AN OVERVIEW OF THE ROLE OF DRUGS AND SYSTEMIC FACTORS ON ORTHODONTIC TOOTH MOVEMENT

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Abstract:
The specialty of Orthodontics is based on the fact that it is possible, by applying appropriate forces, to move the teeth through the alveolar bone of the jaws. Orthodontic tooth movement and the concomitant bone remodeling process are dependent on various local and systemic factors like age, nutrition, consumption of drugs etc. Orthodontic patients may be affected by systemic diseases that might need treatment with drugs that could possibly affect bone metabolism. Patients undergoing orthodontic treatment can experience significant levels of pain. Analgesics are commonly recommended for the control of such orthodontic pain.

This article reviews all the existing published biomedical literature on the effects of some commonly used drugs by the patients for the relief of orthodontic pain and treatment of systemic conditions known to affect the bone tissue and thereby influencing the rate of orthodontic tooth movement. An attempt has been made to propose a complete picture and orient the reader for the better understanding of some commonly used pharmaceutical products.

This is considered essential in order for the orthodontist to take into account all factors related to the therapy and to select the best therapeutic strategy in every individual patient keeping the mechanics as simple as possible.

Key Words: orthodontics, force, drugs, systemic, tooth movement.
INTRODUCTION:
The aim of orthodontic treatment in the movement of teeth through bone is to obtain a more perfect dental occlusion. Orthodontic tooth movement has been defined by Proffit as the result of a biological response to interference in the physiological equilibrium in the dentofacial complex by an externally applied force.

Nowadays, attention is mainly focused on the relation of orthodontic tooth movement to the applied force. The control of pain during orthodontic treatment is of interest to both clinician and patients. Prescription and over the counter analgesics are commonly recommended for orthodontic pain. Interestingly, despite clinical evidence that patients experience pain after orthodontic procedures, there have been few controlled studies that address the use of analgesics to control post appointment orthodontic pain.

The objective of this review is to discuss current data concerning the mechanism of action and effects of some commonly used pharmaceutical products and systemic factors known to affect bone tissue and thereby influencing the rate of tooth movement. This is considered essential in order for the orthodontist to take into account all factors related to the therapy and to select the best therapeutic strategy in every individual patient keeping the mechanics as simple as possible.

An Overview of biological basis of orthodontic tooth movement:
In a recent review on the current concepts in the biology of orthodontic tooth movement Richard and Malcolm said that five micro-environments are altered by Orthodontic force - extracellular matrix, cell membrane, cytoskeleton, nuclear protein matrix and genome. Cell membrane receptor ligand docking is an important initiator of signal transduction and a discovery target for new bone enhancing drugs. Despite progress in identification of regulatory molecules, the genetic mechanism of “orchestrated synthesis” between different cells, tissues and systems remain largely unknown.

Eicosanoids/Autocoids are biologically active derivatives of 20 carbon atom Polynsaturated fatty acids (PUFA) that are released from cell membrane phospholipids. There are two major lipid derived autocoids:
1) Prostaglandins (PG’s), and
2) Leucotrienes (LT’s)

Membrane phospholipid

\[ \text{Cyclo-oxygenase} \]

\[ \text{PGG}_2 \]

\[ \text{PGH}_2 \]

Isomerase

\[ \text{Thromboxane synthase} \]

\[ \text{Prostacyclin synthase} \]

\[ \text{Arachidonic Acid} \]

\[ \text{Chemical or mechanical stimuli} \]

\[ \text{Lipo-oxygenase} \]

\[ 12 \text{ HPETE} \]

\[ 5 \text{ HPETE} \rightarrow 5 \text{ HETE} \]

\[ 12 \text{ HPETE} \]

\[ \text{LTA}_4 \]

\[ \text{LTB}_4 \]

\[ \text{LTC}_4 \]

\[ \text{LTD}_4 \]

\[ \text{LTE}_2 \]

\[ \text{LTF}_4 \]

Biosynthesis of PG’s and LT’s.
Cyclooxygenase is known to exist in two isoforms Cox-1 and Cox-2. While both isoforms catalyse the same reactions, cox-1 is constitutive enzyme in most cells. On the other hand cox-2 is normally present in insignificant amounts but is inducible by cytokines, growth factors and other stimuli during the inflammatory response. It is believed that eicosanoids produced by cox-1, participate in physiological (house keeping) function such as secretion of mucous for protection of gastric mucosa etc. while those produced by cox-2 lead to inflammatory and other pathological changes.

