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High Frequency Acceleration: A New Tool for Alveolar Bone Regeneration

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Abstract

Introduction—A common problem in clinical dentistry is the significant and rapid bone loss that occurs after periodontitis, osteoporosis, tooth extractions, lack of function, or any other pathologic condition that target the alveolar bone. Currently there is no stable solution for the long-term preservation or rehabilitation of alveolar bone. In this article, we review the latest concepts on bone response to mechanical stimulation, and summarize the results of our studies on the effect of high frequency acceleration (HFA) on healthy alveolar bone and on healing alveolar bone after extractions.

Methods—In both studies, we used adult Sprague Dawley rats to test the response of alveolar bone to different frequencies and accelerations applied to the maxillary molars.

Results—Once we determined which parameters of HFA induced a higher osteogenic response, we tested the effect of this mechanical stimulation during bone healing after molar extraction. Our studies strongly show that HFA can stimulate bone formation in the healthy alveolar bone surrounding the tooth/point of application as well as the distant bone surrounding the neighboring teeth. When HFA was applied to the second molar, after extraction of the third molar, it accelerated bone healing and prevented alveolar bone resorption in and around the extraction socket.

Conclusion—HFA is a noninvasive safe treatment that can be used to prevent alveolar bone loss, accelerate bone healing and to improve the quality and quantity of alveolar bone under both physiological and pathological conditions.

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CONFLICT OF INTEREST

The original work on the osteogenic effect of HFA in alveolar bone resulted in a patent filled by New York University in which two of the authors are named as inventors, Mani Alikhani and Cristina Teixeira.

Keywords

High frequency; Acceleration; Bone preservation; Noninvasive therapy; Vibration; Extraction; Osteoporosis

INTRODUCTION

Alveolar bone supports teeth, protects nerves, vessels and glands, and supports muscles of mastication and facial expression. Due to this array of functions loss of alveolar bone can significantly affect the quality of life of patients [1,2]. Despite its importance, irreversible alveolar bone atrophy is very prevalent as the result of numerous conditions such as periodontitis, tooth loss, osteoporosis and lack of function. Current studies demonstrate that the number of patients who suffer from osteoporosis and periodontitis are expected to increase with the aging population [3]. Consequently, while tooth loss due to caries is decreasing, loss caused by atrophy of tooth-supporting alveolar bone is already a stark reality. In this regard, to improve the quality of life of the aging population, health care providers are faced with two main challenges: 1) preventing alveolar bone loss and 2) restoring the alveolar bone that has been lost due to pathology. To have a better grasp on the nature of these challenges, one should understand the different aspects of alveolar bone loss.

In periodontitis, alveolar bone loss is mostly accompanied with reduction in height and width of alveolar bone which based on the location and extent of destruction can manifest itself as different forms of pockets around the teeth. However, in osteoporosis or lack of function, alveolar bone dimension is mostly intact and alveolar bone loss mostly presents itself as a decrease in density [4–7]. This decrease in density in the long term can make the alveolar bone more vulnerable to other pathologies such as periodontal diseases [8–10]. Given a strong link between alveolar bone resorption and tooth loss, the osteoporotic changes of the alveolar bone may directly contribute to premature loss of teeth through non-infectious mechanism. In fact, osteopenia of the jaws may be a more sensitive indicator for tooth loss compared to other clinical measures, such as probing depth and attachment loss.

In condition such as extraction of a tooth, both dimensions and density of alveolar bone decrease significantly due to severe bone resorption. In fact, after extraction there is progressive and irreversible alveolar bone atrophy, with the greatest changes occurring in the first 3–12 months post-extraction, with a loss of nearly 40% in height and 60% in width. This continues until only a narrow ridge remains or the alveolar bone is lost entirely. The scope of this problem can be appreciated when we realized that approximately 50% of the population aged 25–44 years and 70% of people aged 45–64 years have lost one or more teeth (excluding 3rd molars), while 22% of people aged 75+ years are completely edentulous [11,12].Thus, partially or fully edentulous patients are at risk for the devastating sequelae of alveolar bone loss, creating an urgent need for an affordable, conservative and efficacious therapy that preserves or recovers alveolar bone levels [13,14].

