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Evaluation of the Effects of Vibratory Stimulation on Mesenchymal Stem Cells of Dental Tissues

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ABSTRACT

Introduction: The effects of vibration on mesenchymal stem cells (MSCs) derived from dental tissues remain poorly studied. However, their application in clinical dentistry is advancing, making it crucial to understand how these therapies can improve clinical treatments. **Objective:** To discuss the effectiveness of a vibrating device to investigate the effects of mechanical vibration on three cell lines: osteoblasts, dental pulp-derived stem cells (DPSCs), and gingival mesenchymal stem cells (GMSCs). **Material and methods:** A vertical vibration system characterised by a three-axis accelerometer was used, and sinusoidal vibrations at frequencies of 20 and 60 Hz were

applied to the cell lines. The characterisation confirmed the correct direction and magnitude of the vibration. The effects on cell viability and activity were analysed using the resazurin assay and Calcein-AM staining at 24, 48, and 72 h. **Results:** Initial vibratory stimulation affected osteoblast viability, but it normalised after 72 hours. DPSCs were observed to respond best at 60 Hz, while GMSCs had similar results to non-vibrated controls. Vibration therapy demonstrated positive results on cell viability, without affecting the morphology of the cultures studied. **Conclusions:** Low-magnitude, high-frequency vibration emerges as a non-invasive treatment to improve cell viability. Even so, more extensive studies are required to unravel the exact mechanisms and optimise clinical protocols. In addition, the therapy could also mitigate side effects of orthodontic treatment.

Keywords: vibration therapy, orthodontic treatment, dental mesenchymal stem cells, low-magnitude, high-frequency vibrations.

INTRODUCTION

Today, orthodontic treatments are commonly requested in dental offices, for both aesthetic and functional reasons. However, these treatments can lead to adverse effects including root resorption, pain, pulp changes, periodontal disease, decalcification, and temporomandibular dysfunction, and such side effects are not fully understood but are associated with prolonged treatment[1]. Therefore, we believe that reducing treatment time can also reduce side effects[1,2].

Over time, methods have been developed to accelerate tooth movement and shorten the duration of orthodontic treatments, including surgical, pharmacological, physical stimulation, and Low-Intensity Pulsed Ultrasound (LIPUS)[1,3-6]. In dentistry, devices such as AcceleDent® (OrthoAccel® Technologies, Inc., Bellaire, USA) have been developed to facilitate tooth movement through vibratory stimulation, although their effectiveness is a matter of debate. In this context, patients treated with AcceleDent® did not show significant differences in mandibular dentition levelling, pain reduction, or acceleration of interproximal space closure during treatment with fixed appliances, compared to the control group[4,7].

On the other hand, the theory behind devices like AcceleDent® suggests that vibrational forces stimulate cell differentiation and maturation, which could accelerate bone remodelling and tooth movement through an anabolic effect on the bone. Likewise, studies conducted in animal models show that vibration therapy improves fracture healing time and increases the expression of genes related to osteogenesis[8,9].

In vitro studies have investigated the effect of vibration stimulation on osteoblasts, osteocytes, and osteoclasts, as well as mesenchymal stem cells (MSCs). MSCs are multipotent cells that play a crucial role in tissue regeneration and repair[10]. Understanding how mechanical vibrations affect the behaviour and differentiation of mesenchymal stem cells is essential in regenerative medicine and orthodontics.

This study aimed to evaluate the effect of vibrations on three cell lines: osteoblasts, dental pulp-derived MSCs (DPSCs) and gingival MSCs (GMSCs), to establish protocols for the application of mechanical vibrations in orthodontic treatments. The results are expected to contribute to the development of therapies to accelerate tissue regeneration or treat specific medical conditions, including orthodontic treatment.

MATERIALS AND METHODS

This study is an experimental, *in vitro*, observational, and prospective study. To achieve this, a sustained vibration platform was assembled based on previous methodologies[11-13]. Using a function generator (FY3200 Dual Channel Function/Arbitrary Waveform Generator, FeelTech Technology Co. Ltd., Zhongyuan District, China) and an audio amplifier (XH-M542), sinuous signals were emitted that produced vibrations through a 300-watt speaker (XED650C - 6.5" XED Series 2-Way Component Set, Cerwin Vega, Los Angeles, USA). To evaluate the vibration stimulus, the culture plates were fixed to a 3 mm thick acrylic screen, attached to the speaker with spring locks. Frequencies of 20 and 60 Hz were applied, calibrated to an amplitude of +0.3 mm using a three-axis accelerometer (AX3, Axivity Ltd, Newcastle, United Kingdom), and an oscilloscope (MDO3032 Mixed Domain Oscilloscope, Tektronix, Inc., Beaverton, USA). The amplitude was selected based on previous field research using similar equipment[12]. The accelerometer capable of measuring vibrations in three dimensions: X axis, Y axis, and Z axis, was fixed to the base of the acrylic plate, recording the vibrations at a sampling rate of 3200 Hz.

