Chapter 22
Osteogenetic Effect of Low-Magnitude High-Frequency Loading and Parathyroid Hormone on Implant Interface in Osteoporosis

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Abstract Osteoporosis could potentially complicate oral implant treatment because of disease-specific characteristics such as the abnormal bone condition, poor healing ability caused by bisphosphonates (BPs), and bisphosphonate-related osteonecrosis of the jaw (BRONJ). These problems must be resolved to ensure that oral implant treatment is successful in osteoporotic patients.

As a novel therapeutic option for increasing the success rate of oral implantation in patients with osteoporosis, we focused on parathyroid hormone (PTH) and low-magnitude high-frequency (LMHF) loading. Compared to BPs, which inhibit osteoclastic bone resorption and suppress bone turnover, PTH stimulates osteoblastic bone formation and promotes bone turnover. Intermittent PTH administration is a new class of anabolic therapy for the treatment of severe osteoporosis. LMHF loading, which elicits a positive effect on skeleton, has been proposed as a nonpharmacological and adjunctive intervention in the treatment of osteoporosis. Previous investigation reported that both intermittent PTH administration and LMHF loading have an independent osteogenic effect on peri-implant bone healing and implant osseointegration. In addition, our recent study reveals their combined therapy acts locally and synergistically on peri-implant bone healing process, strengthening osseointegration.

Therefore, this can be a new therapeutic option for oral implant treatment in osteoporotic patients without any problems.

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K. Sasaki et al. (eds.), *Interface Oral Health Science 2016*,
DOI 10.1007/978-981-10-1560-1_22

Keywords Oral implant • High-frequency loading • Parathyroid hormone • Osseointegration

22.1 Background

Oral implants are a well-accepted and predictable treatment option for the rehabilitation of partially and completely edentulous patients. The osseointegrated implants' success depends on the mechanical support of the host bone in achieving primary stability and the biological process of bone adaptation and regeneration in achieving secondary stability [1]. Nevertheless, the extended life expectancy in today's society has expanded the indications for oral implantation in elderly patients with systemic diseases.

Osteoporosis is a metabolic bone disorder characterized by low bone mass and microarchitectural deterioration of the bone, leading to enhanced bone fragility and a consequent increase in fracture risk [2]. Regardless of the disease characteristics, osteoporosis is not considered an absolute contraindication for oral implant treatment [3, 4]. However, some studies have reported implant failure because of a lack of primary stability and difficulty in achieving osseointegration in patients with osteoporosis [5, 6]. In addition, bisphosphonates (BPs), which are antiresorptive agents and are widely used as the first-choice therapy for osteoporosis, could be a risk factor for implant failure. Kasai et al. [7] compared the success rate of oral implants placed in female patients taking oral BPs with a control group not taking BPs. The BP group had an 86% success rate, while the control group had a 95% success rate. BPs also are known to induce BP-related osteonecrosis of the jaw (BRONJ), a serious side effect in patients undergoing invasive oral surgery [8]. There are no universally accepted prevention or treatment protocols for BRONJ [9, 10].

Therefore, to treat osteoporotic patients with oral implants successfully, it is necessary to overcome problems associated with the characteristics of osteoporosis, BPs, and BRONJ. As a novel therapeutic option for increasing the success rate of oral implantation in patients with osteoporosis, we focused on teriparatide [hPTH(1-34)] and low-magnitude high-frequency (LMHF) loading. The aim of this review was to evaluate the single and combined effects of LMHF loading and PTH treatment on peri-implant bone healing and implant osseointegration in osteoporosis.

22.2 Teriparatide [hPTH(1-34)]

22.2.1 PTH as a Therapy for Osteoporosis

Teriparatide [hPTH(1-34)] is an analog of human parathyroid hormone (PTH) containing the amino acid sequence 1–34. It is a new class of anabolic agents acting on the skeleton and should be considered as an alternative to existing antiresorptive agents for the treatment of severe osteoporosis and intractable fractures [11]. Indeed, intermittent systemic administration of hPTH(1-34) reduces the risk of fractures

[12, 13] by improving bone microarchitecture and enhancing overall bone mass [14, 15]. Black et al. [16] reported that hPTH(1-34) exceeded BPs in increasing bone mineral density. In contrast with BPs, which inhibit osteoclastic bone resorption and decrease the bone remodeling rate, PTH stimulates osteoblastic bone formation through an increase in the bone remodeling rate [17]. However, the clinical problems of PTH are as follows: PTH is significantly more expensive than antiresorptive agents [11], PTH is administered by subcutaneous injection [11], and the duration of administration is limited to <2 years based on the induction of osteosarcoma in a rat model of carcinogenicity [18, 19].

