Advances In Biology of Orthodontic Tooth Movement – A Review

Anand Patil, MDS, MorthRCSEd
Associate Professor

V. P. Jayade, MDS, FDSRCPS
Professor & Head
SDM Dental College,
Dharwar.

Abstract

Biology of Orthodontic tooth movement has always been an interesting field to Orthodontist. At present many advanced researches are being undertaken globally at different genetic and cellular levels in this arena. Starting from external stimulus such an orthodontic force to the mechanical expression of the same in periodontal ligament and bone this review article unfolds cascade of events occurring at cellular level yielding to gene expression ultimately affecting the bone resorption or bone apposition. This whole cascades passes through various chemical, electrophysical mediators of tooth movement. This article also discusses various clinical applications of knowledge of histological aspects of orthodontic tooth movement.

Keywords

Osteoblast, Osteoclast, Gene expression, Orthodontic tooth movement.

Introduction

We live in an era where science and technology know no limits. Our Orthodontic world is no less; it has evolved into its best at present. Research involving orthodontic tooth movement (OTM) is an interesting field as we are trying to answer number of questions to meet demands of this ultra modern era, such as “can biology help us to move teeth faster?”. This review article is an attempt to summarize the present concepts and future direction of ongoing research of Biology of OTM.

Five types of cells can be identified in the bone.

1. Osteoblasts, which are of mesenchymal origin, are primarily the bone forming cells. Osteoblasts synthesize and secrete the extra cellular organic matrix of bone including type I collagen, osteoclin, osteopontin, osteonectin, alkaline phosphatase, proteoglycans and growth factors. Many factors are shown to influence the development of osteoblasts from mesenchymal pluripotent progenitors or mesenchymal stem cells in PDL and alveolar bone e.g.; Certain growth factors like BMPs, Transforming growth factor-TGF-β etc. These growth factors promote osteoblast precursor proliferation, mineralization of new bone by mature osteoblasts and vasculogenesis. It’s now well understood that many genes control the complex process of osteogenesis, the gene transcription factor such as core binding factor alpha-1 (Cbfa 1) which is the earliest expressed by the cells of osteoblastic lineage and is the most specific marker of bone formation.1

Osteoblasts which are lining the bony socket are now believed to be directly responsive to strain such as orthodontic force2. One of the proteins in the membrane of osteoblasts is the integrin. Integrins translate mechanical strain into a signal which in turn stimulates a gene to make the cell develop ligans.3 Ligans allow intracellular communication, which stimulates undermining resorption allowing OTM.

The field of influencing the development of osteoblasts is the present area of research in many of craniofacial research centers.
2. The second type of cells, which are of interest are the osteocytes. They were histologically thought to be trapped osteoblasts in the matrix and whose function was considered to provide support and sustenance to the bone. Osteocytes are now understood to be very proprioceptive and responsive cells of bone. It has been demonstrated by Skerry et al. that an intermittent force within physiologic limits has an effect in increasing the expressions of glucose-6-phosphate dehydrogenase, 3H-uridine, c-fos, and insulin—like growth factors-I in the osteocytes within six hours after intermittent loading at physiological strain magnitude.

3. The third type of cells viz. osteoclasts which differentiate from monocyte-haemopoietic cells. Active osteoclasts exhibit high content of a specific chemical marker, tartrate resistant acid phosphatase (TRAP), which participates in signaling active bone resorption.

Many chemical mediators of macrophage family are known to influence osteoclast differentiation. They are cytokines (e.g.: tumor necrosis factor TNF, interleukin-1 alpha, 6-alpha), certain growth factors (e.g.: macrophage colony stimulating factor, granulocyte, macrophage colony stimulating factor) and Prostaglandins. Evidence suggests that osteoblast itself regulates the differentiation of osteoclasts. The "talk" between an osteoblast and osteoclast is accomplished through an osteoblast membrane bond RANK ligand (receptor activator nuclear factor kB ligand), which can interact with developing monocytes to cause them to differentiate eventually into osteoclasts. An interesting thing to note here is that another membrane bond molecule and its binding ligand OPG (osteoprotegerin) can develop to block RANK ligand and prevent osteoclast formation.

Kanzaki and Chiba et al have demonstrated in the rat experiments that local OPG gene transfer to periodontium inhibits OTM. Research of this kind may be an exciting thing in future to block the tooth movement specifically at a particular site during the course of OTM. It is also shown in the same experimental study that exogenous injection of PGE2 increases RANKL mRNA expression in PDL cells in rats.

