EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 7
185-194
Year: 2017

EFFECT OF MEDICATIONS IN ORTHODONTICS – A LITERATURE REVIEW

[1]Dr. Praveen Kizhakool* MDS, [2]Dr. Shobha Sundareswaran MDS, [3]Dr. Praveen Santhakumaran Nair MDS, [4]Dr. Latheef Vadakkepediyakkal MDS and [5]Dr. Sreehari Sathyanathan MDS

[1]Senior Lecturer in Orthodontics, Govt. Dental College, Calicut, Kerala, India.
[2]Professor and Head, Department of Orthodontics, Govt. Dental College, Calicut, Kerala, India.
[3,4]Associate Professor, Department of Orthodontics, Govt. Dental College, Calicut, Kerala, India.
[5]Assistant Professor, Department of Orthodontics, Govt. Dental College, Calicut, Kerala, India.

***Corresponding Author: Dr. Praveen Kizhakool**
Senior Lecturer in Orthodontics, Govt. Dental College, Calicut, Kerala, India.

Article Received on 15/05/2017 **Article Revised on 05/06/2017** **Article Accepted on 26/06/2017**

ABSTRACT
The percentage of adults seeking orthodontic therapy has considerably increased during the last two decades. Many of these adults as well as younger patients may be on medications for various systemic diseases or local problems. Apart from the target tissues, these drugs will have a potential effect on paradental tissues as well, thus modifying their responses to orthodontic treatment. It is absolutely important for the orthodontist to be aware of the effect of these drugs for a successful outcome during orthodontic treatment. This review focuses on published data regarding the influence of each of these medications during orthodontic treatment. The effect of these medications from an orthodontic perspective has been presented in tabular format also for ready reference

KEYWORDS: Medication, Orthodontic tooth movement, Calcium regulators, Drugs.

INTRODUCTION

Orthodontic tooth movement (OTM) takes place due to the remodelling of paradental tissues caused by the mechanical force. It is associated with the release of various inflammatory mediators, neurotransmitters, growth factors and other cytokines. Initiation, maintenance, and cessation of tooth movement are mediated by these factors. Sometimes these molecules can cause unwanted side effects like pain and root resorption.

Many orthodontic patients especially adults may be on dietary supplements or medications for systemic problems. Some of these drugs have profound effects on short and long term outcomes of orthodontic treatment.[1]

MEDICATIONS

Eicosanoids

Arachidonic acid is a fatty acid called Eicosatetraenoic acid obtained directly from diet or by conversion of the essential fatty acid linoleic acid. Metabolites are also called EICOSANOIDS. They are a group of signalling molecules derived from arachidonic acid by numerous enzymatic reactions involved in regulation of many processes, regulatory pathways, and various pathologic conditions.

There are four classes of Eicosanoids: leukotrienes, thromboxanes, prostacyclins, and prostaglandins. Leukotrienes are the only eicosanoids converted from arachidonic acid by action of enzyme lipoxygenase. The other three, also called 'prostanoids', are converted from arachidonic acid by the actions of cyclooxygenases 1,2 and 3. (COX 1,2,3). COX-1 mediates synthesis of prostaglandins responsible for protection of stomach lining, whereas COX-2 is induced during inflammatory reactions, mediating synthesis of prostaglandins responsible for pain.

Leukotrienes (Table 1)

Leukotrienes play an important role in inflammation, allergies, and diseases like asthma.
Their effects can be counteracted by

1. Blockage of leukotriene receptors: montelukast and zafirlukast
2. Inhibition of leukotriene synthesis by selective blocking of lipoxygenase: zileuton.

