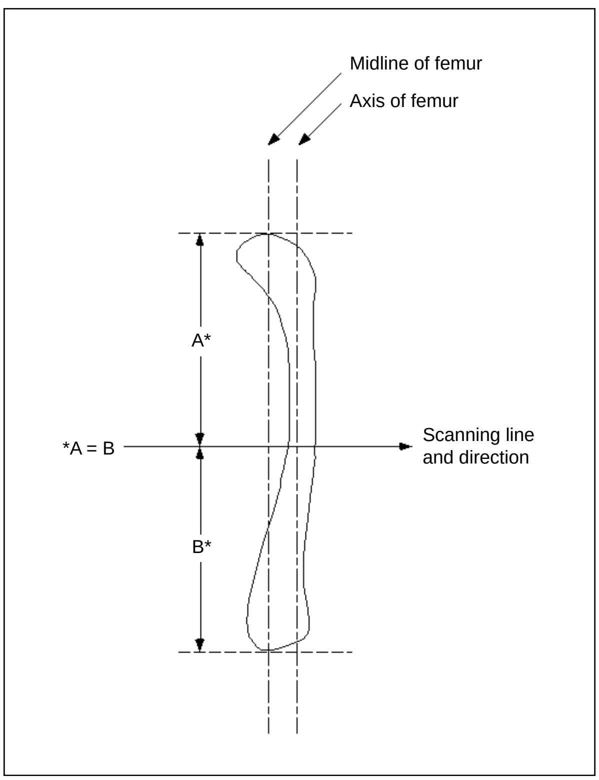


Fig 1 Microdensitometrical measurement of femur. Scan speed: 0.1 mm/second; width of slit: 0.05 mm × 2.0 mm; data sampling interval: 100 milliseconds.

Implant Placement. With the rabbits under general anesthesia as described above, the implants were placed in the conventional manner except for provision of a countersink. In each rabbit, two implants were placed in the tibial metaphysis and two in the mandible using a gentle surgical technique with bone tapping. During drilling and placement, saline solution was used for cooling. After implant placement, the soft tissues, including the periosteum, were sutured, and antibiotics (Flomoxef sodium) were administered intramuscularly at 0.2 g/day per body weight for 5 days.

Measurements of Removal Torque. The animals were sacrificed at 3 months after implant placement. The skin and the periosteum at the surgical site were opened, and removal torque was measured using a torque-gauged wrench (Tohnichi 15 BTG-N, Tokyo, Japan). The torque-gauged wrench gave direct readings of the torque necessary for loosening of the implants in newton centimeters (Ncm).

Measurements of Bone Density. The bone density of the left femur of each experimental animal was examined microdensitometrically following the method of Okumura et al.[11] After the animal was sacrificed, the femur, which was completely separated from the soft tissue, was placed on a 2-mm-thick aluminum plate, and soft radiographic film (Fuji Softex Film FR, Tokyo, Japan) and radiographs were taken at 45 kV, 5 mA, and 60 seconds at 45 cm. Using an interactive image analyzer system (Sakura Densitometer PDS-15, Tokyo, Japan), microdensitometry was applied at the center of the diaphysis to determine the density of transverse sections of the femur (Fig 1). Three kinds of volumetric variables, cortical diameter outside (D), cortical diameter inside (d), and mean density-integrated area/cortical diameter outside ($\sum$GS/D), were estimated.

Preparation of Specimens. Bone blocks around the implants were sampled. The specimens were fixed in 70% ethanol, dehydrated in ethanol and acetone, and embedded in methyl methacrylate resin. Each block was trimmed to 200-µm thickness, which was cut parallel to the long axis of the implant. The undecalcified specimens were then ground to approximately 20-µm thickness. The specimens were stained with toluidine blue O and examined by light microscopy.

Statistical Analysis. The Mann-Whitney *U* test was used to compare the removal torques, bone density ($\sum$GS/D), total body weight, and serum concentrations of both groups. The relationship between bone density and removal torque was examined by Spearman's correlation coefficient.

Results

Events of the Study. No significant difference in mean body weight and serum concentrations of calcium, phosphate, and alkaline phosphatase was found between Group P and Group C at the time of implant placement and implant removal (Table 1).