4.5. Apart from the above three cells of bone; we also have osteoprogenitor cells and bonelining cells.

Osteoprogenitor cells are mesenchymal, fibroblast like cells, regarded to form a stem cell population to generate osteoblasts. They are situated in the vicinity of blood vessels of PDL. Bone lining cells are the undifferentiated flattened cells lining the bone surface. They may represent active osteoblasts, but further confirmation is needed.

In essence, bone remodeling is orchestrated by cells of osteoblast lineage and involves a complex network of cell to cell and cell to matrix interactions involving systemic hormones, locally produced cytokines, growth factors, many of which are sequestered within the bone matrix, as well as the mechanical environment of cells.

**Cascade of events that follow after application of orthodontic force**

Histologically, a typical Orthodontic tooth movement (OTM) as described earlier by 'Schwartz' presents with alveolar bone modeling, i.e. apposition of bone on its surface to alter shape and size on the tension side. A simultaneous process is the activation of osteoclast precursors and then osteoclastic bone resorption, which is followed by bone formation to repair the defect predominantly on the pressure side.

Schwartz's concept was once again proved right as we analyse the study carried out with the aid of modern technologies available today like the three-dimensional evaluation of periodontal remodelling during orthodontic treatment done by Robert A.W. Fuhrmann. In this study on 21 adult patients, 2 or 3 high resolution computed tomography (HR-CT) examinations were performed before, during and after orthodontic treatment with fixed appliances. Comparison of CT examinations permits three-dimensional evaluation of osteoclastic and osteoblastic periodontal remodelling. The picture showed orthodontically induced bone dehiscence that was partly repaired by osteoblastic periodontal remodelling in the retention period.

As we apply orthodontic force on the tooth, following events at the microscopic level occur, based on current understanding.

Primarily, alteration in the blood flow which results in reduced oxygen level at compressed area, and there might be an increased oxygen level at tension side.

Secondly, generation of Piezoelectric signal, which is now stated more appropriately as bioelectric
It has been proved that cells in PDL such as fibroblasts and bone cells such as osteoblasts possess receptors for these substances, and all these are highly interacting and interconnected, presenting a possibility of transducing mechanical force acting on cells and their adjacent matrices. These interactions lead to a transient increase in the intracellular levels of second messengers such as CAMP (Cyclic Adenosine Monophosphate), CGMP (Cyclic Guanosine Monophosphate), IP3 (Inositol phosphatase), Ca++, etc., these second messengers advance signals to the nucleus through series of kinases. In the nucleus of each cell, different second messengers account for the differential patterning, protein synthesis, and gene expression. Such recently identified immediate Early Gene expression (IEG) transcription factors include C-fos, C-jun mRNA, egr-1, SP1, growth differentiation factor 9B and extracellular GLA protein. The transcription factors seem to increase when cells are exposed to mechanical stimulation, cytokines and growth factors. These transcription factors can produce either cellular proliferation or cellular differentiation leading to osteoblastic bone formation or osteoclastic bone resorption.

The above stated cascade of events, in fact, may be a brief summary of current understanding of whole lot of complex activities and interactions occurring in the PDL and alveolar bone after the application of primary stimulus such as mechanical force or action of hormones. In the next part, we will analyze certain important modes of actions of chemical mediators and their complex, internal interactions.

Role of Prostaglandins in Mediating OTM

Prostaglandins are synthesized from fatty acids by a Microsomal enzyme complex (PG synthetase) found in all Mammalian tissues. In Humans, the most abundant precursor is Arachidonic acid, which is present in membrane phospholipids of cells. Arachidonic acid can be released either by phospholipases activated by direct cellular damage or by any nondestructive perturbation of the membrane, be it physical, chemical, hormonal or neurohormonal. Prostaglandins can also be termed as local hormones functioning to coordinate effects of those other hormones which induce prostaglandin synthesis and Prostaglandins function through G-protein linked receptors to elicit their cellular effects.
Classically, Prostaglandins as one of the mediators of inflammation cause an increase in intracellular CAMP and Calcium accumulation by Monocytic cells, which then modulates and activates osteoclastic activity. It is to be noted that elevation CAMP is not only affected by prostaglandins alone, but also influenced by substance P, VIP, Calcitonin gene related peptide and many others.