The displacement produced was calculated using the root mean square error (RMSE) value and the marked equivalences of the callipers and the accelerometer. The equation used to determine the optimum volume on the power amplifier to achieve the designated amplitude was:

$$D = \frac{GA}{2\pi^2 F}$$

Where:
D = displacement (m), G = gravity (constant at 9.81 m/s^2), A = acceleration (g) and F = frequency (Hz).

Three cell lines were used: osteoblasts (hFoB 1.19), dental pulp-derived mesenchymal stem cells (DPSCs) and gingival (GMSCs). The MSCs were from an existing cell bank and were previously characterised according to the criteria of the International Society for Cell & Gene Therapy (ISCT)[14]. DPSCs and GMSCs express high levels of the surface markers CD105, CD90, and CD73. They also have a high expression of CD13, and express moderate levels of HLA-ABC, are negative for the expression of HLA-DR and do not express haematopoietic (CD34, CD45 and CD14) or endothelial (CD31) markers. The cells have a fibroblastoid morphology and the ability to differentiate into adipogenic, osteogenic, and chondrogenic lineages[14]. The hFoB 1.19 cell line was acquired from the ATCC.

DPSCs and GMSCs were cultured in Dulbecco's Modified Eagle Medium (DMEM), supplemented with 10% foetal bovine serum, 1% antibiotic-antimycotic solution and 2 mM glutamine, and incubated under standard conditions (37° C, 5% CO_2). The hFoB 1.19 cells were cultured in DMEM F12 medium, supplemented with 10% foetal bovine serum and 1% antibiotic-antimycotic solution, and incubated under the aforementioned conditions.

Vibratory stimulation at 20 Hz or 60 Hz was performed for 20 minutes before seeding cells in the 12-well plates and was repeated at 24, 48, and 72 hours, inside a laminar flow hood. For the non-vibrated control group (0 Hz), the culture plates were left for 20 minutes in the laminar flow hood on the platform without activating it.

Cell viability was assessed by the resazurin assay (10% of 44µm v/v) in unsupplemented basal medium, incubating the culture plates for 4 h, with a density of 1,500 cells/cm^2 for MSCs and 1,000 cells/cm^2 for osteoblasts (n = 9 samples per condition). Measurement times were 24, 48, and 72 h. A cell-free well containing culture medium and resazurin was used as a blank. Finally, the optical density was measured at 570 nm.

To evaluate the integrity of the cell membrane after vibratory stimulation (at 72 h of culture), Calcein AM (1 µM) (Invitrogen™ Calcein AM, Thermo Fisher Scientific Inc., Carlsbad, USA) staining was used for 10 min at 37° C. Cells were visualised using an Epi-fluorescence microscope (AmScope, Irvine, USA). The number of cells per field was counted using ImageJ software (NIH, Bethesda, USA), each photograph of the field of interest was adjusted to the Otsu thresholding, and converted to 8 bits, then to a binary image, followed by the Watershed plugin and the Analyse Particles function was applied.

Finally, we used one-way ANOVA followed by Tukey's range test to assess statistically significant differences between the groups examined. For the above, the GraphPad Prism software version 10.3.1 (GraphPad Software, Inc., San Diego, USA) was used, and a value of $p \geq 0.05$ was considered statistical significance.

RESULTS

The vibrations were successfully generated by an acoustic device designed to produce sinusoidal waves with a specific frequency and amplitude. The culture plate received the vibration vertically, with linear displacement relative to the stationary base. The frequency and displacement records are shown in Table 1.

