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CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

# The Biology of TMJ Growth Modification: A Review

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## ABSTRACT

Several studies have indicated a positive response of the temporomandibular joint (TMJ) to mandibular advancement, while others have reported that TMJ adaptive responses are non-existent and negligible. Controversy continues to grow over the precise nature of skeletal changes that occur during mandibular growth modification, due to an apparent lack of tissue markers required to substantiate the precise mechanism by which this is occurring. However, evidence suggests that orthopedic forces clinically modify the growth of the mandible. To further our knowledge about the effect of orthopedic treatment on the TMJ, it is necessary that we understand the biologic basis behind the various tissues involved in the TMJ's normal growth and maturation. The importance of this knowledge is to consider the potential association between TMJ remodeling and mandibular repositioning under orthopedic loading. Considerable histologic and biochemical research has been performed to provide basic information about the nature of skeletal growth modification in response to mandibular advancement. In this review, the relevant histochemical evidence and various theories regarding TMJ growth modification are discussed. Furthermore, different regulatory growth factors and tissue markers, which are used for cellular and molecular evaluation of the TMJ during its adaptive response to biomechanical forces, are underlined.

**KEY WORDS:** temporomandibular joint, mandibular condyle, temporal bone, orthopedics, bone remodeling, biological adaptation.

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## INTRODUCTION

Several studies have explored mandibular advancement *via* functional appliance therapy for orthopedic management of skeletal Class II malocclusions (Ruf and Pancherz, 1999) and have shown that a fundamental factor in regulating cellular activities during tissue morphogenesis is mechanical stress (Ruoslahti, 1997). Many studies with rats and monkeys have also shown that new bone formation in the condyle and the glenoid fossa occurs in response to mandibular advancement (Rabie *et al*., 2001).

Histological and biochemical research in this field mainly aims to provide basic information about the nature of the skeletal growth modification in response to orthopedic forces. The current paper is a review of biologic studies on temporomandibular joint (TMJ) growth modification.

## TMJ GROWTH MODIFICATION

The translation of the condyle toward the articular eminence with a posteroinferior rotation of the entire mandible causes space reduction in superior joint spaces in the condyle, while posterior joint space increases. This function applies tensile forces to the disto-superior part of the condyle and the areas of the glenoid fossa facing these areas of the condyle. On the other site, compressive forces are applied on the antero-superior parts of the condyle and their transactional sites on the glenoid fossa (Chu *et al*., 2008).

Growth modification of the lower jaw during mandibular forward positioning is a successful example of bone remodeling in response to a change in biophysical environment (Ruf and Pancherz, 1999). Vertical opening and horizontal forward positioning, as components of the bite-jumping mode, are both important elements in this biophysical change, which induce adaptive remodeling in the mandibular condyle and glenoid fossa. This remodeling occurs by expression of cells' endogenous regulatory factors in the mandibular condyle through the chondrogenesis process, followed by endochondral ossification (Rabie *et al*., 2004b), and in the glenoid fossa by intramembranous ossification (Shen *et al*., 2006a).

Animal studies have proposed that TMJ remodeling is regulated by a variety of biomolecules, such as IGF I and II (Hajjar *et al.*, 2003), Sox9 (Rabie *et al.*, 2003a), PTHrP (Rabie *et al.*, 2003c), Cbfa1 (Rabie *et al.*, 2004a), type II collagen (Rabie *et al.*, 2004b), type X collagen (Shen *et al.*, 2006b), L-Sox5 (Chu *et al.*, 2008), FGF8 (Owtad *et al.*, 2010), VEGF (Rabie *et al.*, 2007; Dias *et al.*, 2012), and BMP (Barnouti *et al*., 2011). In addition, PCNA is evaluated as a marker protein for DNA synthesis and repair, to evaluate cell proliferation (Barnouti *et al.*, 2011; Miron and Zhang, 2012).