Klein and Riasz in 1970 reported first time the involvement of Prostaglandins in OTM. After that, many in vivo and invitro animal experiments have been conducted mainly by Davidovitch and Shanfeld et al. in 1980-83, Yamasaki et al. (first reported human study) 1982-83, Lee.W et al. 1990, J. Liker 1995, Selinkake et al. 2004 and many others. All these experiments indicate a very vital role of prostaglandins in OTM.

In the Indian context only one human study and second of its kind in the world was reported by Anand K. Patil et al. wherein Prostaglandin E2 in lesser dosage of 3μg along with Lingnocaine as a vehicle was injected distal to the Canine in 14 Orthodontic patients.

Studies indicate that Prostaglandins increase the number of Osteoclasts as well as stimulate Osteoblastic cell differentiation and new bone formation. This is specifically true with invitro studies involving PGE2.

Cytokines and growth factors in OTM

The early phase of OTM involves an acute inflammatory response characterized by periodontal vasodilatation and migration of leukocytes out of PDL capillaries. The released inflammatory mediators such as Prostaglandins and interleukins (IL)-1 interact with bone cells. Cytokines secreted by leukocytes may interact directly with bone cells or indirectly, via neighboring cells, such as monocytes/macrophages, lymphocytes and fibroblasts, through their production of cytokine, or a variety of Growth factors. Cytokines released have multiple activities, which include bone remodeling, bone resorption and new bone deposition.

Prominent cytokines involve interleukin IL-6, tumor necrosis factor, Granulocyte- macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF). These cytokines have been shown to stimulate bone resorption and induce osteoclast proliferation. Tumor necrosis factor α (TNF-α) stimulates bone resorption and bone cell replication. Interleukin - 1 α also has been shown to be involved in release of Prostaglandins. There is now a great deal of evidence that cells of osteoblasts regulate the activity of existing osteoclasts and the formation of new osteoclasts through release of cytokines. Research has confirmed that osteoblasts have receptors for Prostaglandins, Parathyroid hormone, and Vit-D.

Growth Factors are also released during inflammation and repair by the cells of PDL and bone. Another theory states that the growth factors may be secreted by bone cells and stored (bound to bound matrix). They are likely to be released and activated during bone resorption. These Factors include fibroblast Growth Factor (bFGF and aFGF), Insulin like Growth Factors (IGF-I, IGF-II), Transforming Growth Factor β (TGF β), Platelet Growth Factor (PDGFS) and Bone Morphogenic Proteins (BMP). IGF- I and IGF-II have been shown to increase Type-I collagen and matrix synthesis by osteoblasts. FGF are known to stimulate replication of both osteoblasts and progenitor population. BMPs are now showing promising results in Periodontics in the field of PDL tissue reconstruction. BMP - 2 has been shown to induce mesenchymal progenitors to differentiate into both osteoblasts and chondrocytes. BMP -2 also has been shown to stimulate committed osteo-progenitors (ROB - C 26 cells) to differentiate into more mature osteoblasts.
Detection of mechanical strain by bone cells

OTM involves application of forces and moments from wires through brackets to teeth, with a goal of repositioning them in dental arches. The system of forces and moments is applied to the tooth which is a rigid body. The PDL and alveolar bone houses the teeth. After the application of orthodontic force, the initial step is the detection of mechanical strain.

Research indicates that the cells responsible for sensing mechanical strains in the bone are osteoblasts, osteocytes or both.

Three theories have been suggested on how these cells sense mechanical strain, and how then the stimuli are passed into the cell and from one cell to another.

a) Strain Released potentials
b) Activation of ion channels
c) Extracellular Matrix and cytoskeleton reorganization.

Strain Released potentials

Application of small bending forces to bones is known to produce flow of interstitial fluid through the canalicular network, generating streaming potentials. The in vitro and in vivo experiments of Cowin et al 1991, and Weinbaum et al 1994, indicate that osteocytes are more sensitive to mechanical stress than osteoblasts, which in turn are more sensitive than fibroblasts.

In vivo studies conducted in Amsterdam Dept. of Oral cell Biology, Academic Centre for Dentistry, indicate that application of forces to bone results in several potential stimuli to bone cell function, including time dependent changes, hydrostatic pressure, direct cell strain, fluid flow induced shear stress and electric fields resulting form electrokinetic effects accompanying fluid flow.

These events effect osteocytes, which are mechanosensor cells of bone. These in turn, activates osteoblasts or osteoclasts to produce adaptive bone remodeling. These events are depicted in the following schematic diagram.