This results in inhibition of bone resorption & stimulation of bone deposition, thereby influencing orthodontic tooth movement

The net effect of inhibition of leukotriene synthesis might be the same as that of blocking leukotriene receptors. Hence pharmaceuticals such as zileuton, montelukast, and zafirlukast might decrease rate of OTM.[2]

Thromboxanes (Table 1)
Thromboxanes act as vasoconstrictors and facilitate platelet aggregation. They are found in increased amounts in oral cavity under inflammatory conditions, e.g. in deep periodontal pockets. Thus inhibition of thromboxane synthesis by drugs like NSAIDs might inhibit rate of OTM.[3]

Prostacyclins (Table 1)
The effects of prostacyclins are opposite to those of thromboxanes on platelet aggregation and vasodilation. They act as vasodilators and prevent platelet aggregation. Synthetic prostacyclin (epoprostenol) or analogues such as iloprost are used for treatment of ischemic conditions and pulmonary arterial hypertension. Hence the effects of prostacyclins and thromboxanes on OTM are comparable, although their effects on platelet aggregation and vasodilation are opposite. Therefore, administration of prostacyclin analogue iloprost and thromboxane analogue U 46619 increases synthesis of prostaglandins, thereby indirectly affecting rate of OTM. They both increase rate of OTM.[3]

Prostaglandins
Prostaglandins play an important role in inflammation, platelet aggregation, peripheral nerve endings, and calcium homeostasis. Synthetic prostaglandin analogues, such as misoprostol, are used for prevention of peptic ulcers and induction of labour.

Exogenous prostaglandin (PGE2) (Table 1)
The effect of exogenous prostaglandins on OTM was studied in monkeys. In a split-mouth design, canine retraction was performed after extraction of first premolars. The results revealed a faster OTM at experimental sides.[4] Exogenous PGE2 increased rate of OTM significantly, in a dose-dependent manner.[5, 6]

An indirect way to influence PGE2 synthesis is a diet rich in omega-3 fatty acids. After 5 weeks of this diet, rats showed lower arachidonic acid and PGE2 concentrations in lipids extracted from alveolar bone than after a diet rich in omega-6 fatty acids. Orthodontic incisor separation with a force of about 56cN was significantly slower in animals receiving diet rich in omega-3 fatty acids.[7]

Exogenous Prostaglandin (PGE1) (Table 1)
Effects of exogenous PGE1 (alprostadil) and its synthetic analogue misoprostol on OTM[8] had the following effects

- ✓ Stimulates synthesis and secretion of mucus lining gastrointestinal tract.
- ✓ Increases mucosal blood flow
- ✓ Increases OTM.

It is co-prescribed with NSAIDS to prevent gastric ulceration.

Non Steroidal Anti-inflammatory Drugs (NSAIDs)
NSAIDs are the most important class of prostanoid synthesis inhibitors. They have analgesic, antipyretic, and anti-inflammatory effects, and are prescribed for conditions like rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, headache, migraine, postoperative pain, & for prevention of cardiovascular diseases and colorectal cancer. All NSAIDs suppress production of prostanoids (thromboxanes, prostacyclins, and prostaglandins) because of their inhibition of COX-1 and COX-2, essential for synthesis of prostanoids. COX-1 is a constitutive form, whereas COX-2 is inducible.

Molecular mechanism behind inhibition of tooth movement by NSAIDs involve elevation of levels & activity of matrix metalloproteinases (MMPs-9 and -2), & collagenase, followed by reduction in pro-collagen synthesis; essential for bone and PDL remodelling. This occurs due to inhibition of COX activity, leading to altered vascular and extracellular matrix remodelling, and reduced pace of tooth movement.[9] based on chemical composition NSAIDs can be divided in to different groups.

Salicylates (Table 1)
Acetylsalicylic acid is the first discovered and most widely used NSAID. It inhibits both types of COX in a non-competitive and irreversible way. E.g. Aspirin.

It has been observed that Acetylsalicylic acid at low doses does not reduce rate of tooth movement with mild forces.[10] But high dosage acetylsalicylate decreases rate of OTM.[11] Copper salicylate reduces OTM.[12]

Arylalkanoic acids
Includes Indomethacin and diclofenac sodium.

Indomethacin (Table 1)
Indomethacin causes reduction in bone turnover & rate of OTM in miniature pigs.[13] A single dose of indomethacin in rats, cats and miniature pigs resulted in significant short-lasting inhibitory effect on mesial movement of molars.[14, 15] Hence, indomethacin can be stated to significantly reduce rate of tooth movement.