Removal Torque in the Tibia. Three months after implant placement, the average removal torque in the tibia was 45.8 ± 15.2 Ncm in Group P, and 62.7 ± 14.9 Ncm in Group C (Fig 2); the difference between them was statistically significant ($P < .05$).

Removal Torque in the Mandible. Three months after implant placement, the average removal torque in the mandible was 29.8 ± 7.4 Ncm in Group P, and 35.2 ± 10.2 Ncm in Group C. There was no significant difference between them (Fig 3).

Bone Density of the Femur. The mean bone density (∑GS/D) of the femur was 3.02 ± 0.22 mmAl in Group P, and 3.53 ± 0.18 mmAl in Group C (Fig 4). There was a significant difference between them ($P < .01$).

Correlation Between Removal Torque and Bone Density. Correlation coefficient between removal torque in the tibia and bone density (∑GS/D) of the femur indicated significant correlation ($P < .01$). However, there was no significant correlation between removal torque in the mandible and bone density (∑GS/D) of the femur (Figs 5a and 5b).

Morphology. *Histologic Findings of the Tibia in Group P.* At the cervical and apical part of the implant, although new bone was formed, there was little contact between new bone and the implant surface; and much fibrous connective tissue was observed between the implant surface and bone (Figs 6a and 6b). At the middle part of the implant, there was almost no new bone formation (Fig 6c).

Histologic Findings of the Tibia in Group C. At the cervical and apical part of the implant, newly formed bone contacted the implant surface, and a very small amount of fibrous connective tissue was observed between the implant surface and bone

Table 1 Changes in Body Weight and Serum Concentrations of Calcium, Phosphate, and Alkaline Phosphatase at the Time of Sacrifice

	Group C (n = 6)	Group P (n = 6)	*P* value*
Body weight at implant placement (kg)	3.0 ± 0.2	2.8 ± 0.1	NS
Body weight at implant removal (kg)	3.6 ± 0.2	3.0 ± 0.6	NS
Serum calcium (mg/dL)	12.0 ± 1.7	12.2 ± 1.2	NS
Serum phosphate (mg/dL)	4.0 ± 1.1	3.6 ± 0.3	NS
Serum alkaline phosphatase (IU/L)	84.0 ± 71.2	87.6 ± 45.8	NS

*NS = nonsignificant difference; mean ± SD.

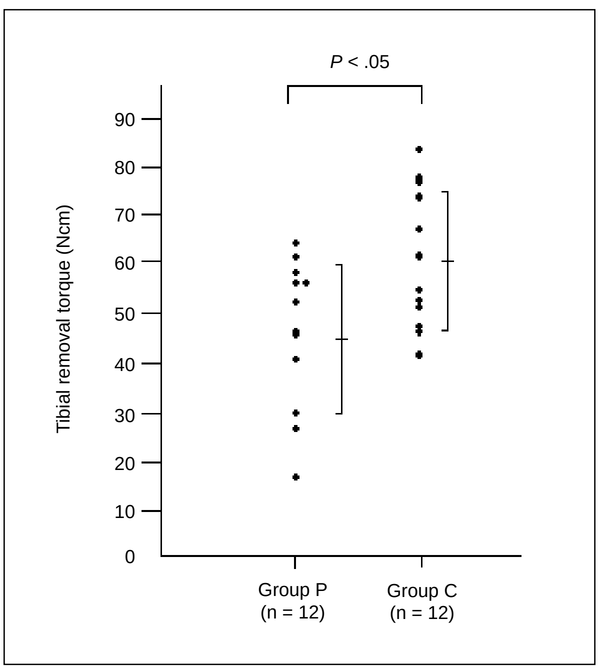


Fig 2 Comparison of tibial removal torque between Group P and Group C. Statistically significant difference of mean value was found ($P < .05$).