To address the first challenge of restoring the lost alveolar bone, different therapeutic measures are essential. In conditions of loss of alveolar bone height or width due to periodontal disease, application of different types of bone grafts in the presence or absence

of membranes have demonstrated some success in re-establishing the morphology of the alveolar bone [15,16]. However, as long as the functional need of the alveolar bone has not been restored by re-establishing the periodontal attachment, the long-term stability and benefit of these grafts are questionable. In addition, in conditions when significant height or width of alveolar bone has been lost, bone grafts are not able to re-establish the alveolar bone around the teeth, and therefore the prognosis for these teeth is very poor [17,18]. Considering, bone grafting carries potential post-operative complications due to excessive inflammation or delayed healing [19], and the clinical time and expenses associated with grafting procedures, the value of these approaches to address the need of a larger population is limited. While bone grafts may have some application in restoring alveolar bone loss in the presence of periodontal disease, alveolar bone loss due to osteoporosis or lack of function cannot be addressed by bone grafts and currently no treatment for these patients is available.

While restoring lost alveolar bone at the individual's level remains a challenge, a preventive measure at the population level is perhaps even more challenging. However, the best way to treat a disease is to prevent the disease. Unfortunately, at this moment there are few approaches directed at preserving/improving the quality and quantity of alveolar bone. The main indirect way to preserve alveolar bone is oral hygiene and cleaning regimens that focus mainly in decreasing the effects of harmful microorganisms on bone, and therefore indirectly decreasing the possibility of alveolar bone loss. These efforts while successfully decrease the incidence of periodontal diseases, cannot prevent alveolar bone loss due to other pathologic factors.

Due to the importance of preventive measures, in this article we focus on the effect of a specific treatment modality, high frequency acceleration (HFA) as a non-invasive and affordable measure to preserve and improve alveolar bone quality and quantity in health and pathological conditions. In this regard, first we study the effect of HFA on improving the quantity and quality of healthy alveolar bone, and then we test if this treatment can prevent decrease in dimensions of alveolar bone and bone density after tooth extraction [20,21].

HFA IMPROVES THE QUALITY AND QUANTITY OF HEALTHY ALVEOLAR BONE

We first dissected the components of mechanical stimulation that could be osteogenic in alveolar bone and safe for application through teeth, using a rat mode l [20]. In our experiments, we applied High Frequency Accelerations (HFA) to the occlusal surface of the right first maxillary molar of the rats for 5 min/day for 28 days. At the end of the experiments animals were sacrificed and maxillae collected for different analysis to evaluate alveolar bone response using microCT analysis, fluorescent microscopy, FTIR microscopy, gene expression by RT-PCR, and histology. We found that at accelerations of 0.3 and 0.6 g, frequencies between 60 and 100 Hz were highly osteogenic (Figure 1A). In absence of any additional load, this mechanical stimulation produced an average peak strain of only 4 – 8 με in the buccal and palatal plates of the alveolar bone in the proximity of point of application (the upper right first molar; data not shown). Our data showed that HFA stimulation caused

an increase in bone volume and in bone mineral density (Figure 1B) accompanied with increased expression of osteogenic markers (Figure 1C) and visible changes in the appearance of cortical bone at crestal level (Figure 1D) when compared to control animals that received only a static force (4–8 με).

More importantly, these experiments demonstrated that it is possible to induce bone formation by increasing both frequency and acceleration, in the absence of significant load and matrix deformation. The microstrain measured, were well below the level that is known to be able to produce bone response [22]. Furthermore, the osteogenic effect of HFA extended beyond the point of application into the adjacent alveolar bone surrounding the neighboring teeth. This gradient effect was characterized by an increase in trabecular thickness (27%) and a consequent decrease in trabecular spacing (26%) that was greater at the point of application but extended into the adjacent bone (data not shown).

These two findings have major clinical relevance, as this procedure could stimulate bone formation from a distance, even in fragile areas such as extraction or implant placement areas, without disturbing those tissues. We will discuss this major breakthrough with more detail in the Discussion &Conclusion section below.