### Different Methods of Evaluation

It is difficult to draw an accurate growth curve for the human condyle by gross measurements alone, such as those obtained by cephalometric analysis.

**Table.** Different Methods for Evaluating TMJ Growth Modification

**Human and animal studies:**
- Facial clinical measurement (Ghoddousi *et al.*, 2007)
- Radiography and cephalometry (Godt *et al.*, 2008)
- Electromyography (Kawai *et al.*, 2008)
- Cone-beam computed tomography (CBCT) (Stratemann *et al.*, 2010)
- Magnetic resonance imaging (MRI) (Toll *et al.*, 2010)

**Animal studies only:**
- Surgical approaches (Whetten and Johnston, 1985)
- Histologic evaluation (Voudouris *et al.*, 2003)
- Micro-radiography (Zheng *et al.*, 2006)
- Biomechanical evaluations (Shen *et al.*, 2006b)
- Micro-computed tomography (Sugisaki *et al.*, 2009)

In this situation, it is of particular significance to investigate the temporal pattern of condylar growth through biochemical studies in an animal experimental model, which could be extrapolated to humans (Shen *et al*., 2005b). Most TMJ investigations have been conducted in various experimental animals. However, in humans, very few post-natal investigations of TMJ development are available (Pullinger *et al.*, 1990). Although many animal studies have demonstrated skeletal mandibular changes in response to mandibular forward posturing (McNamara *et al*., 2003; Shen *et al.*, 2006a), the observations in human studies are more equivocal and controversial. Animal experiments, contrary to human experiments, are performed for more than just linear measurement of condylar growth and provide an insight into the mandibular condyle. Condylar growth can be monitored by histological observation, which has been conducted to identify cellular response during chondrogenesis of the mandibular condyle (Cozza *et al*., 2006). Different methods of TMJ growth evaluations are summarized in the Table.

## TMJ Adaptive Characteristics

The biological response to applied mechanical forces is the physiologic mechanism for skeletal adaptation to environmental changes (Singh and Detamore, 2008). The evidence confirms that the mandibular condyle and the glenoid fossa have the capability of functional adaptation in response to environmental changes. The patterns of this adaptive response are different in the mandibular condyle and the glenoid fossa, but are in harmony with each other (Voudouris *et al*., 2003) (Fig. 1). It has also been reported that, during intermittent posterior displacement of the mandible, the profile and microarchitecture of the condylar cancellous bone can change (Kuroda *et al.*, 2011). It has also been shown that synovial lubrication of the TMJ is significantly influenced by a functional lateral shift of the mandible during the growth period (Kure-Hattori *et al.*, 2012).

The role of the mandibular condyle in the process of the TMJ's growth and development and its adaptive response to mandibular advancement is remarkably higher, particularly during the period of growth spurt. The rate of cellular proliferative and hypertrophic activities and morphological changes in the glenoid fossa is much lower than in the mandibular condyle (Barnouti *et al*., 2011; Owtad *et al*., 2011). If the glenoid fossa does not remarkably remodel or relocate, then the soft-tissue attachments pull the condyle back to its initial relationship within the glenoid fossa, which could be a reason for relapse following functional orthopedic treatment. However, some studies confirm the significant adaptation and relocation of the glenoid fossa in response to mandibular advancement (McNamara *et al*., 2003). A combination of long-term histochemical, serial cephalometric, and electromyographic evaluation is needed for better understanding of the adaptation and relocation of the condyles and the glenoid fossa.

In some histologic studies, acceleration in differentiation of osteoprogenitor cells to pre-chondroblasts was observed. This was followed by the observation of an increase in transformation of pre-chondroblasts into functional chondroblasts, and hypertrophy of the chondroblastic layer with accelerated endochondral bone growth (Shen *et al*., 2006a). A histologic image of the head of the rat's condyle is shown in Fig. 2.