Activation of ion channels

Ion channels are tunnel shaped proteins that cross the width of cell membrane, and serve as selective conductive pathways for ions that cross the membrane as well as membranes surrounding intracellular organelles. Ion channels can be divided into groups depending upon type of stimulus needed to activate the channel. The major groups are voltage gated, ligand gated and mechanosensitive (stretch) ion channels. The voltage gated channels have channel proteins that undergo conformational changes in response to changes in transmembrane potential. Ligand gated channels are also similar domains that respond to specific ligands that may attach to the cell membrane near channel opening. Stretch ion channels react to structural perturbations. The stretch ion channels, response (gated in an open or closed positions) to mechanical stimuli are relevant to OTM.

ION CHANNEL STIMULATED TO OPEN

The Stretch activated ion channels are shown to allow passage of cations i.e. Calcium and potassium. Paul A.G. and Louis Norton 28, 29, in the University of Connecticut, have shown that continuous mechanical load similar to an orthodontic force affects the mechanosensitive ion channels of osteoblastic cells in culture, thereby producing large increase in intracellular calcium. It has been suggested that ion channels may be linked to cytoskeleton, and are opened when their cytoplasmic tail is phosphorylated.

Extracellular Matrix and Cytoskeleton Reorganization

The principle elements of ECM of either PDL or the bone may be considered as collagen fibrous network providing structural support embedded in and interacting with a non collagenous matrix consisting of proteoglycans and various glycoproteins. The macromolecules, which make up the ECM, include collagen and glycosaminoglycans. These macromolecules are secreted at local levels by cells, particularly fibroblasts in the PDL and osteoblasts in the bone. The matrix metallo proteins (MMPS) represent major class of enzymes responsible for ECM metabolism.

The growth and repair of connective tissue is a delicately balanced process of ECM removal and
replacement, with significant control by MMP and primary natural inhibitors or Tissue inhibitors of metalloproteinases (TIMPS).

Cytoskeleton represents a framework attaching cell to cell or cell to extracellular matrix, thereby presenting a possibility of transducing mechanical forces acting on the cells or on their adjacent matrices.

There are two types of cellular adhesions possible in the cytoskeleton framework. One is cell to cell adhesion and the other is cell to ECM adhesion. It is now clearly demonstrated histologically that any cytoskeleton framework has three main components i.e. Microtubuls, microfilaments and intermediate filaments.

The major subunit protein of the microfilaments is actin. There are, however many associated protein such as myosin, tropomyosin, vinculin and talin. The cell membrane integral proteins are also identified as cell surface receptors termed INTEGRINS which span the cell membrane from cytoplasm to extra cellular matrix.

These INTEGRINS mediate cell to cell attachment or cell attachment to ECM molecules such as fibronectin laminin and talin. It has also been shown that actin and vinculin bind to this talin integrin complex..

Integrins when analyzed at molecular levels, are a family of α/β heterodimeric cell surface receptors, composed of at least fourteen distinct α sub units and eight or more β – subunits that can associate non-covalently in various combinations. Osteoblasts have been shown to express the Integrin α2 β1 and α5 β1. Osteoclasts also express Integrin receptors α1 β3 which play an important role in adhesion of osteoclast to the bone surface.

Integrins are found to regulate signaling pathways by changing intracellular calcium, regulating incitol lipid turnover, and phosphorylation of intracellular proteins. The individual binding of Integrins to osteoclasts and osteoblasts has been elucidated with the use of cell adhesion assays, monoclonal antibodies (MABS) and affinity chromatography. The receptor binding site (RGD) arginine-glycine-aspartic acid was first defined. Similarly RGES (arginine glycine glutamic acid) receptor binding site was also identified. In an engineered experimental study, it was found that both RGES and RGDs bind to osteoblast.

It is now clearly demonstrated by Teitetbaum, that both osteoblasts and osteoclasts express multiple Integrins, or bind to many RGD containing proteins including osteopontin and cleaved type-I collagen, which are abundant in bone.

In an experimental study, agents such as echistatin, an RGD containing peptide, derived from snake venom and short RGD peptides injected during the experimental tooth movements in rats have been shown to interfere with aspects of INTEGRIN mediated signals transduction and ultimately to affect bone remodelling. Echistatin can induce disruption of cell matrix interaction and appears to cause an early reduction of PP125FAK phosphorylation. This results in the disassembly of actin cytoskeleton adhesion. The total effect of echistatin attributed to decrease in osteoclast function and osteoclast numbers. It is also demonstrated by C. Dolce et al in an experimental study on rats that orthodontic tooth movement can be completely blocked out at specific sites by local administration of echistatin or arginine glycine aspartic acid RGD peptide. This can be of clinical relevance in orthodontic practice in future.