HFA ACCELERATES BONE HEALING AND PRESERVES ALVEOLAR BONE HEIGHT AFTER EXTRACTION

Despite our earlier exciting results on alveolar bone response to HFA, it was unknown if the same mechanical stimulation could simultaneously improve bone formation and decrease bone resorption in pathological conditions. Therefore, we conducted an investigation to assess if HFA could maintain or improve alveolar bone after extractions of the maxillary right 3rd molar in rats [21]. After extractions, the HFA group received HFA (120Hz, 0.3g) applied to the occlusal surface of the maxillary right 2nd molar for 5min/day for 28 and 56 days. This HFA regimen produced 4με (microstrain) in the surrounding bone. Therefore, the Static group received 4με of static load. Our results revealed that not only was HFA application able to accelerated bone healing in extraction sockets in the first weeks, in the long-term HFA stimulation resulted in preservation of alveolar bone (Figure 2A) including the height of the alveolar ridge. Two months after extraction, the BV/TV in the extraction socket and surrounding area was 18% and 62% for the Static control and HFA groups respectively (Figure 2B), while trabecular thickness was 63% greater, trabecular spacing was 37% less, and bone mineral density was 28% greater in the HFA group than the Static group (data not shown). Furthermore, the Static group lost 52.9% of their alveolar bone height, while alveolar bone height in the HFA group remained unchanged (Figure 2C). Histologically, significantly higher bone formation activity was observed in HFA group with bone completely filling the extraction site and additional bone being deposited throughout the socket (Figure 3A). Because bone and cartilage cells can respond to mechanical stimulation, we decide to evaluate both intramembranous and endochondral pathways in the healing process in response to HFA. Mechanistically, our results suggest that HFA primarily induced intramembranous bone formation. When we looked at the expression of genes involved in the commitment to the osteogenic pathway we found Foxo1 and Runx2 mRNA

levels increased 5.4- and 6.9-fold in the HFA group and 3.2- and 4.8-fold in the Static group, respectively while Sox9 mRNA did not change significantly in either group (Figure 3B). Osteopontin (8.4-fold) and osteocalcin (9.3-fold) expression, two important markers of bone, were also significantly higher in the HFA group than the Static group (data not shown). In addition, the HFA group exhibited a decreased number of osteoclasts (Figure 3C) when compared with the Static group, suggesting ananti-resorptive effect of HFA in addition to the osteogenic effect.

Similar to our results in healthy bone and dentate animals, HFA's osteogenic effect on alveolar bone extended beyond the point of HFA application as stimulus applied to the 2nd molar significantly improved bone fill in the 3rd molar socket.

DISCUSSION & CONCLUSION

The skeleton's ability to adapt to different levels and patterns of mechanical loading can and has been used as a potential target for bone therapy. While extensive studies on the effect of exercise and external loading support the anabolic effect of mechanical stimulation on weight-bearing bones [23,24], there are very few studies on how to use mechanical stimulation to increase bone formation in non-weight bearing bones such as alveolar bone. Due to different embryonic origin and mechanical environments, the strategies that have been used to increase bone formation in weight-bearing bones cannot simply be adapted for non-weight bearing bones. Weight-bearing bones have endochondral origin, which enables growth under heavy mechanical loads—while the majority of craniofacial bones are not exposed to heavy loads, and form directly from mesenchymal cells (intramembranous origin) [25]. In addition, weight-bearing bones are exposed to direct loading, but alveolar processes are exposed to indirect loading via teeth and the periodontal ligament, which produces a complex pattern of strain distribution.

The main limiting factor in developing a mechanical regimen to stimulate bone formation in alveolar bone is our poor understanding of how mechanical stimulation can increase bone formation in the first place. Previously, it was assumed that the adaptation of bone depends on the magnitude of matrix deformation (strain) and therefore, to stimulate an anabolic reaction in the bone a threshold of 0.1% strain would have to be exceeded [22,26] Under this assumption that matrix deformation is the critical parameter driving bone adaptation, for many decades studies have focused on measuring the osteogenic effects of the different properties of strain [27–31]. In all of these studies it was assumed that a high magnitude of matrix deformation is necessary for mechanical stimulation to be osteogenic. Unfortunately, mechanical intervention that relies on the application of large loads may be infeasible for many clinical situations that involve fragile bones or non-weight bearing bones. First, the majority of craniofacial bones are not exposed to heavy forces. Second, to be practical these forces should be applied through the teeth with a minimum load to minimize tooth damage and discomfort. Third, in many clinical scenarios of alveolar bone loss or repair such as periodontal disease or early stages of dental implant integration, the application of high loads is contraindicated since they lead to further bone loss [32]. Therefore, to take advantage of the osteogenic effect of mechanical therapy in alveolar bone, other properties of mechanical stimulation had to be considered.