Diclofenac sodium (Table 1)
Attempted tipping of first molars by a force of 50 or 100cN in rats along with injections of diclofenac (10mg/kilogram at days 1 and 3**)**, stopped OTM completely.[16]

Arylpropionic acid (Table 1)
Administration of ibuprofen also significantly reduced tooth movement.[11,17] However, no inhibitory effect was found at low dose (10mg/kilogram/day) of flurbiprofen on mesial movement of rabbit first molars with a force of 100cN.[18] Steen Law et al. demonstrated that pre-emptive administration of 400mg ibuprofen, one hour before separator placement, decreased pain during chewing, up to 2 hours after procedure.[19] It is assumed

that pre-emptive analgesia will block afferent nerve impulses before they reach CNS, abolishing process of central sensitization.[20]

Oxicams
No experimental data are available in literature on effects of oxicams on rate of OTM.

Coxibs (Table 1)
Effect of local injections of selective COX-2 inhibitor Rofecoxib (1mg/kilogram at days 1and 3) on mesial movement of first molars by a force of 50 or 100cN in rats revealed that no OTM occurred with 50cN force, but 100cN induced mild OTM.[16]

Other analgesics
Paracetamol (Table 1)
Paracetamol (acetaminophen) is a commonly used analgesic. It lacks anti-inflammatory properties.
Significant features of Paracetamol:-

1. It has no effect on blood clotting.
2. No detrimental effects on stomach lining.
3. NSAIDS block COX-1 and/or COX-2, but Paracetamol blocks a third isoform, COX-3, expressed only in brain and spinal cord. Hence Paracetamol has minimal effect on prostaglandin synthesis.

Paracetamol does not affect rate of OTM at analgesic dosages.

Recent studies suggest that it should be the analgesic of choice for pain associated with orthodontic therapy.[11,21]

Polat et al. compared the effects of naproxen sodium (550 mg) and ibuprofen (400 mg) administered preoperatively, before arch wire placement. It was found that naproxen sodium is more effective in relieving the pain than ibuprofen, 2 h, 6 h, and even during night time after arch wire placement.[22]

Nabumetone, reduces the amount of root resorption along with the control of pain from intrusive orthodontic forces, without affecting the pace of tooth movement.[23]

Corticosteroids (Table 2)
Osteoblasts and osteoclasts express glucocorticoid receptors and are influenced by proinflammatory factors, such as IL-6 and IL-11. Glucocorticoids are prescribed for various inflammatory and autoimmune conditions & as immunosuppressive medications after organ transplantation.

Anti inflammatory effect
Has indirect blocking of phospholipase A2 and suppression of synthesis of both COX-1 and COX-2. This leads to inhibition of synthesis of prostaglandins and leukotrienes.

Action on bones
It stimulates osteoclastic activity and inhibits bone formation

Over secretion causes osteoporosis. It results from a pathologic dissociation of normal processes of bone remodelling. Patients taking corticosteroids for longer than few months should be examined for radiographic signs of osteoporosis.

Estrogens (Table 2)
Estrogens are female sex hormones that occur naturally in 3 forms.

Estradiole
First and most prominent form of estrogen produced from menarche to menopause, which aid in the regulation of oestrous cycle.

Estrone
Second form produced after menopause, when total amount of estrogens has decreased.

Estriole
expressed primarily during pregnancy.

Estrogen supplementation is used to overcome postmenopausal osteoporosis. But these increase risk of breast cancer, strokes, and cardiac problems. This led to development of specific estrogen receptor modulators such as Raloxifene, which has an estrogenic effect in bone, but reduces risk for breast cancer. Therefore, it is considered a good alternative for hormone replacement therapy for treatment of osteoporosis.