Tooth movement during orthodontic treatment requires remodeling of periodontal ligament tissues, especially in the alveolar bone. Force application disrupts the equilibrium that exists between bone formation on the pressure side and more bone formation than resorption on tension side. Resorption of bone by osteoclasts is coupled with subsequent bone formation by osteoblasts. Local and systemic factors include cytokines, hormones, growth factors and mechanical stimulation to produce the receptor activator of NF-κB (RANKL) which is vital for osteoclasts differentiation and activity. RANKL is expressed on the surface of osteoclastic cells and bone marrow stromal cells and binds to the RANK receptor on the surface of osteoclastic precursors, thereby stimulating the differentiation and activation of osteoclasts.

### Table 1
Factors affecting bone remodeling process

<table>
<thead>
<tr>
<th><strong>Hormones and systemic factors</strong></th>
<th>PTH</th>
<th>Calcititin</th>
<th>Insulin</th>
<th>Growth hormone</th>
<th>Vitamin D</th>
<th>Glucocorticoids</th>
<th>Sex steroids</th>
<th>Thyroid hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth factors</strong></td>
<td>Insulin like GF I and II</td>
<td>TGF β</td>
<td>Fibroblast growth factor</td>
<td>Platelet derived growth factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>IL-1, 4, 6, 11, 13, 18</td>
<td>TNF</td>
<td>Osteoclast differentiating factor</td>
<td>Interferon γ</td>
<td>Osteoprotegrin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colony stimulating factors</strong></td>
<td>M-CSF</td>
<td>G-CSF</td>
<td>GM-CSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Prostaglandins</td>
<td>Leukotrienes</td>
<td>Nitric oxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intracellular secondary messengers play an important role in the differentiation of osteoclasts from monocytes in bone resorption during force application. Davadovitch et al measured cGMP and cAMP levels in the alveolar bone of cats under orthodontic treatment and reported that Ca++, cGMP and cAMP acts as a key mediators or secondary messengers in the function of many drugs and hormones. It is now clear that OTM is influenced both by drug and the systemic factors. An attempt has been made to review the past and present literature published in various articles in different journals on the factors that tend to influence the OTM, and same will be discussed as presented in Table II and Table III.
### Table II

**Effects of drugs on tooth movement**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effects on bone tissue</th>
<th>Effects on tooth movement</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) NSAIDS</td>
<td>- Decreased bone resorption</td>
<td>- Decreased rate of tooth movement</td>
<td>- Inhibition of cyclooxygenase enzyme.</td>
</tr>
<tr>
<td>- Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acetaminophen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ibuprofen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rofecoxib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Valdecoxib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Celecoxib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Eicosanoids / Autocoids</td>
<td>- Increased bone resorption</td>
<td>- Increased rate of tooth movement</td>
<td>- Increases cAMP and cGMP levels.</td>
</tr>
<tr>
<td>- Prostaglandins</td>
<td></td>
<td></td>
<td>- Activates osteoclasts.</td>
</tr>
<tr>
<td>- Leukotrienes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Bisphosphonates</td>
<td>- Decreased bone resorption</td>
<td>- Decreased rate of tooth movement</td>
<td>- Inhibit bone turnover.</td>
</tr>
<tr>
<td>4) Fluorides</td>
<td>- Increased bone mass and mineral density - Decreased bone resorption</td>
<td>- Decreased rate of tooth movement.</td>
<td>- Increases bone mass/density</td>
</tr>
<tr>
<td>5) Corticosteroids</td>
<td>- Increased bone resorption - Decreased bone formation</td>
<td>- Increased rate of tooth movement.</td>
<td>- Inhibit osteoblast formation.</td>
</tr>
<tr>
<td>6) Epidermal growth factor (EGF)</td>
<td>- Increased bone resorption</td>
<td>- Increased rate of tooth movement.</td>
<td>- Enhances osteoclasts recruitment.</td>
</tr>
<tr>
<td>7) Osteoprotegrin gene transfer</td>
<td>- Decreased bone resorption</td>
<td>- Decreased rate of tooth movement</td>
<td>- Inhibits RANKL mediated osteoclastogenesis.</td>
</tr>
<tr>
<td>8) Echistatin (RGD peptide)</td>
<td>- Decreased bone resorption</td>
<td>- Decreased rate of tooth movement</td>
<td>- Inhibits Integrin receptors.</td>
</tr>
<tr>
<td>9) Tezosentan</td>
<td>- Increased bone resorption</td>
<td>- Increased rate of tooth movement</td>
<td>- Enhances bone resorption via ETA receptors.</td>
</tr>
</tbody>
</table>