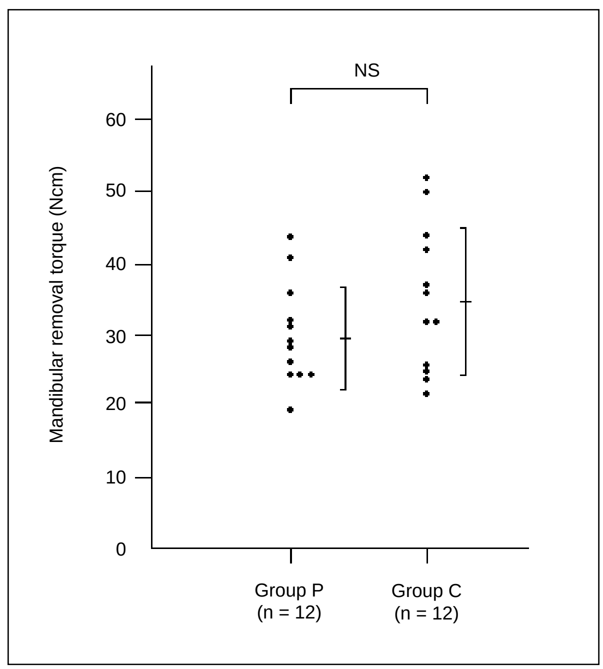


Fig 3 Comparison of mandibular removal torque between Group P and Group C. No significant difference of mean value was seen between the two groups.

(Figs 7a and 7b). At the middle part of the implant, small trabeculae were formed along the implant surface. However, there was little contact between the trabeculae and the implant. In the medullary cavity, a large number of myelocytes were observed (Fig 7c).

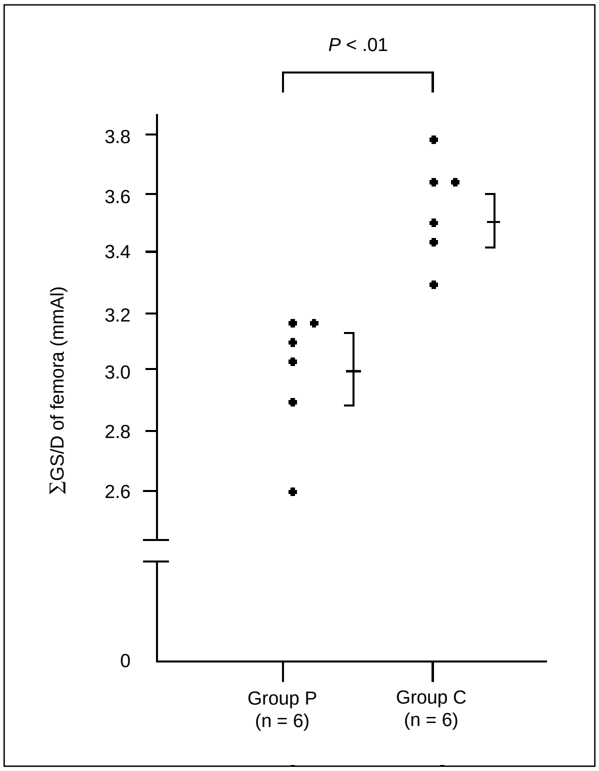


Fig 4 Comparison of microdensitometric readings (ΣGS/D) of femora between Group P and Group C. Statistically significant difference of mean value between them was seen ($P < .01$).

Histologic Findings of the Mandible. The specimens of both Group P and Group C demonstrated new bone formation, which had direct contact with implant surface in half the area at the cervical and apical part of the implant (Figs 8a and 8b). No remarkable differences were observed between the two groups.

Discussion

Steroid-induced osteoporosis is a well-known complication of corticosteroid therapy. However, the effects of steroid administration on the osseointegration of titanium implants placed in the jaws have not been clarified. This study examined the effects of steroid administration on osseointegration in an animal model.

In past years, animal models of steroid-induced osteoporosis using rats,[12–15] guinea pigs,[16] and rabbits[17–19] have been reported. A large number of studies have used rabbits to make a steroid-induced osteoporosis model. For example, Storey[17] found osteoporosis in rabbits that received daily injections of 25 mg of cortisone acetate for 4 days. Ashcraft et al[19] demonstrated osteoporosis in rabbits by daily injections of 15 mg/kg of cortisone acetate for 4 days; the rabbits showed significantly lower bone density. Net dosage of 15 to 25 mg/kg of cortisone acetate is equivalent to 2 to 4 mg/kg prednisolone. In the present study, 10 mg/kg of prednisolone was administered because the calcium concentration of foods was slightly higher than it was in those of other studies.