**Production of second messengers**

As we understand, the primary stimulus or first messenger may alter activity through cell membrane. The responsive cells possess receptors on the cell membrane for these substances. Their interactions lead to increase in intracellular levels of second messengers. The production of second messengers such as CAMP – and CGMP - during Orthodontic force was demonstrated way back during 1973-76 by Davidovitch and Shanfeld. This can be of clinical relevance in orthodontic practice in future.
Intracellular CAMP levels can be inhibited by Ibuprofen, a drug commonly used as pain killer, and many other NSAIDS.

Inositol phosphate is another second messenger, which is also similar in its production as that of generation of CAMP. Inositol phosphate in presence of phospholipase gets converted to phosphatidylinositol biphosphate (IP?). Phospholipase then cleaves IP? into Inositol Triphosphate (IP?) and Diacyl glycerol with subsequent release of calcium from intracellular stores. The calcium thus released is responsible for Protein Phosphorylation in nucleus. The Diacyl glycerol formed activates protein Kinase C. This protein Kinase C is an enzyme responsible again for Protein phosphorylation.

Now the research is focused on how this mechanical strain ultimately influences the biochemical reactions within the nucleus of each cell of PDL and bone.

In the signaling cascade process, receptor activation is followed by second messenger generation i.e. CAMP and inositol triphosphate. They advance signals to the nucleus through series of kinases. In the nucleus, different second messenger account for the differential pattern, Immediate Early Gene expression (IEG) or also termed as third messenger. This transcription of IEGs i.e. C-fos gene, C-jun gene and egrn1-gene has been shown to be influenced when exposed to cytokines, growth factors or mechanical stimulation. These transcription factors released, depending on presence of various stimuli, can either produce cellular proliferation or differentiation.

In rat experiments, it was shown that within three hours of applying orthodontic force there was an increase of 1.7 fold in C-fos mRNA expression, when compared to respective controlled side where no orthodontic tooth movement was applied. At 24 hours after initial orthodontic force application, significant induction of 1.9 fold was detected. Final 1.5 fold induction was seen after 7 days of force application. These results show a peak of C-fos induction in cyclic fashion i.e. at 3 and 24 hours and at 7 days after appliance activation. The authors speculate that C-fos may play a role in both early and in the later phases of orthodontic tooth movement cycle.

A study conducted at the center for craniofacial and molecular biology, University of California by H.B. Moon et al has demonstrated that more than 130 genes were regulating orthodontic tooth movement up or down after one day of application of orthodontic force in mice experiments. Among them were several transcription and growth factors such as SP1, growth differentiation 9B, myogenic factors as well as extra cellular matrix CLA protein.

Clinical application of knowledge of histological aspects of orthodontic tooth movement

Clinical application of chemical mediators of OTM has been a subject of great interest to all orthodontists. Research in the field of orthodontics is now mainly focused on biology of orthodontic tooth movement. Advanced molecular biology and genetic engineering have opened wide scope in this particular aspect of orthodontics. Enhancing rate of tooth movement pharmacotherapeutically or electrophysiologically or genetically would be an ultimate goal for all present day researchers.

Among the chemical mediators affecting orthodontic tooth movement, Prostaglandins (PGs) head the list. History of PGs dates back to 1939 with their discovery by Von Euler from human semen. It was in 1970 that Klein and Riasz reported first time that PGs are important mediators of OTM. A series of in vivo and in vitro experiments there after have been reported, since the initial experiments by Zeev Davidovitch and Yamasaki et al. Following this many in vivo and in vitro studies have been reported in the literature but till now only, two human studies have been reported. First study was by Yamasaki et al, wherein a total of 40μg of PGE1, was injected in the vestibular region at the upper right canine area during orthodontic tooth movement. The results of this particular clinical experiment showed almost twice faster orthodontic tooth movement on the PGE1 injected side as compared to non-injected side of canine retraction.

The other experimental studies listed above mainly conducted in animals by various authors, have shown...
increased tendency of root resorption with exogenous application of PGs. The tendency for root resorption is dose dependent. As the PG dose increases root resorption tendency also increases. J. Leiker has suggested application of minimal dosage of PGs (1-3μg) in animal experiments during orthodontic tooth movement with no root resorption tendency.