### Table III

**Effects of systemic factors on tooth movement**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effects on bone tissue</th>
<th>Effects on tooth movement</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Estrogen</td>
<td>- Decreased bone resorption</td>
<td>- Decreased rate of tooth movement</td>
<td>- Inhibits cytokine involved in bone resorption.</td>
</tr>
<tr>
<td>2) Androgen</td>
<td>- Decreased bone resorption</td>
<td>- Decreased rate of tooth movement,</td>
<td>- Enhances DNA transcription.</td>
</tr>
<tr>
<td>3) Vitamin D</td>
<td>- Increased bone resorption - Enhances reestablishment of supporting tissues</td>
<td>- Increased rate of tooth movement.</td>
<td>- Activates DNA and RNA within target cells.</td>
</tr>
<tr>
<td>4) Thyroid</td>
<td>- Increased rate of bone remodeling</td>
<td>- Increased rate of tooth movement.</td>
<td>- Activates a specific DNA sequence called Thyroid hormone response element.</td>
</tr>
<tr>
<td>5) Parathyroid</td>
<td>- Increased rate of bone resorption</td>
<td>- Increased rate of tooth movement.</td>
<td>- Increases cAMP formation and intracellular Ca in target cells</td>
</tr>
</tbody>
</table>

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1. EFFECT OF DRUGS ON TOOTH MOVEMENT;

NSAID'S:

All drugs grouped in this class have analgesic, antipyretic and anti-inflammatory actions in different measures. They are also called non narcotic, non opioid, or aspirin like analgesics. They act primarily on peripheral pain mechanisms but also in CNS to raise pain threshold, by inhibition of cyclo-oxygenase, which modulates the transformation of PG's from arachidonic acid in the cellular plasma membrane.

They are the most common group of medications used in orthodontics for relief of pain.\(^6\),\(^7\),\(^8\) Numerous studies evaluated the pain reducing effects of various NSAID's. Then drugs have become the focus of recent research in orthodontics.

Amongst the earliest studies carried out Chumley et al\(^8\) evaluated the effect of indomethacin (an aspirin like drug) and recommended that aspirin like drugs not to be administered to patients undergoing orthodontic treatment as it may extend the treatment time. Walker et al\(^9\) evaluated the impairment of O.T.M caused by NSAID's and results showed that they can impair O.T.M and until long term human data are obtained, acetaminophen remains an appropriate alternative to NSAID's. Similar results were found by Arias et al\(^10\) who compared aspirin, acetaminophen and ibuprofen and found that acetaminophen did not affect OTM. Even Roche et al\(^11\) concluded that acetaminophen has no effect on rate of OTM. Kehoe et al\(^12\) also suggested acetaminophen as the analgesic of choice for minor discomfort associated with orthodontic treatment. But in a recent contrasting study Bradley et al\(^13\) compared Ibuprofen and paracetamol for the control of pain and found that pre-operative and post-operative Ibuprofen to be more effective than paracetamol. In another study by Polat et al\(^14\), Naproxen sodium was found to have lower levels of pain than patients taking ibuprofen.

Moreover the use of over the counter drugs have also shown aberrant remodeling of the periodontal vasculature affecting the tooth movement. Kyrkanides et al\(^15\) investigated the effects of indomethacin on collagenase activity and procollagen synthesis. Cyclooxygenase inhibition resulted in exacerbation of IL-1 beta mediated collagenase B (MMP-9) production and activity, as well as alteration of type IV procollagen synthesis levels by endothelial cells in vitro.

The studies mentioned above showed that NSAID's effectively reduce the pain and discomfort caused by orthodontic tooth movement but these drugs may also affect the sequence of tooth movement by inhibiting or at least by reducing the associated inflammatory and bone resorption process. One approach to deal with this is the use of selective cox-2 inhibitors, also called as coxibs, which are replacing conventional NSAID's. In comparison to NSAID's, Cox-2 inhibitors have longer dose intervals, different side effect profile, similar onset of action and similar analgesic effect.