The TMJ disc is an interior circumferential extension of the capsule, and a biconcave fibrocartilaginous tissue. The disc is mainly composed of collagen, glycosaminoglycan, and proteoglycans, and its histological, biochemical, and biomechanical properties allow for smooth jaw movements during eating, speaking, and other normal mandibular functions. The disc moves with the condyle during condylar translational movements, since it is tightly connected to the lower half of the capsule. The disc follows the condyle, moving in a short, passive manner to best fit its surrounding structures. It has been reported that functional mandibular advancement does not have adverse effects on the disc-condyle relationship. In addition, mandibular advancement in cases of partial or total anterior disc displacement can significantly improve the disc position (Kinzinger *et al.*, 2006; Kiga, 2012).

## Hypotheses of Growth Modification in the TMJ

It is necessary to discern the nature of the TMJ tissues and their relationships during normal growth, maturation, and orthodontic treatments, for an accurate understanding and consideration of the potential association between the tissue responses in the TMJ and orthodontic treatment. During the post-natal period, the TMJ becomes a secondary growth site. It is important to consider the processes involved in controlling the growth of condylar cartilage by the regulatory mechanisms of occlusion, including interactions between and among the central nervous system, masticatory muscles, and tissue receptors, in relation to condylar growth and development. Considering all the biological and biomechanical aspects of TMJ growth modification, it is almost impossible to formulate this phenomenon. However, there are few theories and hypotheses available that are useful in explaining the nature of TMJ growth modification. Among these, the growth relativity hypothesis, the functional matrix theory, and the ratchet hypothesis were mainly cited in the literature (Whetten and Johnston, 1985; Moss, 1997; Voudouris and Kuftinec, 2000).

The growth relativity hypothesis presents the mechanism of condyle-fossa growth modification with mandibular advancement. It describes viscoelastic forces applied to the TMJ through

several different attachments during mandibular advancement. It also addresses the transduction of forces radiating beneath the fibrocartilage of both the condyle and the glenoid fossa. In this hypothesis, balance interactions among 6 major factors are discussed: skeletal, dental, neuromuscular, non-muscular viscoelastic tissues including synovial fluids, maturational age, and biodynamic intrinsic and extrinsic factors. These all contribute to adaptation in the TMJ complex by condyle-fossa growth enhancement, growth redirection, and, ultimately, TMJ growth remodeling (Voudouris and Kuftinec, 2000; Voudouris *et al*., 2003) (Fig. 1).

The other hypothesis is the functional matrix theory, which describes the possible mechanism of bone remodeling in the TMJ complex in response to propulsive forces transferred by attached soft tissues (Moss, 1997). In addition, the ratchet hypothesis suggests that the condyle is in effect a functional rectifier or ratchet, the growth of which is the ultimate determinant of downward and forward mandibular translation. The condyle's ability to resist episodic compression and then grow when unloaded would serve to preserve the downward and forward portion of the mandible's envelope of motion (Whetten and Johnston, 1985). However, the nature of TMJ growth modification is still not fully understood and not clearly explained.

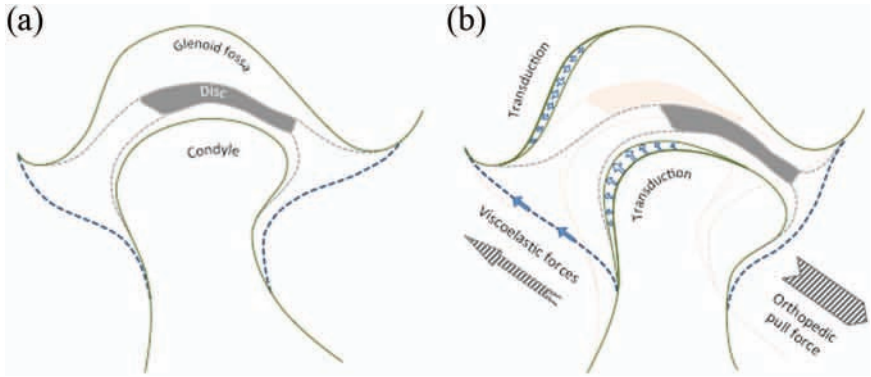


**Figure 1.** Schematic views of TMJ structures. **(a)** The TMJ structures before mandibular advancement; the dotted lines represent soft tissues attached to the neck of the condyle and the temporal bone. **(b)** Force transduction and viscoelastic forces in TMJ during mandibular forward and downward displacement are illustrated; the underneath shadow shows the TMJ before advancement.

