Adjunctive techniques for enhancing mandibular growth in Class II malocclusion

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Abstract
Class II malocclusions are generally characterized by mandible retrusion. For this reason, forward bite jumping appliances, also known as functional appliances were originally designed to enhance mandibular forward projection. However, there is still insufficient evidence to support the effectiveness, predictability and stability of functional appliances in modifying mandibular growth. This article was aimed at presenting evidences and hypotheses that mandibular growth may be enhanced through the use of adjunctive methods in conjunction with functional appliances. In formulating our hypothesis, we considered relevant data, mostly derived from animal studies, concerning alternative methods, such as low-intensity ultrasound and light-emitting diode, as well as their related cellular and molecular mechanisms. According to the evidences covered in this article, we suggest that both methods are potentially effective, and theoretically able to act in synergistic way to enhance functional appliances treatment on mandibular and condylar additional growth. The rationale for the use of these methods as adjunctive therapies for mandibular underdevelopment is attributed to their abilities on stimulating angiogenesis, cell differentiation, proliferation, and hypertrophy, as well as enhancing matrix production and endochondral bone formation, especially on the condyle of growing animals. This article also proposed a study design which would be able to either prove or refute our hypothesis. If ratified, it would represent a significant scientific accomplishment which provides support for further investigations to be carried out on well-designed clinical trials.

Introduction
Class II malocclusion was originally described as having all the lower teeth occluding posterior to normal [1], and it is considered one of the most common orthodontic problems [2–4]. This type of malocclusion, especially when upper incisors are protruded, is likely to produce several consequences. Among these complications, for instance, there are significant esthetic [5] and social [6] impact on children, as well as on their dental health [7]; or it might even predispose them to upper front teeth trauma [8,9], or to upper airway complications, in severe cases [10].

Most of the Class II malocclusions are generally correlated to mandibular retrusion, rather than maxillary protrusion [11,12]. Besides, Class II dentoskeletal disharmony does not tend to self-correct with growth; rather it worsens [13]. Hence, in order to attempt stimulation of mandibular supplementary growth, a great variety of functional appliances were introduced [14–19]. Even though with diverse designs, such functional appliances are essentially based on the same principle on which the forward protruding position of the mandible would enhance condylar and mandibular bone growth, and, as a consequence, enable Class II malocclusion correction. However, according to several systematic reviews, there is still limited evidence to support a clinically significant change in mandibular length induced by functional appliances [20–22]; or to prove its predictability [23] and stability over time [24].

Therefore, many experimental studies on animal models have been carried out in order to investigate alternative methods of stimulating mandibular growth, such as pulsed electromagnetic field [25,26], low-intensity pulsed ultrasound (LIPUS) [27–33], light emitting diode (LED) [34], low-level laser (LLL) [34], growth hormone [32], and gene therapy [33,35,36].

Among these, pulsed electromagnetic field therapy is excessively time-consuming, growth hormone might still have its toxicity comprehensively investigated, and gene therapy still has some important questions to be answered regarding its safety, optimization, and mechanisms before human researches begin to be even considered [37]. Further, on recent study comparing the effects...
between LED and LLL methods on mandibular growth of rats, LLL-treated animals demonstrated more mandibular growth than LLL groups [34].

Alternatively, LIPUS has been systematically investigated over the last years, with promising results concerning the enhancement of mandibular growth [27–33]. In addition, LIPUS, as well as LED, present little potential side effects, and relatively lower cost, which makes it suitable for implementation on clinical settings.

Hence, this theoretical article is intended to present key evidences capable of supporting our hypothesis that mandibular growth can be enhanced through simultaneous use of adjunctive methods, such as LIPUS and LED, in conjunction with functional appliances. In order to formulate our hypothesis and to suggest means to test it, we will objectively consider data concerning related treatment protocols, their effectiveness, and respective cellular and molecular mechanisms. Therefore, during the appraisal of the related literature, special attention will be paid to animal studies in which the sole or synergetic use of mandibular-protruding appliances and alternative methods were investigated.