Sari et al\(^16\) showed that the inhibition effect of aspirin on PGE\(_2\) was more than that of Rofecoxib. In another study Young et al\(^17\) concluded that valdecoxib may be a better approach to prevent discomfort of initial archwire placement. In a previous study by Carlos et al\(^18\) found no substantial advantage in using a selective cox-2 inhibitor compared with non specific cox inhibitors. But in a recent study Carlos et al\(^19\) evaluated orthodontic tooth movement after different coxib therapies and concluded that celecoxib and parecoxib, but not rofecoxib, seem appropriate for discomfort and pain relief while avoiding interference during tooth movement.

Gameiro et al\(^20\) evaluated the effects of short and long term celecoxib on orthodontic tooth movement and concluded that although celecoxib administration did not affect the number of osteoclasts, the osteoclasts activity might be reduced, which could explain the inhibition of tooth movement observed.

However the effect of these drugs on orthodontic root resorption is not well understood. Gameiro et al\(^21\) did histological analysis of orthodontic root resorption treated with celecoxib and found that short and long term celecoxib did not suppress the root resorption.

Therefore, it is recommended that patients undergoing orthodontic treatment should be advised not to take these over the counter drugs without the dentist’s prior knowledge.

**EICOSANOIDS / AUTO COOIDS :**

**Prostaglandins :**

Arachidonic acid is metabolized by cyclooxygenase resulting in prostaglandin production.\(^22\) Experiments have shown that PG's are an important mediators of mechanical stress during OTM.

Ngan et al\(^23\) observed that PG's cause hyperalgesia by facilitating pain stimulus and increasing the effects of histamine and bradykinin. Chao et al\(^24\) observed that PGE\(_2\) injection increased the number of osteoclasts in pdl membrane. Davidovitch et al\(^25\) demonstrated in vitro direct effect of PG's on bone resorption along with increase in cAMP and cGMP levels. Sandy et al\(^26\) found that inhibition of PG synthesis by flurbiprofen, a PG inhibitor, showed inhibition of osteoclast activity and bone resorption. In another study by Gurton et al\(^27\) found that PGI\(_2\) and TXA\(_2\) analogs increase the number
of multinuclear osteoclasts, osteoclastic bone resorption and rate of OTM. Similar results were also shown by Yamasaki et al.\(^2\)

Studies were also conducted in order to evaluate the effect of PG's on root resorption. Leiker et al.\(^2\) found that the amount of root resorption did increase with the use of PG injections, specifically PGE\(_2\). In a contrasting study by Boekenoogen et al.\(^3\) concluded that PGE\(_2\) appeared to have no effect on the number or depth of resorption lacunae. In a similar study Brudwick et al.\(^4\) found no significant difference in root resorption but trend towards more root resorption was seen on teeth where PGE\(_2\) injection had been performed. In a recent study Seifi et al.\(^5\) showed the importance of Ca\(^2\+) ions working in association with PGE\(_2\) in stabilizing root resorption while significantly increased OTM.

**Leucotrienes:**

They are also metabolites of arachidonic acid, produced by lipo-oxygenase enzymes. They are also important mediators of OTM. Their role in OTM is clearly demonstrated when inhibitors of leucotrienes are used in different experiments.

It is a well known observation that inhibition of one pathway of arachidonic acid will shunt the effect into an increase in the conversion via the other pathway. Mohammed et al.\(^6\) investigated role of a LT inhibitor AA861 in OTM and found that it caused significant LTB\(_4\) inhibition and simultaneous increase in PGE\(_2\) production, suggesting LT role in mediating OTM. However inspite of - PG levels, a selective inhibition of LT synthesis caused a significant reduction in tooth movement.

Consequently leucotriene inhibitors can delay orthodontic treatment, whereas leucotrienes and prostaglandins can have future applications that could result in enhanced tooth movement.\(^7\)

**BISPHOSPHONATES:**

The pharmacologic agent bisphosphonates are analogues of pyrophosphate. Recently\(^8\) they have received much attention in dental literature. Bisphosphonates in oral or IV forms are used to that various diseases such as certain cancers, bone and calcium related disorders, osteoporosis etc. Bisphosphonate inhibit bone turnover and result in increased bone mineral density. The most serious side effect of Bisphosphonate treatment is osteonecrosis of the mandible or the maxilla represented by exposed non healing bone. Other related complications include decreased bone healing and an inhibition of orthodontic tooth movement.

Sato Y et al.\(^9\) did a study to clarify the effects of Bisphosphonate administration on structure and function of osteoclasts in alveolar bone resorption during experimental tooth movement and found that BP significantly impair the osteoclast structure and reduces expression of both vacuolar type H(+) ATPase and cathepsin K in osteoclasts during tooth movement. Liu et al.\(^10\) also suggested the inhibitory effect of clodronate on tooth movement and osteoclasts may be due to inhibition of cox-2 dependent PGE\(_2\) production and RANKL expression in pdk cells.