22.2.2 Effect of Intermittent PTH Administration on Peri-implant Bone

Recent studies have also reported that intermittent hPTH(1-34) administration promotes peri-implant bone healing in animal and clinical models [20–22]. Our present study also confirmed that intermittent hPTH(1-34) administration has a potent osteogenic capability in stimulating implant osseointegration in ovariectomized (OVX) rats as described in Sect. 30.4. Although there are clinical problems associated with PTH, replacement of BPs with PTH is expected to improve bone density and quality in surgical sites, promote peri-implant bone formation, and prevent the development of BRONJ.

22.3 Low-Magnitude High-Frequency (LMHF) Loading

22.3.1 Effect of LMHF Loading on Skeletal Tissue

LMHF loading, which is generally defined as an LM of <1 g (1 g = 9.98 m/s^2) and HF of 20–90 Hz, elicits a positive effect on the skeleton (Fig. 22.1) [23, 24]. Numerous studies have evidenced that LMHF loading, applied by means of whole-body vibration (WBV), stimulates bone formation and fracture healing [25–28]. WBV loading has already been used clinically as a nonpharmacological intervention in the treatment of osteoporosis [29–34].

22.3.2 Effect of LMHF Loading on Peri-implant Bone

Regarding titanium implant osseointegration, which has similarities with bone fracture healing, the coauthors' previous studies showed that LMHF loading has an osteogenetic effect on peri-implant bone [35–37]. In particular, Ogawa et al. [35, 38] confirmed that the specific parameters of a loading regimen, such as the

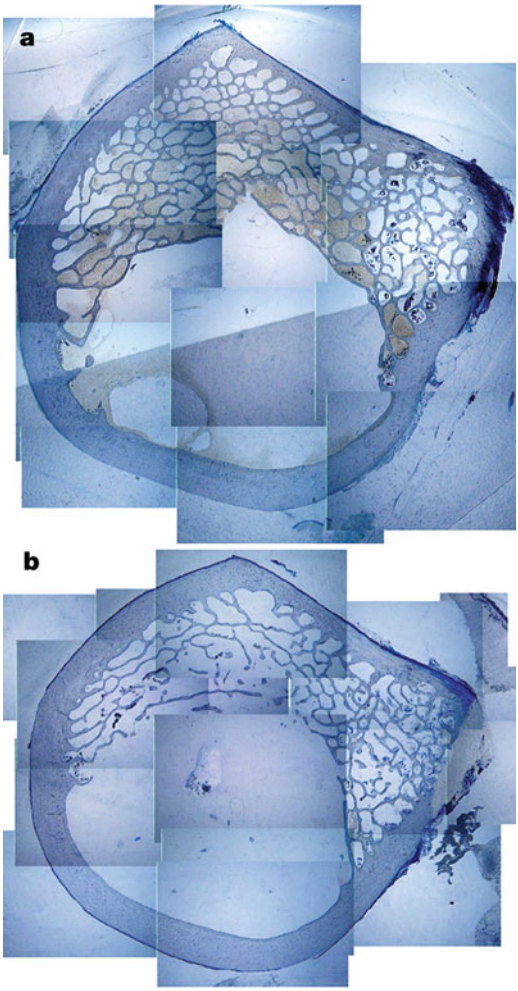

Fig. 22.1 Osteogenetic effect of LMHF loading. Montages of photomicrographs of the proximal sheep femur used for static histomorphometric evaluation after 1 year of exposure (20 min per day) to a 0.3 *g*, 30-Hz mechanical stimulus. There was 32 % more trabecular bone in the proximal femur of experimental animals (**a**) compared with age-matched controls (**b**) ($P < 0.04$) [23]

duration, session distribution, frequency, and amplitude of loading, play an important role in the impact of LMHF loading on the bone (Fig. 22.2). Additionally, the application of LMHF loading reportedly enhances bone-implant osseointegration in OVX rats [39–41], which was observed in our present study as described in Sect. 30.4.