It has been previously shown that increasing the frequency of the applied load stimulates bone formation in weight-bearing bones with a matrix deformation of less than 0.001% strain [33,34]. The mechanism by which such low-level mechanical signals can cause bone formation is not clear, but this amount of matrix deformation is too small to be recognized by cells, suggesting that other aspects of the mechanical stimulation may also have an anabolic effect. In fact, it makes more sense for cells to be sensitive to a direct stimulus that does not rely on matrix deformation and thus cannot damage to the surrounding matrix. Indeed, application of small oscillatory accelerations, independent of matrix deformation was able to enhance bone formation in weight-bearing bones [35]. This property of mechanical stimulation can become very useful in the development of a mechanical regimen to increase bone formation in non-weight bearing bones, such as the jaws, since it does not rely on application of high loads. Another aspect of a mechanical stimulation regimen that can be manipulated as an osteogenic source is acceleration. While the mechanism through which acceleration stimulates bone formation is not clear, it has been suggested that oscillation of nuclei in cytoplasm may activate cytoskeleton, which may increase osteoblast activity. However, higher accelerations are usually accompanied by higher strains, which limit the application of higher acceleration in the mouth. Therefore, changes in frequency are a safe compensation for this shortcoming when designing a mechanical therapy to stimulate bone formation in non-weight bearing bones such as alveolar bone.

Our studies support HFA as a simple, non-invasive, and cost effective treatment to preserve and stimulate alveolar bone formation. Applying HFA for just 5min/day as part of a home care regimen may significantly improve the outcome of procedures such as tooth extraction, implant, and bone graft integration. The fact that the stimulation can be applied from a distance, allows the osteogenic response to occur without the need to disturb the fragile and sensitive bone structure after those procedures. We would recommend using HFA stimulation after extractions, to maintain the alveolar bone structure including height, in preparation for implant placement, and after implant placement for faster and stable integration. Likewise, after grafting a deficient ridge HFA could accelerate osteogenic integration and stimulate bone growth into the grafting material.

HFA may also improve alveolar bone volume, trabecular thickness and mineral density after destructive diseases such as osteoporosis or periodontitis. In fact, as a preventive measure, HFA may be recommended to halt osteoporotic changes in the jaws and avoid tooth loss. In terms of periodontitis, currently there is no preventive treatment other than the approaches directed at controlling and or delaying the progress of the disease. It is well established that periodontitis can occur in destructive booths of active disease followed by periods of quiescence [36]. HFA may provide a non-invasive therapy to improve the quantity and quality of the remaining alveolar bone decreasing its susceptibility to the destructive effect of further rounds of active disease or to recover alveolar bone structure after the active disease subsides.

Another common situation where a robust osteogenic response in the tooth supporting alveolar bone could have significant impact is during orthodontic retention. In response to orthodontic forces a temporary inflammatory reaction in the periodontal ligament is generated that stimulate alveolar bone remodeling and therefore tooth movement [37]. After

the final occlusion is established by the orthodontist, HFA stimulation could help to stabilize the teeth in their aligned position by inducing new bone formation and increasing bone mineral density and trabecular thickness. Current work in CTOR laboratories is testing the efficacy of HFA in all these clinical situations.

In conclusion, we have developed high frequency acceleration as a non-invasive and cost effective treatment that is both preventative because it strengthens the alveolar bone and regenerative because it increases alveolar bone volume and density under both physiological or pathological conditions.