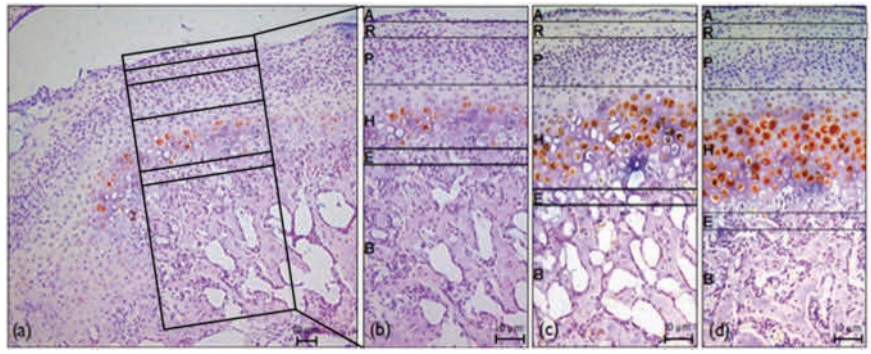


**Figure 2.** Histology of the head of the condyle of Sprague-Dawley rats. (**a-d**) Hematoxylin and eosin staining in addition to immunohistochemical staining for FGF8. (a) The section from a 24-day-old rat's condyle. (b) Higher magnification view of the box in (a), showing the zone-like cellular layers of the condyle, from the superficial layer downward, consecutively: (A) the articular zone, (R) the resting zone, (P) the proliferative zone, (H) the hypertrophic zone, (E) the erosive zone, and (B) bone. (c) A histologic section of a 48-day-old rat's condyle; control group, without mandibular advancement. (d) A histologic section of a 48-day-old rat's condyle; experimental group, after 14 days' mandibular advancement with a fixed functional appliance. The higher level of cellular activity is evident in the hypertrophic layer of the experimental group (Owtad *et al*., 2011).

## MANDIBULAR CONDYLE ADAPTIVE REMODELING

The mandibular condyle is an active growth site for the mandible, and it has been studied as the primary focus of functional orthopedic therapy for mandibular disorders (Gong *et al*., 2011). Forward mandibular positioning produces biomechanical forces, which induce cellular and molecular changes in the mandibular condyles. Even though several studies have reported a positive response of the condyle to mandibular advancement, controversial issues remain in this regard, and the triggering mechanisms are not completely understood (Rabie *et al*., 2004b; Shen *et al*., 2006a).

It has been demonstrated in adult rats that, by 30-day continuous mandibular advancement, adaptive morphological changes could be achieved in the mandibular condyle (Xiong *et al*., 2004). It should be considered that the changes in the mandibular condyle in response to mandibular advancement are highly related to the duration of functional therapy, direction, amount, and types of the forces (Shen *et al*., 2005a; Shen and Darendeliler, 2006). However, it is still undetermined if growth modification increases the total amount of mandibular growth, or only increases the rate at which the genetically predetermined amount of mandibular growth is achieved.