Some investigators have used removal torque values to evaluate osseous-titanium bond strength in rabbits.[9,10,20] These values are related to implant surface, length, width, composition, shape, and healing

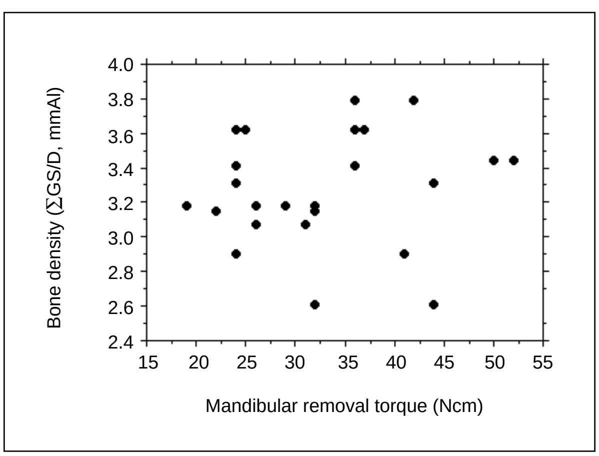


Fig 5a Correlation between the removal torque of the implants placed in the mandible and the bone density of the femur (ΣGS/D). There was no significant correlation between them ($r = .110$).

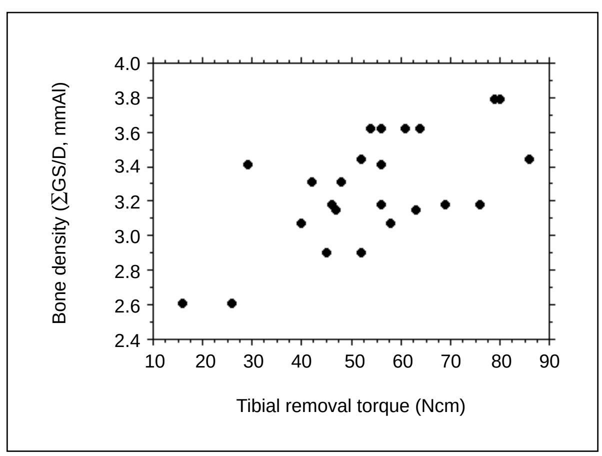


Fig 5b Correlation between the removal torque of implants placed in the tibia and the bone density of the femur (ΣGS/D). There was significant correlation between them ($P < .01$; $r = .635$).

Figs 6a to 6c Photomicrographs of an implant placed in the tibia in Group P (toluidine blue stain; original magnification × 50).

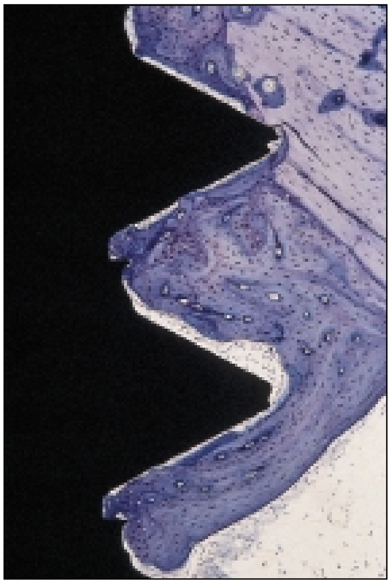


Fig 6a The cervical part of the implant, showing few direct bone-implant contacts. Fibrous connective tissue can be seen between the implant surface and the bone.

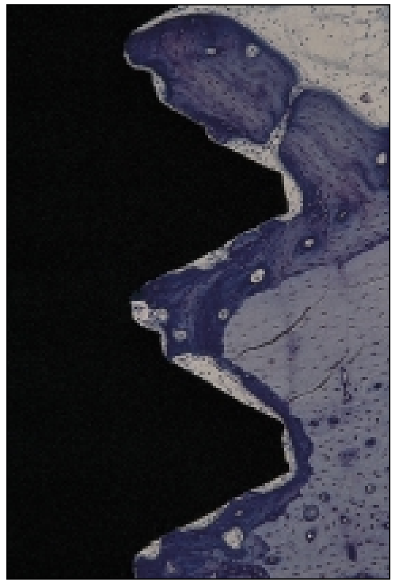


Fig 6b The apical part of the implant.