Table 1.
Record of frequency and amount of displacement

Programmed Frequency	Recorded average	Maximum	Minimum	RMS displacement	Peak-to-peak acceleration	
					Value	*Average*
20 Hz	19.95 Hz	20.05 Hz	19.83 Hz	7.4 µm	232 mV	237 m
60 Hz	60.04 Hz	60.41 Hz	58.88 Hz	6 µm	202 mV	196 m

The generation of sinusoidal waves with frequencies of 20 Hz and 60 Hz affected all the cell lines studied. The optical density (O.D.) of the blank was subtracted from the O.D. of the resazurin cell viability assay of all cell lines, including the control group. Vibration stimulation had a negative effect on osteoblast viability at 24 hours, with an average O.D. of 0.5177 (SD ± 0.003) at 20 Hz and 0.4906 (SD ± 0.025) at 60 Hz, compared to the control, which had an O.D. of 0.5519 (SD ± 0.001). At 48 hours, viability decreased further, with an O.D. of 0.3206 (SD ± 0.0659) at 20 Hz and 0.2270 (SD ± 0.0659) at 60 Hz, compared to the control, which had an average O.D. of 0.6257 (SD ± 0.0072). At 72 h, viability had recovered, showing an O.D. of 0.6508 (SD ± 0.0416) at 20 Hz, and 0.9066 (SD ± 0.0737) at 60 Hz, while the control was 0.7514 (SD ± 0.0351). The differences and statistical analysis are presented in Figure 1. A.

For DPSCs, vibration stimulation improved cell viability. At 24 h, an average O.D. of 1.354 (SD ± 0.0115) was observed at 20 Hz and 1.468 (SD ± 0.001) at 60 Hz, compared with the control, which had an O.D. of 0.2116 (SD ± 0.00125). At 48 hours, cell viability increased further, reaching an O.D. of 1.604 (SD ± 0.0072) at 20 Hz, 1.468 (SD ± 0.0156) at 60 Hz, compared to the O.D. of 0.6117 (SD ± 0.0605) of the control. After 72 hours, viability was similar between groups, with significant differences observed only between the 20 Hz (O.D. 1.689) and 60 Hz (O.D. 1.631) groups, while the control showed an O.D. of 1.660 (SD ± 0.0173).

GMSCs maintained similar viability throughout all culture times, showing only slight variations. At 24 hours, viability showed an O.D. of 1.354 (SD ± 0.0036) at 20 Hz and 1.467 (SD ± 0.052)

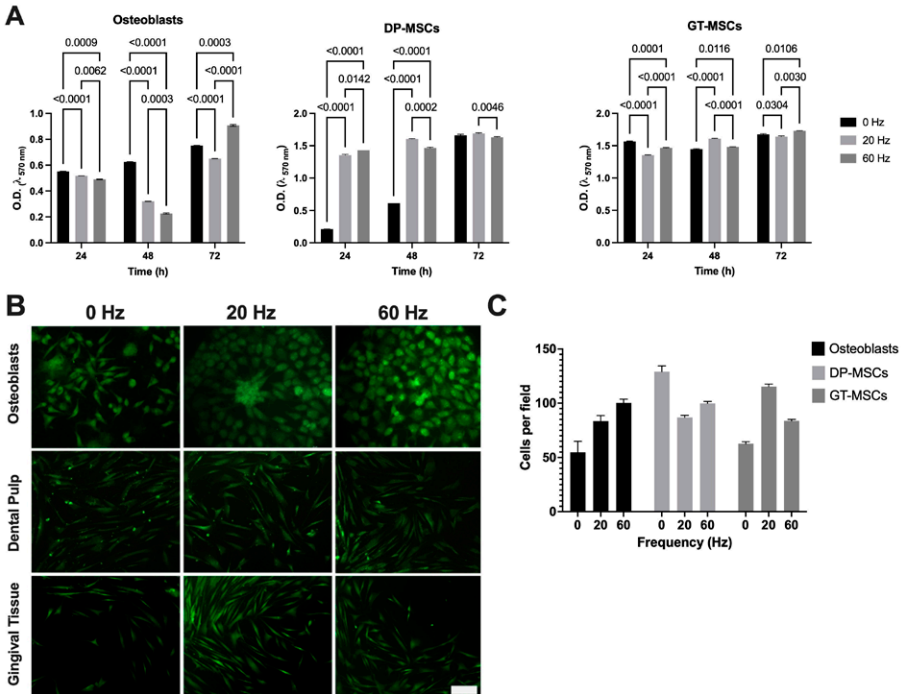

Figure 1. Effects of vibration *in vitro*. A. The effects on the viability of osteoblasts, dental pulp-derived mesenchymal stem cells (DPSCs), and gingival mesenchymal stem cells (GMSCs) using the resazurin assay are shown. Brackets indicate the results of ANOVA and Tukey *post hoc* statistical analysis. **B.** Representative images of Calcein AM fluorescent staining. Bright green fluorescence indicates a positive result, with no changes in cell viability or morphology at 72 hours of culture following vibration stimulation. Osteoblasts show complex aggregates and long cytoplasmic processes. Magnification 20X, scale bar 50 µm. **C.** Cell count per field was performed using ImageJ software in photographs at 20X magnification without finding statistically significant differences. On the other hand, simple visual examination showed a greater number of cells per field in the vibrated groups compared to the non-vibrated ones; 9 fields (n=9) were analysed per experimental condition or control, after 72 hours of culture. Optical Density (O.D.).