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ABBREVIATIONS

HFA	High Frequency Acceleration
με	Microstrain
Micro CT	Micro Computerized Tomography
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
mRNA	Messenger Ribonucleic Acid

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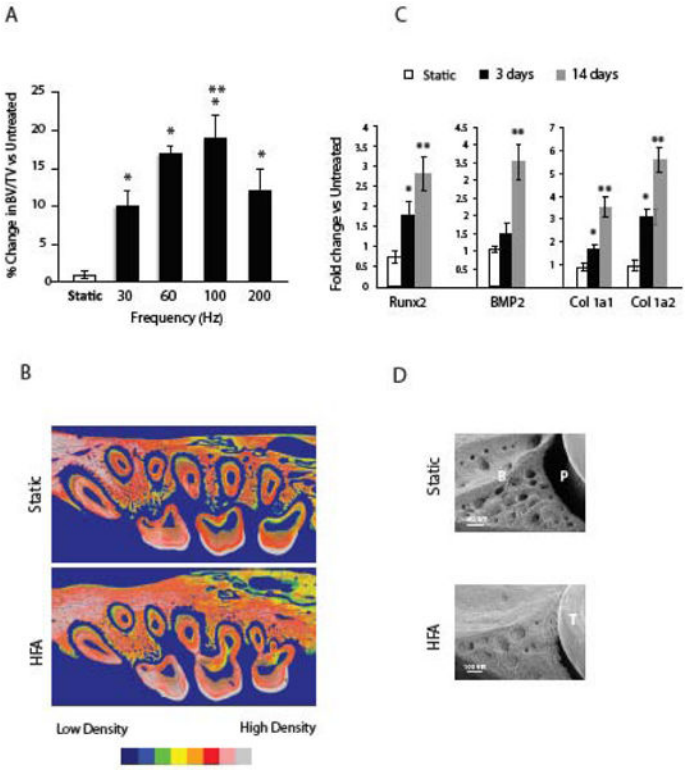

Figure 1.

HFA increase alveolar bone volume. (A) Change in BV/TV obtained from CT analysis of maxilla exposed to different frequency at peak accelerations of 0.3g and peak strain of 4με in comparison with untreated animals, 28 days after extractions. Each Value represents the mean + SEM of 5 samples. *Significantly different from untreated animals. ** Significantly different from 30 Hz and 200Hz. (B) Scanning electron microscopy (SEM) of longitudinal sections of HFA (60Hz, 0.3g, 4με) and static group (4με) alveolar bone at 28 days post-treatment, color coded to visualize differences in mineral density. (C) Mean “-fold” increase in expression of osteogenic factors (Runx2 and BMP2) and extracellular matrix protein (collagen Type I) are shown for the static group (after 14 days) and the HFA (60 Hz, 0.3g, 4με) group at 3 days and 14 days. Data shown as fold change in gene expression when compared to the untreated group. *Significantly different from untreated group, $p < .05$. **Significantly different from day 3, $p < .05$.(D) SEM images of the cortical bone around the medio-buccal root of the maxillary right first molar show bone modeling activity and changes in appearance of bone at crestal level (T - tooth, B - bone, P - periodontal space).

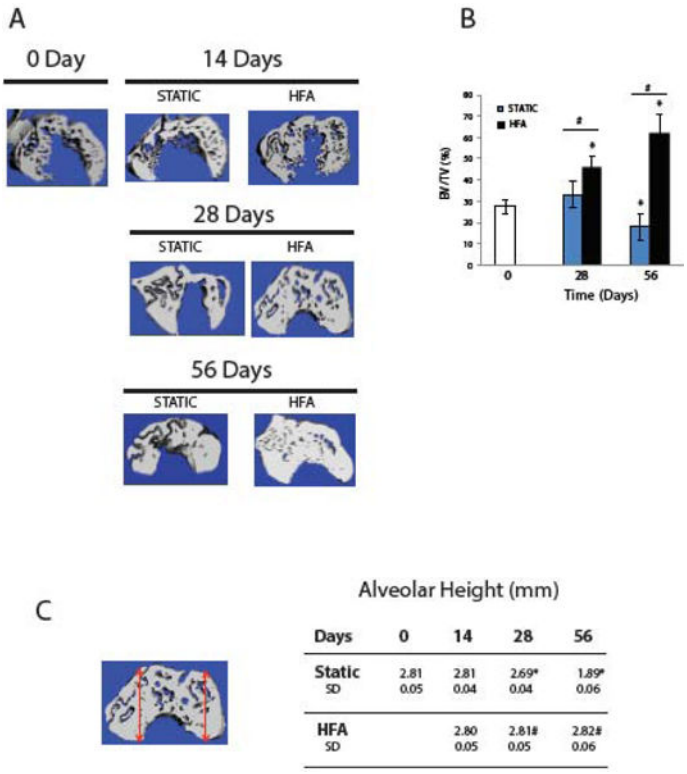

Figure 2.