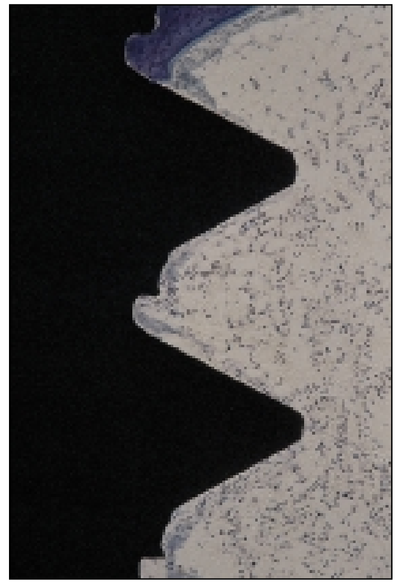


Fig 6c The middle part of the implant, showing almost no new bone formation.

Figs 7a to 7c Photomicrographs of an implant placed in the tibia in Group C (toluidine blue stain; original magnification × 50).

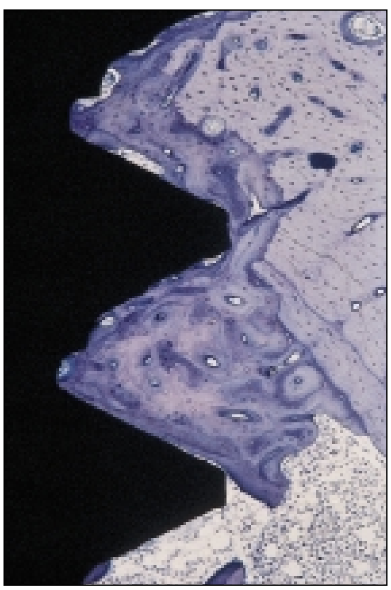


Fig 7a The cervical part of the implant; newly formed bone is in contact with the implant surface, and a small amount of fibrous connective tissue can be observed between the implant surface and the bone.

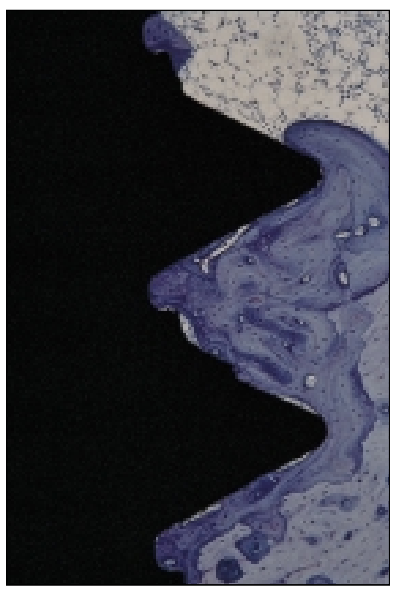


Fig 7b The apical part of the implant.