### Histologic Features

Proliferating chondrocytes in the condylar cartilage originate from the fibrous tissue layer covering the condyle. The fibroblasts and mesenchymal cells within the articular layer are found to be oriented in the direction of mandibular advancement. However, in mandibular natural posture, the cells in this layer are packed parallel to the articular surface, showing no signs of strain. Functional appliances result in the tension of the posterior fibers of the disc and might also increase cellular density due to transverse compression, followed by an increase in

cell-cell interaction. The maturation of the chondrogenic cells is triggered by mandibular condylar advancement, followed by an increase in endochondral ossification in the condyle (Shen *et al.*, 2006a; Miron and Zhang, 2012). This indicates that the mandibular condyle will adapt and remodel in response to the biophysical environment of the TMJ, regardless of the presence or absence of growth potential.

The physical stretching and re-orientation of mesenchymal cells in the articular layer might trigger the enhanced differentiation and maturation of chondrocytes. A source of mesenchymal cells could be the blood supply in the posterior connective tissue of the condyle. The blood vessels supplying the condyle are mainly localized in this particular area. Mandibular protrusion causes the posterior fibers of the disc to stretch, subsequently leading to an increased emergence of new blood vessels, or neovascularization, in this area (Rabie *et al*., 2003a; Shen *et al*., 2006a). More mesenchymal cells are brought to the area by the increased neovascularization and induce an enhanced differentiation and maturation of chondrocytes. Subsequently, increased bone formation replaces the terminally hypertrophic cartilage, followed by an increased synthesis of type X collagen and increased bone formation (Shen *et al*., 2006b).

It has been reported that longitudinal bone growth during endochondral bone formation depends on chondrogenesis and the increase in the cartilage matrix, which is closely correlated to the bone formation in response to mandibular advancement (Rabie *et al.*, 2003a; Shen *et al.*, 2006a). It also could be inferred, from a comparison of the growth site between the longitudinal bone and mandible, that the chondrogenesis and endochondral ossification in the condylar cartilage are similar to those of the epiphyseal cartilage in the long bone. However, the growth plate and the ordered columns of cartilaginous cells, as seen in the long bones, do not exist in the condylar cartilage; because of this structural and histological characteristic, the mandibular condyle has a multidirectional growth capacity, while growth in long bones is unidirectional. Furthermore, the biological characteristics of articular chondrocytes are evidently different from those of epiphyseal chondrocytes of the long-bone growth plate. The epiphyseal cartilage undergoes profound phenotypic changes after pubertal growth, while articular chondrocytes are present throughout post-natal life and remain unchanged in their biological features (Shen and Darendeliler, 2005). In addition, there are differences in the mode of proliferation and differentiation, cell alignment, invading capillary pattern, and extracellular matrix composition in these 2 structures (Wang and Detamore, 2007).

In the mandibular condyle, the hypertrophic activities are significantly increased by mandibular advancement, while proliferative activity is not. This indicates that thickening of the posterior part of the condyle as an adaptive response to the condyle's forward positioning is due to cellular morphologic changes (Owtad *et al*., 2011) (Fig. 2).

As has been shown in several studies, the level of cellular activity increases in the condyle in response to functional advancement of the mandible. However, more investigations about the interaction between different cellular layers are required. There is also a need for standardization in cellular measurement methods obtained by different laboratory techniques and the use of different biomarkers in cellular evaluations of the condyle. Considering that it is almost impossible to evaluate a healthy human's condyle at the histologic level, it is very important to raise the standards of the animal studies in this field to draw conclusions that are more precise.

### Biochemical Changes

Mandibular advancement accelerates and enhances the expression of Sox 9 and type II collagen, leading to the acceleration and enhancement of chondrocyte differentiation and cartilage matrix formation in the mandibular condyle. However, for most of the growth period, this enhancement of growth did not result in a subsequent change in the pattern of normal growth. Therefore, functional appliance therapy could induce true enhancement of condylar growth (Rabie *et al*., 2003a).