Another human study was reported by Anand K. Patil, S.D. Gaitonde et al. This was the second human trial till date. In this study, 1μg/ml PGE₂ (along with lignocaine as vehicle) was injected in the vestibular region on the right side of the upper quadrant in 14 patients during separate canine retraction stage on the 1st, 3rd, 6th day. Left side was the control side with injection of plain lignocaine. The total dosage of PGE₂ used in this study was only 3μg. The 60 days of post canine retraction results showed a one and half times more increased tooth movement on the prostaglandin E₂ injected side. No macroscopic/roentgenographic side effects were observed throughout the experimental procedure.

From these above studies, one can deduce certain merits and demerits involving the clinical application of prostaglandins.

The prostaglandins have definitely shown increased tooth movement when injected or systemically administered. The disadvantages of injection mode of prostaglandins as reported on animals or human experiments include: potential risk for root resorption when used in higher doses, associated pain and inflammation, and leakage of drug at the site of injection resulting in anchor loss.

An interesting study reported by Massound Seifi et al, wherein the injection of PGE₂ was supplemented with oral administration of calcium in rats during OTM. This study indicates no tendency for root resorption.

Ali Reza Sekhawat et al have reported a study involving oral administration of stable PG₁ analog such as misoprostol during orthodontic tooth movements in rats. They reported that oral misoprostol can be used to enhance orthodontic tooth movement with minimal root resorption.

Other ways of modifying OTM include injection of Vit. D metabolite as reported by Takano-Yamamoto et al in 1992, Selin Kale et al 2004 reported comparison of effects of 1, 25 dihydrocalciferol (biologically active form of Vit D) and PGE₂, on orthodontic tooth movement (OTM). In this rat experimental group, both PGE₂ and 1, 25 DHCC enhanced the amount of tooth movement significantly. The number of osteoblasts on the external surface of alveolar bone on the pressure side was significantly greater in 1, 25-DHCC group than PGE₂ group. Authors suggested that 1, 25 DHCC more effective in modulating bone turnover during OTM, because of its effect on bone formation and resorption is well balanced.

Application of steroid therapy. In the rat experiments reported by Colin K.L. Ong, Laurence J. et al, suggests that steroid treatment suppresses clastic activity.

Application of infusion of parathyroid hormone in experimental tooth movement in rats by Soma S. Iwa et al in 1999, showed increased clastic activity.

An injection of L-arginine (nitric oxide precursor) in experimental tooth movements in rats was reported by Mohsen Shirazi et al 2002, which suggests a definite role of nitric oxide in orthodontic tooth movement. It has been shown that increase in nitric oxide production...
increases bone remodelling and orthodontic tooth movement\textsuperscript{44}.

In another mouse experiment by Fumio Hashimoto, it has been shown that administration of osteocalcin accelerates OTM due to enhancement of osteoclastogenesis on the pressure side\textsuperscript{45}.

Alternative to chemical mediators, Giovannelli, F. Festa from Italy reported electric stimulation to affect orthodontic tooth movement. In this study, ten patients were selected, who required first premolar extraction for correction of orthodontic treatment. Small electric devices were adapted to tooth that had to be moved. The results suggested that application of direct currents potentiates the effect of mechanical force during orthodontic tooth movement\textsuperscript{46}.

Recent reports from university of Florida headed by by Dr. Timothy Wheeler mentioned a new drug being investigated \textsuperscript{46} Relaxin. It is naturally occurring human hormone that helps women’s pelvic ligaments to stretch in preparation for giving birth. This hormone, according to an ongoing research reports is showing promising results to augment OTM and retention\textsuperscript{47}.

As of now, all the above reported in vivo and in vitro studies definitely show us a very bright future, though they are still in experimental stage and will definitely need controlled human trials (of course with strict ethical clearance board permission) to make the “future Ortho world” a fascinating one.

Communications

Anand K. Patil, MDS.MorthRCSEd
Associate Professor
SDM Dental college, Dharwar
Ph.No: 9886279490
Email: akptimes@yahoo.com

References

22. Devid Covell PSCO Bulletin 2004 Sept 20, Palm Springs
40. Balaji S.I., Shetty Surendra V. JIOS 1995;27:85-92
45. Fumio Hashimoto, Yasuhiro Kobayashi et al. Euro Jour Orth 2001;23(5):535-545
47. http://www.annalsnyas.org/cgi/content/ab