Root resorption associated with tooth movement in an unsolved problem in orthodontics. If such root resorption could be prevented, it would be an important contribution towards reducing risk factors in orthodontic treatment. The use of BP to reduce the amount of inflammatory root resorption has been investigated and were found to be effective in this regard.

Liu et al.\(^11\) found that local clodronate inhibited root resorption incident to tooth movement and suggested it to be a useful therapeutic adjunct in orthodontic treatment. Igarashi et al.\(^12\) evaluated topical administration of residronate on root resorption and found that it did not appear to inhibit the repair process of root resorption.

The clinical utility of Bisphosphonates resides in their ability to inhibit bone resorption. In Orthodontics, undesirable movement of anchor teeth during tooth movement and relapse of moved teeth after treatment are the main cause of unsuccessful results. If these tooth movements could be prevented with pharmacological agents, a less complex orthodontic force system and less extensive retention would be required.

Igarashi et al.\(^13\) evaluated the anchorage and retentive effects of a BP (AHBuBP) on tooth movement in rats and concluded that it could be useful in enhancing anchorage or retaining teeth. Kim et al.\(^14\) evaluated the effect of Bisphosphonate administration on osteoclastic bone resorption during relapse and found that it decrease the extent of initial relapse via mechanism involving impairment of the structure and resorption functions of osteoclasts.

In another study by Adachi et al.\(^15\), found that the topical administration of residronate may be helpful in anchoring and retaining teeth under orthodontic treatment.

Therefore it is imperative that Bisphosphonate medical screening, patient counseling, informed consent, and changes in treatment planning should be considered for every patient by the orthodontist.\(^16\)
FLOURIDE:
The effect of fluoride on bone metabolism has been well reported in the medical field, because it has been used as a drug by itself or as an adjunct in the treatment of osteoporosis. Fluoride treatment results in an increase in bone mass because of the stimulation of bone formation.

Helsing et al evaluated the effect of fluoride on OTM and found that the velocity of TM is influenced by hormones as well as trace elements. In another study use of F as a variable was found to increase the mean osteocalcin concentration (a bone protein that has been used to mark bone turnover). Foom et al evaluated the effect of systemic F intake on root resorption and found that F reduces the size of resorption craters, but the effect is variable.

The clinical utility of F agents includes caries preventive treatment protocols such as following oral prophylaxis, proximal stripping/slicing etc. may increase the orthodontic treatment time due to its anabolic effects on bone, as fluoride increase both bone mass and density.

CORTICOSTEROIDS:
Orthodontic patients may be affected by systemic diseases that might need treatment with drugs that could possibly affect bone metabolism. Synthetic corticosteroids have been used in therapeutic regimens for the treatment of a wide variety of ailments ranging from arthritis to renal, collagen, allergic and neoplastic diseases. Supra-physiologic doses of these drugs when administered induce the same osteoporosis found in naturally occurring status of hypercortisolism. Corticosteroids inhibit osteoblastic function by mediating its effects on osteoblast and its precursors resulting in decreased bone formation. The latter may be due to elevated PTH levels caused by direct inhibition of Ca+ absorption by the steroids. End result being increase in bone resorption. Ascroft et al found that rabbits subjected to corticosteroids induced osteoporosis underwent more rapid O.T.M and subsequent relapse. Mavragni et al found that low dose doxycyline may have an inhibitory effect on orthodontically induced resorptive activity.

In a recent study Verna et al investigated the effect of acute and chronic corticosteroid treatment on orthodontically induced root resorption and found more root resorption in acute group. When compared to chronic group and suggested that it may be due to lack of balance between blastic and elastic activities during initial phase of drug administration.

Because acute corticosteroid ingestion reduces bone turnover, in these patients orthodontic treatment might best be postponed until a time the patient is free of the drug. Chronic steroid ingestion leads to an increased biological reaction to mechanical perturbation indicating that the Orthodontic force level should be reduced and controlled more frequently in patients on chronic steroid treatment. Moreover specific attention must be paid to the retention protocol as the tooth movement is less stable. As a consequence, careful monitoring of patients undergoing corticosteroid treatment is suggested.