Condylar adaptation to forward positioning has invariably been reported by a series of experimentations in rats, indicated by increased synthesis of growth regulatory factors such as Indian hedgehog (Ihh) (Tang *et al.*, 2004; Kinumatsu *et al.*, 2011) and parathyroid-hormone-related peptide (PTHrP) (Rabie *et al*., 2003c). A considerable increase in endochondral ossification of the condyles, in response to mandibular forward positioning, has been reported from detection of the expression of type X collagen in rat samples. During chondrocytes' maturation, the calcification of the degraded cartilage, a preliminary stage of endochondral ossification, is facilitated by type X collagen (Shen *et al.*, 2006a). In addition, in a study of mutant mice, it was shown that coordination of chondrocyte maturation, intramembranous bone formation, and chondrogenic condylar growth needs ciliary transport protein Kif3a in cartilage (Kinumatsu *et al*., 2011). Overall, tracking biomolecules during mandibular advancement shows that the biology of the condyle is significantly modified in response to environmental changes.

## GLENOID FOSSA ADAPTIVE REMODELING

The mandibular glenoid fossa is rarely studied as a primary objective in investigations of the effects of functional appliances (Rabie *et al.*, 2003b; Shum *et al*., 2004). Forward mandibular positioning and continuous bite jumping significantly increase bone formation in the glenoid fossa (Rabie *et al*., 2001). Glenoid fossa formation is induced by a wide range of repetitive motion and pressure against the temporal bone, with cortical bone apposition (Voudouris *et al.*, 2003).

Changes in the glenoid fossa are demonstrated in some human studies after treatment by functional orthodontic appliances such as the Herbst appliance (Serbesis-Tsarudis and Pancherz, 2008). Magnetic resonance imaging (MRI) for patients who received Herbst appliance therapy has also shown that a combination of condylar growth and remodeling of the glenoid fossa occurs during the TMJ's adaptive response to mandibular advancement in humans (Ruf and Pancherz, 1999). Its adaptive capacity has also been demonstrated in human studies of condylar fractures (Cascone *et al*., 2008).

MRI assessment in clinical studies with the use of the Herbst appliance shows that the glenoid fossa remodeling and temporal adaptive responses occur later than the condylar adaptive

response (Pancherz *et al*., 1999). The difference between the intramembranous ossification of the temporal bone and the endochondral ossification of the condyle could be the reason for this non-parallel adaptive response. However, it should be considered that intramembranous ossification does not result in a marked change in MRI signal intensity, because it is not associated with a large increase in water content of the tissue. Therefore, the mentioned delayed ossification in the glenoid fossa and new bone apposition along the post-glenoid spine might be due to its later visualization in the MRI, at the time when the newly formed bone has consolidated (Pancherz *et al.*, 1999). Bone formation in the posterior, middle, and anterior parts of the glenoid fossa substantially increases during mandibular protrusion, with the highest level of bone formation in the posterior regions (Rabie *et al*., 2001).

### Histologic Features

In the glenoid fossa, mesenchymal cells directly differentiate into osteoblasts, known as osteoprogenitor cells. Fibroblast-like cells proliferate to pre-osteoblasts or early osteoblasts, ultimately to form bone, which indicates an intramembranous ossification in the glenoid fossa. The cellular layers are narrower in the glenoid fossa and barely distinguishable in comparison with those in the mandibular condyle (Rabie *et al*., 2001).

The mesenchymal cells beneath the fibrous layer are arranged in line with the articular surface during mandibular advancement. However, the axes of the mesenchymal cells and other cells in the extracellular matrix are oriented in the direction of the pull and became increasingly aligned with the presumed direction of the pull (Rabie *et al*., 2001). Mechanical strains can bring such "strain alignment", which may influence migration or condensation of the mesenchymal cells. When mandibular advancement results in the stretch of the sub-periosteal extracellular matrix, its matrix density will increase because of the transverse compression caused by the Poisson effect. This may attract more cells from the adjacent extracellular matrix as a source of mesenchymal cells (Sato *et al*., 2005). ["When a tensile stress is applied to a material, the material elongates in the direction of the applied stress, and contracts perpendicular to the direction of the applied-stress. This relationship, called the Poisson effect, is a natural response to applied stress that occurs with all materials, but is particularly apparent with ductile materials" (Gercek, 2007).]