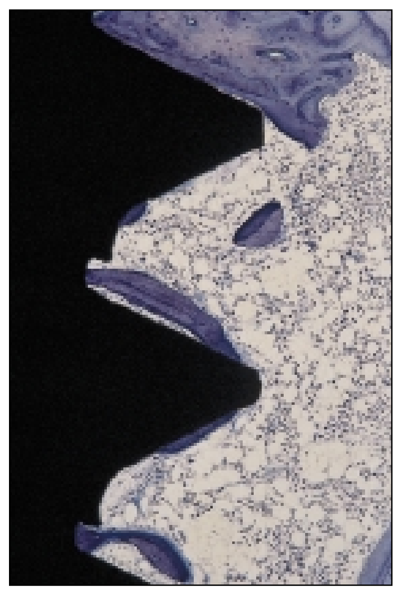
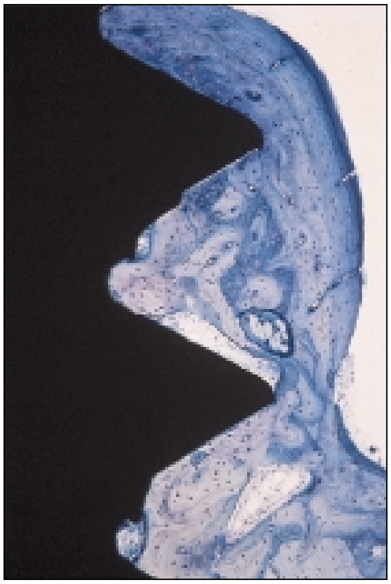
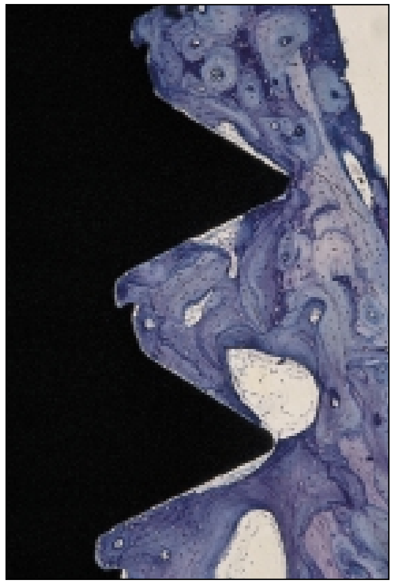


Fig 7c The middle part of the implant. Small trabeculae have formed along the implant surface, although there is little contact between the trabeculae and the implant.





Figs 8a and 8b Photomicrographs of the implant placed in the mandible (toluidine blue O stain; original magnification × 50).

Fig 8a *(Left)* The cervical part of the implant placed in Group P, showing direct bone contact with the implant and mandible. No remarkable differences from Group C are observed.

Fig 8b *(Right)* The cervical part of the implant placed in Group C, showing a small amount of soft tissue between the implant surface and the bone.

period. It has been reported that an average removal torque was 35 to 68 Ncm in the tibia and 41 to 42 Ncm in the mandible[9,20] after 3 months of integration. The results of the present study coincide with these data. All implants used in this study were osseointegrated and did not show any mobility.

In this study, removal torque of the implants placed in the tibia was reduced by steroid administration, and removal torque in the mandible was not reduced by steroid administration. Additionally, the relationship between bone density of the femur and removal torque of implants placed in the tibia indicated significant correlation. However, the relationship between bone density of the femur and removal torque of the implants placed in the mandible did not indicate significant correlation. These results suggest that steroid administration could have less effect on the osseointegration of titanium implants in the mandible than in the skeletal bone.

The relationship of bone density between jaw bone and skeletal bone is controversial.[21–24] Sawaki et al[23] reported that there was no correlation of bone mineral content between the mandible and second metacarpal bone. Kribbs[24] described significant differences in mandibular bone density between normal and osteoporotic populations. A method to examine jaw bone density must be established for the evaluation of the risk of implant placement.

It has been reported that 34% of women receiving more than 5 mg of prednisolone a day for rheumatoid arthritis experienced a fracture at some site during a period of 5 years.[25] In the management of asthma, there has been a substantial increase in the doses of inhaled glucocorticoids used. Packe et al[26] reported that bone density was significantly decreased in both patients who had taken intermittent systemic steroids (oral prednisolone in a median dosage of 7 mg) and continuous systemic steroids. To prevent and treat steroid-induced osteoporosis, prescription of calcitonin,[27,28] bisphosphonates,[29,30] and vitamin D[31,32] is effective. Sex hormone replacement therapy is also effective as a first-line therapy in both men and women.[33,34] Additionally, it is important to limit other risk factors such as alcohol and smoking. Steroid-induced bone loss could be prevented to some degree by using these treatments alone or in combination.[35] If a patient can be treated by these therapies, implant treatment in a patient who has received steroid administration may not always be contraindicated.

Conclusion

The present study revealed that osseointegration of titanium implants in the mandible, as measured by torque removal force, is not affected as strongly by steroid administration as is osseointegration in the skeletal bone.

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