MISCELLANEOUS:
1) Epidermal growth factor:
Recently the use of epidermal growth factor (EGF) to develop a suitable environment and stimulate selective differentiation and proliferation has been proposed. It has also been suggested that it may be involved in responses of osteoblastic cell lives to mechanical stimuli. Saddi et al found that local administration of EGF located within liposomes had an additive effect on the rate of osteoclasts recruitment, producing faster bone resorption and tooth movement.

2) Biological agents – Relaxin:
Using biological agents to modify the rate of tooth movement have been shown to be effective in animals. Relaxin main action is to increase the turnover of fibrous connective tissue. Madan et al evaluated effect of human relaxin on OTM and found that it does not accelerate OTM, it can reduce the level of PdI organization and mechanical strength and increase tooth mobility at early time periods.

3) Osteoprotegrin gene transfer:
It has been reported that osteoclastogenesis is primarily activated by the receptor activator of nuclear factor Kappa b ligand (RANKL) and inhibited by osteoprotegrin (OPG). PdI cells which exists between teeth and alveolar bone, induce osteoclastogenesis in vitro through the up regulation of RANKL expression via PGE2 synthesis when subjected to mechanical compressive force.

Kanzaki et al found significantly diminished tooth movement on local OPG gene transfer to PdI tissue as it inhibited RANKL mediated osteoclastogenesis and inhibited experimental tooth movement.

4) Echistatin and RGD peptide:
Recently a study done on effect of echistatin, an Arginine-glycine-aspartic acid peptide by Dolce C et al showed that ELVAX loaded with RGD peptide which was surgically implanted next to maxillary
molars inhibited OTM. The RGD peptide also reduced molar drifts, therefore it shows the feasibility of using them to deliver integrin inhibitors adjacent to teeth to limit local tooth movement in response to orthodontic force.

In another recent study Talic et al. evaluated the effect of echistatin on orthodontically induced root resorption and concluded that targeting αvβ3 integrin receptor expressed by odontoclasts can be effective in reducing root resorption during tooth movement.

5) Endothelin Antagonist : Tezosentan

Endothelin is a cytokine peptide present in the pdl in physiological conditions. Its concentration in the pdl doubles after 3 hours of axial loading of a tooth.

In a recent study by Sprogar et al., evaluated the effects of TBC 3214, a selective endothelin ETA receptor antagonist on OTM in rats and found that ETA, is involved in OTM probably by enhancing bone resorption via ETA receptors. In another study Drevensék M et al. found that Tezosentan, an endothelin antagonist, enhanced orthodontic tooth movement in rats.

EFFECT OF SYSTEMIC FACTORS ON ORTHODONTIC TOOTH MOVEMENT:

THYROID AND PARATHYROID HORMONE:

The movement of teeth during orthodontic treatment requires bone remodeling. The role of bone metabolism, however, in controlling tooth movement have been considered secondary to the force applied. This is largely a result of the difficulty in altering bone metabolism systemically, in addition to the fact that the force is the most easily manipulated factor. Consequently, several papers have focused on the changes in bone remodeling in relation to the applied force. In addition to applied force, tooth movement seems to depend on calcium metabolism is alveolar bone.

A study by Midgett et al. indicated that animals with hyperparathyroidism had significantly decreased bone density, as well as increased bone remodeling changes. Engstrom et al. demonstrated that although the level of PTH in serum plays an important role in the regulation of the resorptive activity in bone, a change in serum calcium level is determining factor for root resorption. This indicates that force-induced root resorption is dependent on more than one endocrine system.

In addition to parathyroid hormone, bone resorptive activity is also regulated by L-thyroxine. Patient with untreated hyperthyroidism show increased bone resorption. The administration of high dose of thyroxine in rats has been shown to increase bone resorption, in contrast to low dose administration, which was found to reduce periosteal resorption. Pournia et al. also found that thyroxine administration seems to lower the frequency of root resorption in rats. Shirazi et al. evaluated the effect of thyroxine hormone on OTM in rats and found that administration of 20/mg/kg i.p. / day L-thyroxine significantly increased the amount of OTM and the extent of root resorption decreased with thyroxine administration.

PTH is secreted by parathyroid glands, regulated by plasma Ca²⁺ concentration; there is no trophic hormone for it. The PTH receptor is a G protein coupled receptor which on activation increases cAMP formation and intracellular Ca²⁺ in target cells. In bone the target cells appears to be the osteoblasts because PTH receptors are not expressed on the surface of osteoclasts. It has been proposed that PTH-osteoblast complex some how increases the activity of osteoclasts as well as the birth rate of bone remodeling units in which osteoclasts precursors are recruited.

