Low intensity pulsed ultrasound in periodontal regeneration

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Introduction

Dental caries and periodontal diseases are the two most diseases of the oral cavity. Not only do they present physical and social hazards but also seriously compromise human health and quality of life. Tissue engineering has contributed to the cessation of many oral diseases. Several methods have been described to enhance cellular performance and low intensity pulsed ultrasound (LIPUS) has shown to play an important role in cell metabolism. LIPUS stimulation is a classical therapeutic modality for bone regeneration and its efficiency has been widely reported over the years. Interestingly, recent studies have provided evidence that LIPUS plays an important role in the metabolism of periodontal cells and tissues as well.

Lipus and Biologic Mechanisms

Normal bone physiology is known to be regulated by mechanical stimulation. Both osteoblastic and osteoclastic activity have been proved to be mediated by mechanical stimuli[1]. Osteoclasts initiate bone resorption in response to determined signals and osteoblasts are recruited to deposit bone matrix in response to a coupling signal. Osteoclast and osteoblast activity could thus be related to opposite strain modalities. During orthodontic tooth movement, for example, the networked reactions that occur in and around periodontal ligament and alveolar bone cells change compressive and tensile stresses into molecular events, resulting in bone resorption and formation, respectively[2]. Other types of mechanical stimulation could thus modify cell metabolism, including ultrasound. LIPUS (intensity ranging from 30 - 100 mW/cm2) is an acoustic radiation that can be transmitted into the living tissues as pressure waves resulting in biochemical events at the cellular level[3]. LIPUS has been shown to stimulate bone and cartilage cells in vitro, indicating that ultrasound exerts direct anabolic effects such as production of growth factors and other signaling molecules, osteogenic differentiation and extra cellular matrix production[4]. The mechanisms involved in LIPUS-stimulated tissue repair is by the anabolic biophysical effects caused by mechanical stress and fluid micro-streaming which has an impact on the cellular plasma membrane. This triggers a cascade of intracellular signal transduction which in turn causes a subsequent gene transcription[5].

Lipus and Bone Regeneration

Mechanical stimulus to bone is of a great importance for maintaining the bone mass and structural stability of the skeleton. When bone is mechanically loaded, movement of fluid within the spaces surrounding bone cells generates a disparity in fluid levels. This in turn stimulates osteoclasts and osteoblasts, resulting in an enhanced anabolic activity for bone remodeling. Bone repair and regeneration, accelerated bone fracture healing, and an enhanced osteogenesis at the distraction site have been demonstrated during invivo studies with the use of Therapeutic LIPUS[6]. LIPUS stimulation has also been shown to enhance expression of bone formation-related genes such as collagen type I and X, aggrecan, transforming growth factor beta, runt related gene-2, osteocalcin[7], insulin-like growth factor-I, bone sialoprotein and alkaline phosphatase. In addition, LIPUS has been reported to promote protein synthesis and calcium uptake in various osteoblastic cell lines[8]. The enhancement of COX-2 gene expression and synthesis of endogenous prostaglandin E2 (PGE2 plays an important role in bone remodeling[9].

Lipus and Periodontal Ligament Regeneration

Periodontal ligament is subjected to various kinds of mechanical stress during every stage of cell proliferation and differentiation[10]. In a previous study, cyclic stretch stimulation mediated periodontal ligament cells differentiation, thus regulating the function of the periodontal ligament as a source of cementoblasts and osteoblasts through the EGF/EGF-R system[11]. It has been reported that LIPUS is effective in releasing fibroblast growth factors from a macrophage like cell line[12] and also helps in inducing early cementoblastic differentiation from the periodontal ligament by promoting the formation of substrate and increasing alkaline phosphatase (ALP) activity, and also enables the regeneration of periodontal tissue destroyed by periodontal disease and repair of root resorption[13]. Mostafa et al. (2009) demonstrated that ALP and OPN expressions were also induced in human gingival fibroblasts treated with LIPUS helping in osteogenic potential differentiation[14].

Lipus and Cementum Regeneration

Cementum is a thin mineralized tissue covering the tooth root surface and assists in anchoring teeth to surrounding alveolar bone, maintaining the structural stability and physiological function of the dentition[15]. A certain degree of root resorption occurs in most treatment cases, ranging from just a slight apical resorption to a complete tooth root loss[16]. The cementum layer covering the root surface plays a crucial role in preventing resorption during tooth movement. Cementoblasts share many characteristics with osteoblasts, including similar molecular properties and the ability to promote mineralization. Studies have shown that cementum metabolism is also controlled by mechanical stimulus similar to bone. It has been reported that mechanical loading enhances the expression of phenotypic makers such as OCN and BSP in cementoblast however, the expression was just moderately stimulated compared to osteoblasts[17]. El-Bially et al. (2004) have published studies showing that LIPUS prevented root resorption during experimental tooth movement in humans[18]. Studies also have showed that LIPUS up-regulated the expression of several genes related to mineral metabolism in mouse cementoblasts[19]. LIPUS simulation also significantly up-regulates COX-2 mRNA expression and enhanced PGE2 production inducing cementoblastic differentiation and matrix mineralization through EP2/EP4 prostaglandin receptors pathway[20]. Furthermore, assessment was done to see the inhibitory effect of LIPUS application on root resorption using an experimental model of tooth replantation involving luxation and immediate replacement of maxillary first molars in rats[21]. The results evidenced that the area of root resorption lacunae was statistically decreased in LIPUS treated sample. In addition, some in vitro studies have shown that LIPUS may contribute to the reduction of the trauma-induced inflammatory reaction through impairment of the TNF-α signaling pathway, suggesting its potential as a therapeutic tool to optimize the regenerative potential of periodontal tissues on replanted teeth[22].