at 60 Hz, compared to the control, which showed an O.D. of 1.571 (SD ± 0.410). At 48 hours, viability increased showing an O.D. of 1.6083 (SD ± 0.0055) at 20 Hz and 1.4826 (SD ± 0.0032) at 60 Hz, while the control showed an O.D. of 1.447 (SD ± 0.072). Finally, at 72 hours, the viability O.D. was 1.675 (SD ± 0.0141) in the control, 1.641 (SD ± 0.0146) at 20 Hz and 1.7283 (SD ± 0.040) at 60 Hz.

Viability assays indicated that DPSCs had higher metabolic activity, while GMSCs showed greater stability without abrupt changes. Microscopic observation showed that the cells remained intact and well distributed. At 72 hours, Calcein AM staining demonstrated that the integrity of cell membranes in the vibrated and non-vibrated groups was similar (Figure 1. B and C), indicating that the vibratory stimulus does not substantially contribute to or affect the adhesion of the cells used in this study. However, no statistically significant differences were found between groups (Figure 1. C).

Osteoblasts formed elongated intracellular structures with vibration at 20 Hz and to a lesser extent at 60 Hz (Figure 1. B). DPSCs and GMSCs maintained their fibroblastic shape, developing extensive cytoplasmic processes with stimulation at 20 and 60 Hz. These extensions facilitated greater cell-cell contact in the experimental groups compared to the control.

DISCUSSION

Currently, few studies address the effects of vibration on cultured mesenchymal stem cells (MSCs) derived from dental tissues[15]. Although vibration therapy is already being used in clinical dentistry, understanding its effects is crucial for improving therapies and treatment plans[4].

Studies to date have focused on osteogenic differentiation by osteoblasts or bone marrow MSCs, and on markers of cellular stress/inflammation in epithelial cells[16, 17]. Clinical trials focused on the effects of vibration on muscle and bone tissue, finding that vibration therapy has an anabolic effect on bone, improving fracture healing and increasing the expression of alkaline phosphatase, osteocalcin, Col-1, Runx2, and Osterix[18-20].

Devices such as the AcceleDent® have been developed to promote orthodontic tooth movement through vibratory stimulation at 30 Hz, although the results are contradictory[4, 7, 21]. During bone resorption, the extracellular matrix releases growth factors that recruit MSCs for bone remodelling, a process regulated by signalling pathways involving parathyroid hormone and tumour growth factor beta (TGF-β)[22]. MSCs contribute to bone regeneration by differentiating into osteoblasts and secreting paracrine factors that promote angiogenesis, in addition to recruiting haematopoietic and immune cells to the remodelling site (Figure 2)[16,23].

To study the effects of mechanical vibrations on MSCs derived from dental tissues and osteoblasts, a vertical vibration system characterised by a three-axis accelerometer was developed, confirming that the vibration was perpendicular to the culture surface. Odd harmonics and frequencies slightly higher than expected were observed, possibly due to mechanical resonances of the acrylic plate, although these did not affect the displacement of the culture wells. This characterisation allowed the direct evaluation of the *in vitro* vibration effects.