HFA stimulates alveolar bone formation in the extraction socket and surrounding alveolar bone.(A) 3-D microCT reconstructions show higher level of bone formation and faster filling of alveolar socket in the area of the upper right 3rd molar in the HFA samples in comparison with Static group, 0, 14, 28 and 56 days after extraction. (B) MicroCT quantitative analysis was performed in area of the extraction socket and surrounding alveolar bone. Average bone volume fraction (BV/TV) was calculated in both Static and HFA groups 28 and 56 days after extraction. Each value represents the mean ± SEM of 5 animals. * Significantly different from baseline (Day 0), # Significantly different from Static group at same time point. (C) Buccal and palatal cortical plate height was measured in 3 sections of alveolar ridge in the area of extraction (mesial, middle and distal). Each number represents the mean ± SEM of measurements from 5 animals.* Significantly different from baseline (Day 0), # Significantly different from static group at same time point.

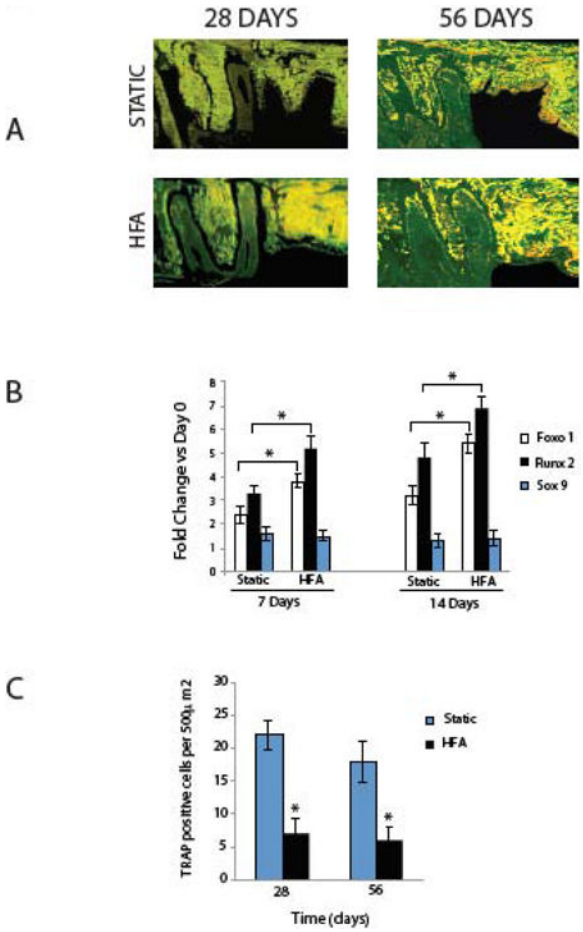

Figure 3. HFA stimulates intramembranous bone formation and inhibits bone resorption

Rats received calcein (15 mg/kg, i.p.) and xylenol orange (90 mg/kg, i.p.) injections alternating on Days 0, 26 and 54 and were euthanized on Day 56. **(A)** Fluorescence microscopy of sagittal sections at day 28 and 56 shows increased intensity of the labels in extraction area of HFA samples indicative of extensive bone formation. **(B)** RNA was collected from alveolar bone surrounding the extraction socket at Baseline (Day 0), and Static and HFA groups at Day 7 and 14 after extraction of upper right maxillary 3rd molar, and the expression of osteogenic and chondrogenic factors was evaluated by RT-PCR. Data shown as fold change in comparison to Day 0. * Significantly different from Static group at same time point. **(C)** Sagittal sections of right maxilla were produced through the roots of 2nd molar in Static and HFA samples. TRAP staining sections were used to count the number of osteoclasts present in the area of the extraction socket 28 and 56 days after extraction. Each value represents the mean ± SEM of five animals (* significantly different from Static group at similar time points).