Background

Therapeutic effects of bite-jumping appliances, LIPUS, and LED

Bite-jumping appliances are devices that are specially designed to continuously position the mandible forward further than regular bite in an attempt to improve patients’ profiles. The use of such appliances has consistently demonstrated to induce replication and differentiation of cells, as well as new bone formation in the mandibular condyle and glenoid fossa [38–53]. There is a large body of evidence showing that mechanical manipulation of the condyle induces metabolic alterations, and changes in the expression of growth factors and other signaling molecules [54].

The supposed mechanisms through which forward mandibular positioning enhances mandibular growth are abundant [39,40,42–45,47,49,52,53]. It has been demonstrated, for instance, that anterior mandibular positioning increases VEGF (vascular endothelial growth factor) expression which is an important factor in angiogenesis, and subsequent bone formation in the condyle [39,44], and glenoid fossa [40,45] of growing rats. The close correlation between VEGF production and bone formation is inferred to be a result of the recruitment of required osteoprogenitor cells by new blood supply [55].

Mandibular protrusion also led to an up-regulation of the expression of the transcription factor Sox9 (sex determining-region Y-box 9) [42,52] and collagen, type II gene [42,43,47,49,50,52], involved in the chondrocytes differentiation, and in the collagenous matrix formation, respectively.

Another important mechanism was reported through which mandibular advancement elicits Runx2 (runt-related transcription factor 2) gene expression in condylar cartilage, which is responsible for mediating chondrocyte terminal maturation, and endochondral ossification, after osteoblast differentiation [47]. Forward mandibular positioning through bite-jumping appliances has also demonstrated to increase the expression of growth members, such as Ihh (Indian hedgehog: stimulates cellular proliferation and differentiation) [50]. In response to bite-jumping appliances, the increased expressions of BMP2 and BMP4 (bone morphogenetic proteins 2 and 4), which accelerates and enhances the differentiation of mesenchymal cells into bone-forming cells, has also been significantly observed [53].

Hence, the induced forward positioning of the mandible has demonstrated to evoke important mechanisms related to the stimulation of the differentiation and replication of chondrocytes, formation of blood vessels providing new mesenchymal cells, which are also stimulated to differentiate into bone-forming cells. In addition, anterior posture of the mandible might also favor the production of collagenous matrix. The recognition of these cellular/molecular events that take place after mandibular induced forward positioning indicates the “field” where current efforts should operate in order to “boost” mandibular growth. Thus, in the next paragraphs, important mechanisms triggered by LIPUS and LED will be presented and discussed.

As previously stated, the use of LIPUS has been documented to present promising results in the growth of the mandible [27–33]. In a study of rabbits [27], LIPUS significantly stimulated the differential mandibular growth. Histologically, treated sites presented hyperplasia of the fibrocartilaginous layer, hypertrophy of the chondroblasts of the chondrogenic layers, marked endochondral ossification, excessive bony trabeculae, and dilated blood capillaries, which was posteriorly observed by other authors as well [31]. Oyonarte et al. [29] used experimental rats in which LIPUS stimulation also increased the cartilaginous layer thickness, but apparently to a lesser degree. In addition, chondrocytes were more hypertrophic, and there was an increase in the matrix secretion in the maturation zone. At the subchondral bone level, the stimulated groups demonstrated elongated, longitudinally oriented trabeculae, and significantly increased medullar area and trabecular perimeter.

In addition to the evident enhanced endochondral ossification, LIPUS seems to play an important role in some of the mechanisms also elicited by mandibular forward positioning, such as neo-vascularization and matrix production. An in-vitro study, has confirmed LIPUS ability to stimulate chondrocyte proliferation, as well as to increase the collagenous matrix production by chondrocytes in human cells [56].

In a preliminary report [28], this ability was confirmed, when baboons treated with LIPUS had better morphological and histological results than those treated only with bite-jumping appliances. While non-LIPUS group showed more thickening of condylar cartilage and less bone formation, it was observed more bone formation and highly matured and organized bony trabeculae with few marrow spaces in the group that used both appliance and LIPUS.