Estrogen supplementation might slow OTM. Rate of OTM is inversely related to serum estrogen level.[24]

Calcium regulating substances
Dietary Calcium (Table 2)
Low-calcium regimen will lead to a significantly higher rate of OTM than high calcium diet. Increase in number of osteoclasts and osteoblasts with low-calcium diet results in increased bone remodelling phenotype. Excessive bone resorption prevails over deposition which increases OTM.[25,26]

Vitamin D3 (1,25 dihydroxycholecalciferol) (Table 2)
Vitamin D receptors have been demonstrated not only in osteoblasts but also in osteoclast precursors and in active osteoclasts. So it can stabilise the orthodontic tooth movement by resorption and deposition. $1,25(OH)_2D3$ stimulated the rate of OTM in a dose-dependent manner favoring the coupling of formation and resorption in alveolar bone remodeling during orthodontic tooth movement.[6,27]

Parathyroid hormone (Table 2)
The tooth movement and osteoclast numbers were significantly increased in the parathyroid hormone. The

expressions of receptor activator of nuclear factor kappa B ligand and insulin-like growth factor-I was significantly stimulated by parathyroid hormone which in turn increases the orthodontic tooth movement.[28,29]

Calcitonin (Table 2)
No experimental data are available on effect of Calcitonin.

Thyroid hormones (Table 2)
The thyroid gland produces 2 hormones: thyroxine and calcitonin. Exogenous thyroxine significantly increases rate of OTM.[30] Intraperitoneal administration of thyroxine can cause a dose-dependent stimulation of molar movement in rats.[31]

Bisphosphonates (Table 3)
They are drugs used to treat bone metabolism disorders and work by inhibiting bone resorption by osteoclasts thus limiting bone destruction. They are used for prevention and treatment of osteoporosis, Paget's disease, bone metastases, multiple myeloma, bone metastasis of various cancers, hypercalcaemia, fractures and impaired bone healing.

There are 2 classes of bisphosphonates
Nitrogen containing
Non-nitrogen-containing

Bisphosphonates have a high affinity for calcium and are targeted to areas of bone resorption with hydroxyapatite activity and inhibit osteoclastic activity. So significant improvement of periodontal disease occurs. The drug has antiangiogenic properties that decrease capillary formation and blood flow leading to avascular osteonecrosis. According to BEAT, (Bisphosphonate Effect Accumulation Theory) after long term intake, programmed cell death and vascular compromised bone results. They act on different pathways, but their final effect is inhibition of bone resorption, although their effectiveness differs considerably. Studies revealed that a dose-depended decrease in the rate of OTM.[32-34] Sato et al. reported irregular ruffled borders in osteoclasts of rats administered with bisphosphonates & decrease in subcellular localization and expression of both vacuolar types H (+) –ATPase and Cathepsin K, enzymes essential for bone resorption.[35]

Long-term use of bisphosphonates can cause osteonecrosis in alveolar bones. In a study on effect of zoledronate, complete cessation of OTM was reported in 1 patient.[36]

Doxycycline (Table 3)
Doxycycline reduces root resorption, without influence on alveolar bone by reduction in number of odontoclasts, osteoclasts, and mononuclear cells, thus slowing bone remodelling & pace of OTM.[37]

Drugs used for managing TMJ disorders
Muscle relaxants like cyclobenzaprin (Flexerol; 10mg thrice daily), tricyclic antidepressants like amitryptilin (Elavil;10mg, at night), and benzodiazepins like diazepam (Valium;5mg, at night) prescribed in TMJ disorders can cause xerostomia, thus affecting oral hygiene & increasing risk of caries & periodontitis.[38]

Drugs in Rheumatoid arthritis (Table 3)
It is an immune-mediated inflammatory synovitis that invades and destroys extracellular matrices of joints, cartilage and bone. Specific CD4+ T cells mediate immune response following an unknown exogenous or endogenous antigen. Consequently recruited monocytes, macrophages, and fibroblasts produce cytokines such as tumor necrosis factor (TNF) alpha and interleukin-1 within synovial cavity, ultimately triggering the production of matrix metaloproteinases (MMPs) and osteoclasts, causing irreversible damage to soft tissues and bones.

Drugs used in Rheumatoid Arthritis include immunomodulatory agents(Leflunomide), TNF antagonists (Etanercept, Infliximab, Adalimumab) or interleukin antagonists(Anakinra).

Leflunomide modulates nuclear factor kappa B, tyrosine kinases in signalling pathway, interleukin-6, MMPs and PGE2, which are essential for bone remodelling.