Experiments have shown that PTH can induce bone resorption that would increase the rate of OTM. Soma et al. evaluated the effect of local and chronic application of PTH on tooth movement and found that local injection of PTH in a slow release formulation is applicable to orthodontic therapy.

It is suggested that thyroid and parathyroid function is an important clinical factor in patients undergoing orthodontic treatment. Orthodontist should take a thorough history of the patients to determine whether they are on any hormonal supplementation drugs as it might adversely affect the treatment. Administration of thyroxine can be considered in some patients, especially in those who show beginning root resorption, or those who have low thyroid function.

VITAMIN D:

Vitamin D is the collective name given to antirachitic substances synthesized in the body and found in foods activated by UV radiation. The role of Vit. D in the maintenance of Ca homeostasis in human beings has been well documented. It is a steroid hormone that has specific receptors in many target organs and tissues. It exerts its actions by activating DNA and RNA within the target cell to produce proteins and enzymes that can be used in bone resorption process. In particular, the active form of Vit.D, 1,25 dihydroxy cholecalciferol is the most potent stimulus of osteoclastic activity known. It is also involved in the formation of osteoclasts from precursor monocytes.
Calcitriol enhances resorption of calcium and phosphate from bone by promoting recruitment and differentiation of osteoclast precursors in bone remodeling units, but mature osteoclasts lack Vit.D receptor. Though osteoblastic cells express Vit. D receptor and respond to it, calcitriol appears to help bone mineralization indirectly by maintaining normal plasma calcium and phosphate concentration. Its action is independent of but facilitated by PTH.

Collins et al.\(^6\) found on histologic levels an increase in the number of mononuclear osteoclasts recruitment and activation resulting in bone resorption on pressure side upon injection of Vit.D metabolite 1,25D into Pdl. Yamamoto et al.\(^7\) found that injections of 1,25(OH\(_2\)), did not change serum Ca, PO\(_4\), and ALPase activity and there were no apparent clinical or microscopic side-effects. Nevertheless Vit. D (1,25(OH\(_2\)),D\(_3\)) enhances the re-establishment of supporting tissues, especially alveolar bone of teeth, after orthodontic treatment.\(^{58}\)

**ESTORGEN:**

It has become increasingly evident hat estrogen is the most important hormone to affect bone metabolism in women. The various cytokines involved in bone resorption are inhibited by estrogen. Since mechanically induced bone modeling and remodeling are essential for orthodontic tooth movement, the response to orthodontic force may vary depending upon the phase of menstrual cycle.

Zhao Q et al.\(^{44}\) explored the influence of OTM on estrous cycle and estrogen and found that estrous was the appropriate time for orthodontic force. In another study Jin Z et al.\(^{70}\) suggested that estrogen promoted the alveolar bone forming and inhibited bone resorption. Haruyama et al.\(^{11}\) also concluded that cyclic changes in the estradiol level may be associated with the estrous cycle dependent variation in tooth movement through its effect on bone resorption.

Osteoporosis is commonly seen in the postmenopausal women due to the deficiency of estrogen. In order to evaluate the two most commonly used drugs for osteoporosis Wagle et al.\(^{72}\) determined the effects of FOSAMAX and EVISTA on OTM. Fosamax (alendronate) and Evista (raloxifene) showed evidence of preventing bone resorption. Alendronate inhibits orthodontic activity but not osteoclast recruitment, while raloxifene regulates osteoclastic activity by binding and modulating estrogen receptors to affect osteoclast number and activity. The author concluded that orthodontic treatment may be contraindicated when taking these drugs.

Estrogens are commonly recommended for contraception. Moreover in orthodontic clinics, there are more female patients than male patients. Also there is an increase in the number of adult female patients seeking orthodontic treatment worldwide. Orthodontist should pay special attention and should take this factor into consideration as then drugs have shown to reduce the velocity of O.T.M by inhibiting bone resorption.

**ANDROGENS:**

Androgens are the substances which cause development of secondary sex characters in the castrated men. Anabolic steroids are used by the athletes during the period of training which are supposed to have higher anabolic and lower androgenic activity. As then drugs also inhibit bone resorption, it may affect the duration of the orthodontic treatment. Therefore a thorough history regarding the use of such drugs should be taken from the adult males.