The perivascular connective tissue that surrounds the new blood vessels could be known as the other source of mesenchymal cells. These blood vessels are recruited in response to the tensile effect (Rabie *et al*., 2003d). In the cancellous bone layer, at the beginning of mandibular protrusion, the osteoblasts and osteocytes are randomly packed (Rabie *et al*., 2001).

The biomechanical mandibular forward positioning changes the extracellular matrix and the undifferentiated mesenchymal cells in the sub-periosteal connective tissue in the glenoid fossa (Rabie *et al*., 2001). Bone formation and the number of replicating cells in the posterior region of the glenoid fossa are significantly higher than in the anterior and middle regions, which could be due to the primary attachment of the posterior fibrous tissue of the articular disc to this particular zone (Rabie *et al.*, 2003d).

It has been shown that the glenoid fossa significantly responds to environmental changes. However, the modification rate in the glenoid fossa is less than that of the condyle (Owtad *et al.*, 2011). It can also be concluded that, based on the type and direction of the forces transferred to the fossa, the cellular responses would be different throughout various parts of the fossa.

### Biochemical Changes

A significant intramembranous bone formation is seen in the fossa in response to propulsive mechanical stimuli of the condyle. The growth and remodeling process is mediated by several intrinsic and extrinsic biofeedback factors (Rabie *et al*., 2001a; Shum *et al.*, 2004). Furthermore, the changes in cell-cell and/or cell-extracellular-matrix interactions activate the mechanical signal transduction cascade, through a transduction molecule (Wang and Detamore, 2007).

New bone formation is directly correlated with the amount of blood vessel invasion in the glenoid fossa during natural growth and in response to mandibular advancement. A significant increase in vascular endothelial growth factor (VEGF) expression and new bone formation occurs mainly in the posterior region of the glenoid fossa (Rabie *et al.*, 2002; Wey *et al*., 2007). Neovascularization is enhanced by VEGF, which increases the number of mesenchymal cells in the perivascular connective tissue and stimulates the vascular endothelial cells to secrete growth factors and cytokines (Shum *et al.*, 2004; Dias *et al*., 2012).

Even though some biochemical aspects of glenoid fossa's growth modification have been investigated in the literature, more investigations are required for a better understanding of the nature of the fossa's growth modification.

## CONCLUSIONS

The mandibular condyle is a secondary, fibrous-type cartilage, which does not originate from a primary cartilage precursor. It is highly responsive to mechanical stimulation and grows appositionally from its peripheral. The anatomic position of the condyle is altered by continuous repositioning of the mandible to its best possible functional advantage, during craniofacial growth and TMJ adaptive remodeling. Changes in the biophysical environment of the TMJ by forward mandibular positioning lead to the release of regulatory factors and enhance condylar growth. In addition, these regulatory factors also lead to osteogenesis, as well as a change in the condyle's morphology and angular relocation of the condylar head, mainly located in the posterior part of the condyle. Mandibular posture maintenance is facilitated by both mechanisms of TMJ remodeling and continuous mandibular reposturing. The mandibular condyle has its own intrinsic growth but does not appear to generate tissue-separating forces.

Remodeling of the glenoid fossa and the compensatory growth of the mandibular condyle adjust with the anatomic position of the mandibular condyle in the glenoid fossa. In the fossa,

the subarticular proliferative zone can support both anabolic and catabolic bone modeling to change the shape and position of the temporal fossa in response to environmental changes.

Mandibular growth modification is the result of cellular morphologic differentiation and hypertrophic changes in both the mandibular condyle and the glenoid fossa. Widely ranging evaluations and comparisons within different structures are required for better investigations. These evaluations can reveal more details about the correlations and possible interactions between and among different tissues during natural growth and development, and under the effects of different orthodontic appliances.

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