Lipus and Gingival Regeneration

LIPUS application in implant dentistry have reported accelerated soft-tissue healing as well as osseointegration. In addition, it was suggested that the ultrasound treated wounds were at a more advanced stage in the repair process[12]. The cellular mechanisms underlying LIPUS induced tissue regeneration was done and studies by Ikai et al. (2008) showed that a daily LIPUS treatment protocol of 20 minutes for a period of 4 weeks has a beneficial effect on gingival epithelium cells, accelerating periodontal wound healing after flap surgery[8]. In other study using gingival epithelial cells, Shiraishi et al (2011) reported that LIPUS accelerates soft-tissue healing by increasing the expression of connective tissue growth factor (CCN2/CTGF), an important gene for wound healing and angiogenesis in periodontal tissues[9].

Lipus and Implant Osseointegration

The use of endosseous dental implants for replacing missing teeth increased considerable over the last few years and may be considered as the current most popular treatment option for edentulous patients. LIPUS helps in enhancement of endogenous bone healing around biomaterials through different forms of biophysical stimulations[23]. A study done by Tanzer et al. (1996) showed that LIPUS enhanced the rate and extent of bone growth into fully porous coated implants inserted into dog femora[24]. Studies done by Hsu et al. (2011) showed that ultrasound stimulation helps in good blood flow and mature type I collagen fibers around titanium implants, and accelerated bone formation. In addition, pulsed ultrasound effectively promotes cell migration and new bone regeneration in tissue culture of MG63 osteoblast like cells[25]. Studies done by Ustun et al. (2008) showed that LIPUS stimulation increases the area, bone volume and bone implant contact ratio values in tibial bone suggesting that LIPUS application may accelerate and promote bone healing around dental implants leading to a higher quality and faster osseointegration[26].

Lipus and Gene Delivery

Periodontal disease or inflammatory root resorption is relevant pathologic condition that can lead to tooth loss. In this regard, several tissue-engineering techniques have been proposed to restore periodontal integrity[27]. Administration of growth factors has proved to exert positive effect with some clinical limitations such as proteolytic degradation, rapid diffusion, and solubility of the delivery vehicle[28]. In order to optimize the results, gene transfer methods were introduced with limitation of progress in clinical periodontal gene therapy by the immunogenicity and cytotoxicity of viral vectors and low transfection efficiency with regard to non-viral vectors[29]. Therapeutic ultrasound associated to echo contrast agents such as nano/microbubbles can optimize gene transfection in vitro and in vivo[30]. Recently, it has been shown that therapeutic ultrasound also provides an effective gene delivery system for bone and periodontal regeneration[31]. Studies done by Watanuki et al. (2009) showed that LIPUS stimulation in mouse calf muscles injected with BMP-4 plasmids and transcutaneous electroporated showed increased ectopic calcium and total collagen content and bone area[32].

Discussion

Among the causes of teeth loss, inflammatory root resorption has received a great concern due to its unpredictability, difficult control and lack of biological understanding. The resorption of hard tissue in primary teeth is a normal physiologic phenomenon. On the other hand, the hard tissues of permanent teeth are not resorbed under healthy conditions and the resorption is thus considered a pathologic process[33]. Different causes have been attributed to the root resorption process including pressure, inflammation, neoplastic process and systemic conditions[34]. The major problem encountered after tooth replantation and orthodontic tooth movement is the resorption of root. Approaches aiming to inhibit root resorption and restore periodontal integrity during the dental practice are still the subject of debate and investigation. Some therapeutic approaches have been proposed to inhibit root resorption after tooth replantation and can induce periodontal regeneration[35]. In this context, non-invasive modality such as LIPUS therapy has been given increased attention and risen as promising therapeutic tool for the regeneration of periodontium. The effectiveness of LIPUS for bone regeneration is already universally accepted and some recent papers have provided evidence that it can exert beneficial effects in other kinds of tissues, including teeth. In addition, LIPUS presents low toxicity, low immunogenicity, non-invasiveness, highly targeted selectivity, and repeated applicability. However, the diversity of techniques, application protocols and ultrasound specifications found in the literature may cause confusion for the clinician. Bains et al. (2008) have pointed out that ultrasound application in both diagnosis and periodontal therapy seems to present promising results; however, long-term evidence-based studies are required to use ultrasound in routine periodontal practice[36].

Conclusion

Despite LIPUS therapy has been widely used in the fields of orthopedic surgery and rehabilitation, its availability by dental professionals is still incipient. The effects of LIPUS in bony tissue seem to be well understood, but the literature has still lacked for available information about its effects on periodontal tissues. The present review brings out current evidence that LIPUS has a positive effect on tooth and periodontal cells metabolism, suggesting that LIPUS can be a promising therapeutic tool for the regeneration of tooth support tissues.

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