**CONCLUSION:**

Since orthodontist plays a pivotal role in clinical pharmacology in the dental practice, they should have an understanding of the fundamentals of drug therapy. Orthodontist should be able to converse with patients about medications prescribed for them, including reviewing potential adverse effects, drug interactions, and how to take the medication. A thorough medical history should be reviewed with the patient, including any prescription, and over the counter products, as many patients use drugs on daily basis which have therapeutic as well as adverse effects.

Drugs like NSAID's, Bisphosphonates, vitamin D metabolites, fluorides can decrease the velocity of tooth movement. On the contrary drugs and systemic factors like eicosanoids, corticosteroids, thyroid and parathyroid hormones can increase the velocity of tooth movement. Orthodontist should be aware of such medications so that treatment plan best suited for the individual patient could be made and keeping the mechanics as simple as possible.

**REFERENCES:**

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Near-end of Treatment Panoramic Radiograph in the Assessment of Mesiodistal Root Angulation


This study aimed to test the hypothesis that there is no difference between the mesiodistal root angulation and the mesiodistal root angulation as measured on the panoramic radiograph. This was evaluated using a typodont dentition set into Class I occlusion.

Wire struts were placed on the buccal surface of each tooth to represent their long axes and the each the dentition was fixed into a natural skull for imaging. The radiographic and true mesio-distal angulation of each tooth to the horizontal reference plane was measured. The measurements were repeated after altering the mesiodistal root positions to a more mesial and more distal position.

Only 26.7% of the root angulations were within the clinically acceptable angular variation range of ±2.5°. The greatest variation in the upper arch was in the canine premolar region where the roots were projected as being more divergent. The greatest variation in the lower arch occurred in the lateral incisor-canine region where these roots appeared more convergent. Radiographic distortion was statistically more in the lower than in the upper arch.

Conclusion: There is a clinically significant variation between the radiographic and the true root angulations recorded and caution is advised when interpreting mesio-distal root angulation using OPG.

Torque expression of self-ligating brackets

Hisham M. Badawi, Roger W. Toogood, Jason P.R. Carey, Giseon Heo and Paul W. Major.

This study measured the difference in third-order moments that can be delivered by engaging 0.019x0.025 - in stainless steel archwires to 2 active self-ligating brackets (In-ovation and Speed) and two passive self-ligating brackets (Damon 2 and Smart Clip) using a novel torque measurement device.

There was a significant difference in the engagement angle between the two types of brackets. For the active self-ligating brackets, torque started to be expressed at 7.5° of torsion and at 15° for the passive self-ligating brackets. The torque expression was higher for the active self-ligating brackets at clinically usable torsion angles (0-35°). The passive self-ligating brackets started producing moments at high torsion that cannot be used clinically.

Thus the clinically applicable range of torque activation and torque control was greater for the active self-ligating brackets.

Botulinum toxin type A (Botox) for the neuromuscular correction of excessive gingival display on smiling (gummy smile)

Introduction: Previously, botulinum toxin type A (BTX-A) (Botox; Allergan, Irvine, Calif) was shown to be effective in reducing excessive gingival display in 5 patients with gummy smiles. This study was conducted to determine whether the doses and the primary injection sites used in the pilot study for the correction of gummy smiles provide consistent, statistically significant, and esthetically pleasing results.

Methods: Thirty patients received BTX-A injections to reduce excessive gingival display. Gingival display was defined as the difference between the lower margin of the upper lip and the superior margin of the right incisor. Patients were followed at 2, 4, 8, 12, 16, 20, and 24 weeks post-injection, with changes documented by photographs and videos. At week 2, the patients rated the effects of BTX-A. A group of specialty clinicians also evaluated the effects of BTX-A.

Results: Pre-injection gingival display averaged 5.2±1.4mm in the 30 patients. At 2 weeks post-injection, mean gingival display had declined to 0.09mm (±1.06mm) in 30 patients (t=26.01, P<.00001). The average lip-drop at 2 weeks was 5.1mm for 30 patients. Gingival display gradually increased from 2 weeks post-injection through 24 weeks, but, at 24 weeks, average gingival display had not returned to baseline values. Based on predictions from a third-order polynomial equation, the baseline average of 5.2mm would not be reached until 30 to 32 weeks post-injection. Patients and specialty evaluators rated the effects of BTX-A as highly favorable.

Conclusions: BTX-A injections for the neuromuscular correction of gummy smiles caused by hyperfunctional upper lip elevator muscles was effective and statistically superior to baseline smiles, although the effect is transitory.