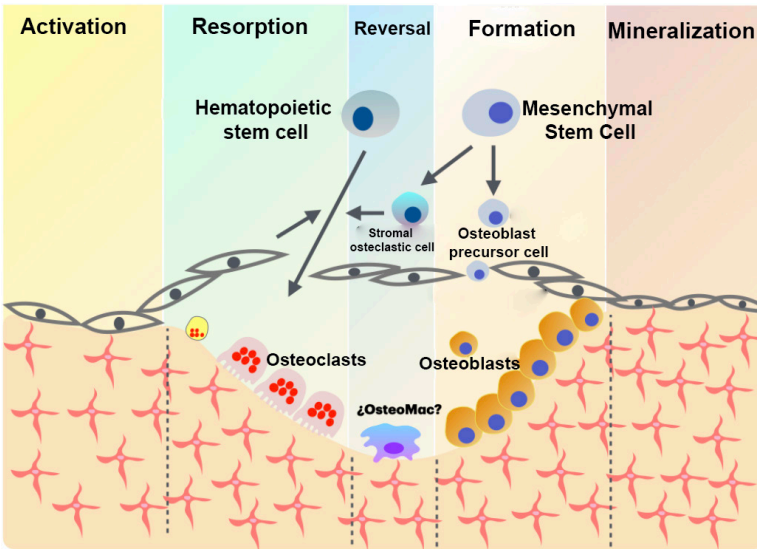

Figure 2. Bone remodelling process. During bone resorption, the extracellular matrix of the bone releases growth factors that recruit MSCs from resident sites and from the bone marrow to resorption sites, giving rise to the bone remodelling process, which occurs between the stages of formation and resorption. Osteomac is a term that refers to a specialised subgroup of macrophages that play a crucial role in bone homoeostasis and remodelling. Osteomacs are thought to be associated with osteoblasts and mesenchymal stem cells in the bone microenvironment and contribute to bone formation and maintenance, along with fracture healing.

In an inflammatory environment, mechanical stimuli significantly influence the activity of MSCs and osteoblasts during bone remodelling[10]. Understanding the interrelationship between MSCs, signalling molecules, and the bone microenvironment is essential for developing effective therapies for bone repair. Our study presents an *in vitro* model capable of replicating mechanical stimuli, contributing to a better understanding of the processes related to vibration therapy.

Sinusoidal vibration stimulation at 20 and 60 Hz was effective in all cell lines studied. Initially, there were negative effects on osteoblast viability, which normalised after 72 hours, highlighting the importance of mechanosensitivity in bone architecture. Similar studies report that frequencies between 30 and 90 Hz do not cause toxic effects on osteoblasts *in vitro* and activate the oestrogen receptor alpha pathway[24]. They also stimulate osteogenesis in MSCs derived from bone marrow and adipose tissue, with greater effects observed between 40 and 50 Hz[11,24].

In dental pulp-derived MSCs (DPSCs) and gingival MSCs (GMSCs), vibratory stimulation had positive effects on viability, being more notable in DPSCs at 60 Hz. While GMSCs showed similar responses between the non-vibrated and vibrated groups, perhaps because gingival tissue has greater exposure to physical and chemical stimuli and may therefore be more resistant to mechanical stimulation. The effects observed in DPSCs suggest that vibration therapy could prevent changes in the dental pulp during orthodontic treatment. Therefore, modification of the frequencies used is proposed to avoid potential side effects[25,26].

Vibrations between 30 and 90 Hz have been observed to stimulate osteogenic differentiation of MSCs and frequencies of 30 Hz induce the expression of RANKL through the cyclooxygenase and prostaglandin 2 (COX/PGE2) pathway, molecules related to pain[27]. The above could justify the use of vibrating devices to control pain during orthodontic treatments.

The process of osteoblastic differentiation includes proliferation, deposition, maturation and mineralisation of the extracellular matrix (Figure 2), which requires cell proliferation and migration processes. Studies in periodontal ligament MSCs show that low-magnitude, high-frequency vibration promotes proliferation, migration, and osteogenic differentiation[15]. In the present study, although no statistical differences were found between the number of cells per field between vibrated and non-vibrated groups, it was observed that both osteoblasts and MSCs were distributed over larger areas on the plate in the vibrated groups, so the stimulation could have effects on cell migration, which requires a more in-depth study. Likewise, both MSCs and osteoblasts formed extensive intercellular structures, reflecting a phenotypic characteristic of complex architectures, similar to what occurs in bone tissue[28, 29].

In vitro studies show variability in the parameters used, making definitive conclusions difficult[10,30]. Nevertheless, magnitudes below 1 gravity and frequencies between 20 and 100 Hz stimulate osteogenic differentiation in MSCs[10,16,31]. One of the limitations of our study was that the cultures were not studied under differentiation conditions, or for a longer period of time, so it would be important to explore the effects of vibration under various differentiation conditions on the cells studied.

CONCLUSION

The results of this study, along with previous research, suggest that low-magnitude, high-frequency vibrations may be a non-invasive and cost-effective treatment in orthodontics. In particular, the frequency of 20 and 30 Hz, which is suggested for the use of devices such as

AcceleDent®, seems to be appropriate for bone tissue. Larger studies addressing the effects of therapy on dental tissue-derived MSCs are needed to understand the mechanisms under which this therapy influences the cellular biology of bone remodelling, as well as more clinical trials to optimise its application protocols.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest associated with this work.

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