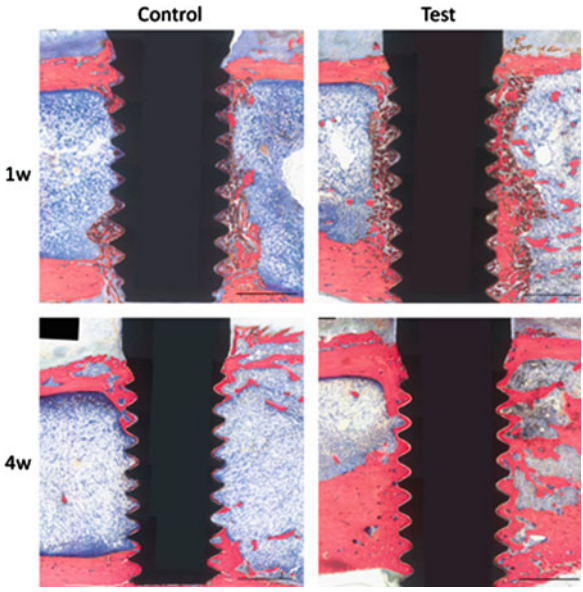

Fig. 22.2 Effect of LMHF loading on peri-implant bone healing and implant osseointegration. Representative images of the test (loaded) and control (unloaded) group from the 1-week healing period (**a**) and the 4-week healing period (**b**). *Scale bars*: 1 mm. After 4 weeks of healing, the bone neoformation and cortical bone width were much greater in the test group than in the control [35]

22.4 Effect of LMHF Loading and Intermittent PTH on Peri-implant Bone

Both LMHF loading and intermittent hPTH(1-34) administration have an independent osteogenic effect on peri-implant bone healing and implant osseointegration. However, there are no reports on the impact of their combined therapy on peri-implant bone. It seems likely that combined therapy would act synergistically on the bone healing process and strengthen bone-implant osseointegration. Additionally, the potential synergistic effect may shorten the healing period, thereby relieving the clinical problems associated with PTH.

Our recent study compared the osteogenic impact of LMHF loading and intermittent hPTH(1-34) administration on peri-implant bone healing and implant osseointegration in an osteoporosis model and evaluated their combined effect on these processes. Thirteen-week-old ovariectomized rats ($n = 88$) were divided into three groups: each group of rats received PTH (40 μg/kg, 5 days/week), alendronate (15 μg/kg, 2 days/week), and saline (volume-matched vehicle control), respectively. After 3 weeks, a titanium implant was inserted in both tibiae. Again, each group was subdivided into two groups: with or without LMHF loading via whole-body vibration (WBV, 50 Hz at 0.5 *g*, 15 min/day, 5 days/week). The rats were sacrificed 1 or 4 weeks after implant installation. Peri-implant bone healing and implant osseointegration were assessed using removal torque tests (RT value) and micro-CT analyses (relative gray (RG) value, water = 0 and implant = 100). The data were analyzed by three-factor ANOVA (loading, drug, healing period) followed with a Tukey-HSD test ($\alpha = 0.05$). RT value was significantly influenced by all three factors

($P<0.01$). In particular for PTH-WBV group, these values were highest in all groups after 4 weeks of healing. In the cortical bone, RG value was significantly influenced by the loading ($P<0.01$). In the trabecular bone, on the other hand, RG value was significantly influenced by the drug ($P<0.01$). The RG values of the PTH-treated groups were significantly higher than those of other drug-treated groups ($P<0.01$). The results reveal that LMHF loading and PTH act locally and synergistically on bone healing process, thereby strengthening implant osseointegration. Interestingly, a previous study reported that the combination of ALN and LMHF loading did not lead to a synergistic reaction influencing the bone healing response [41]. Similar to the present study, no obvious positive effect was found in the ALN and ALN+WBV groups. This might be because ALN inhibits osteoclastic bone activity, which is required in the process of bone adaptation and therefore of implant osseointegration. The results also indicate that PTH combined with LMHF loading has a bone-stimulating effect superior to that of ALN and LMHF loading.

22.5 Conclusion

There were four main findings in this review. In osteoporosis model:

- LMHF loading has an osteogenetic effect on the peri-implant bone.
- Intermittent hPTH(1-34) administration has a potent osteogenic capability in stimulating implant osseointegration.
- Two treatment modalities act locally on the bone healing process. The cortical bone was influenced by LMHF loading. The trabecular bone was influenced by PTH.
- The combined application of LMHF loading and PTH synergistically stimulates implant osseointegration. Additionally, PTH combined with LMHF loading has a bone-stimulating effect superior to that of ALN and LMHF loading.

Therefore, this can be a new therapeutic option for oral implant treatment in osteoporotic patients without problems such as failure of osseointegration, delayed healing, or BRONJ.

Conflicts of Interest The authors report no conflicts of interest.

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