Thus, there appears to be plenty of evidences which support LIPUS as a potentially adjunctive therapy to enhance mandibular growth. Such effect was finally observed on a clinical pilot-study [57] in which five children with hemifacial microsomia were treated with a modified functional appliance associated with LIPUS application on the underdeveloped side. After one year of treatment, there were significant clinical and radiographic improvements.

Even though positive results were presented in this initial trial [57], they cannot be overestimated, since only a limited number of children was evaluated. Besides, LIPUS use to enhance mandibular growth in human still requires adaptations. In order to be effective, such therapeutic approach required one year of compliance. Such fact indicates a significant challenge for the clinical application of this technique which, if implemented, would demand extremely high cooperation from the patients.

On the other hand, the effect of LED on condylar growth still has not received due scientific attention. According to our knowledge, only one study, already referenced [34], has been performed so far. The results of this research indicated that LED has proved to effectively enhance mandibular growth in rats; and histologic data indi-
cated that it significantly increased all condylar surface layers. Another study has indicated that LED application might increase new bone formation area, number of osteoblasts/osteoclasts, and vessels on rats subjected to orthopedic maxillary expansion [58]. Further researches have also demonstrated LED ability on promoting angiogenesis [59–60], and as an important adjunctive factor involved in the improvement of dentalocclusal osteogenesis [61]. It thus seems likely that the beneficial effects of LED are the same as reported to LLL, which include increased osteoblastic proliferation, collagen deposition, and bone neoformation [62]. Even though the LED effects and mechanisms on bone formation are not fully understood, and its molecular effects on mandibular condylar development are unclear, it still might be considered an alternative therapeutic approach to be comprehensively tested, since positive cellular events are observed after its application.

Since the associated use of functional appliances and LIPUS may be clinically unsuitable [37,57], the addition of LED, as an adjunctive therapy in addition to LIPUS might be beneficial to improve the effectiveness of functional appliance therapy in enhancing mandibular forward growth.

In the following paragraphs, we will roughly propose a study design in animals with the objective of testing our hypotheses. In our opinion, for the future, larger human clinical trials should be postponed until well-designed animal studies obtain clearer results on the efficacy/effectiveness, stability, mechanisms, and eventual synergistic effects involved with the treatment modalities we addressed here (functional appliances, LIPUS, and LED).

Evaluation of the hypothesis

Proposal of an experiment

The authors would like to suggest an animal study in young rats, which will be divided in groups as follows: negative control (no therapy); positive control (functional appliance); treatment group 1 (functional appliance + LIPUS); treatment group 2 (functional appliance + LED); and treatment group 3 (functional appliance + LIPUS + LED). The functional appliances will be kept in position for 30 days and the LIPUS or LED applications will be performed during 20 minutes per day on the right condyle. In treatment group 3, LIPUS and LED will be applied in alternate days to the right condyle during the same treatment period performed in the other experimental groups. The positive control, as well as all of the treatment groups will have half of their animals sacrificed on day 30 (when treatment will be concluded), and the remaining will be euthanized on day 60 (30 days after treatment conclusion).

After dissection, hemimandibles will be subjected to morphologic and histomorphometric analysis; and part of the samples will be used to measure the levels of expression of Sox9, Runx2, type II collagen and VEGF genes.

This study design aims at evaluating the synergetic effect of adjunct therapies in the mandibular growth enhancement. A secondary intent of this future study would be to investigate the long-term effect of the different treatment protocols, which is also under-appreciated by scientific literature. Another important objective of this proposed study would be to comprehensively understand the mechanisms involved in the eventual additive effects of therapies. The eventual acceptance or rejection of our hypothesis would represent an important step toward the investigation of such potential therapeutic approaches in well-designed clinical trials in patients.

Conflict of interest statement

All authors disclose that there was no conflict of interests that could inappropriately influence (bias) our work.

References

Corrigendum


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The authors regret that the affiliation of Dr. Alhadlaq A was missed to be mentioned in the previous version. The authors would like to apologise for any inconvenience caused.