TNF-alpha antagonists block TNF-alpha in inflammatory cytokines. Anakinra inhibits interleukin-1 which is important for inflammatory response and induction of interleukin-6 and COX-2.[39]

Hence all these drugs influence inflammatory response, reducing bone remodelling, & thereby tooth movement.[40]

Drugs in Seizure disorders
These are characterized by sudden, involuntary, time-limited alterations in neurologic function resulting from abnormal electrical discharge of cerebral neurons.

Treatment involves multiple anticonvulsant medications like Valproic acid, Phenytoin and Gabapentin. Valproic acid induces gingival bleeding with minor trauma & Phenytoin induces gingival hyperplasia with involvement of interdental papilla, making application of orthodontic mechanics, as well as maintenance of oral hygiene difficult. Gabapentin produces xerostomia.

However orthodontic treatment is not contraindicated in these patients.[41]

Drugs in Asthma
Asthma is characterised by episodic narrowing of airways resulting in breathing difficulties and wheezing. Orthodontic treatment is not advisable in patients with frequent flare-ups. For patients at low to moderate risk,

morning appointments with short waiting times are advised. Patient should have his/her inhaler present at time of appointments.[42]

Asthma involves periodic production of proinflammatory cytokines in airway mucosa and skin. Primed leukocytes derived from these tissues travel through circulation into tissues surrounding orthodontically treated teeth. Consequently, these patients are at a high risk for developing root resorption. Hence low forces are to be prescribed.[43]

Chronic use of steroid inhalers results in oral candidiasis and xerostomia. Adequate Oral hygiene measures, topical fluoride application, appropriate antifungal agents and salivary substitutes should be used.

Drugs in Childhood cancer (Table 3)
It is now estimated that one in every 900 young adults between ages of 16 and 44 is a survivor of childhood cancer.[44] Numerous patients attend orthodontic clinics for treatment. Orthodontists should be aware of ensuing adverse reactions. There may be disturbances in dental & general body growth & development.

Patients previously on cyclophosphamide, and busulfan belong to high-risk group for orthodontic treatment. These drugs damage precursor cells involved in bone remodelling.[43]

Patients on cyclosporin A (immunosuppressant) also belong to high-risk group. This drug causes gingival hyperplasia.[44]

Drugs in Psychiatric problems
Medications for Attention-deficit/hyperactivity disorders, depression, eating disorders, anxiety disorders, & oppositional defiant/conduct disorders have influences on dental care.

1) Attention deficit hyperactivity disorder
It is treated with CNS stimulants, like methyl phenidate, dextroamphetamine, atomoxetine, buproprion, clonidine, guanfacine. These drugs may impact patient compliance & oral hygiene.[45]

2) Depression
Is managed with antidepressants and mood stabilizers. Though these patients are concerned about their appearance, they are non-compliant.

3) Anxiety disorders or psychological stress
Managed with benzodiazepines. These patients are concerned about treatment outcomes, but may disrupt office visits. Psychiatric disorders of developmental origin (exautism) are treated with second-generation neuroleptics (exaloanzipine). They have unreasonable worries, inflexibility, odd behavior and misbehavior with staff. Hence staff should be educated about possible behavioural alterations and management strategies.[45]

Psychological stress affects hypothalamic–pituitary–adrenal (HPA) axis and immune system. Modification of immune function by stress may impact osteoclasts and odontoclasts & may cause excessive root resorption.[43]

Psychological stress may lead to partial/total loss of scalp hair (alopecia areata and alopecia totalis). Davidovitch et al. reported a case of an adolescent orthodontic patient with a normal medical background who developed alopecia totalis caused by psychological stress evoked by orthodontic treatment.[46]

Immunosuppressant drugs
Patients with chronic renal failure/kidney transplants and on immunosuppressant drugs might encounter problems during orthodontic treatment.

Cyclosporine A produces severe gingival hyperplasia, making treatment & maintenance of oral hygiene difficult. It is advised to defer orthodontic treatment for first 6 months in such patients. Treatment is started after proper oral hygiene maintenance & surgical removal of excessive gingival tissue.

Fixed appliances should be kept for a minimum period. Use of removable appliances is not recommended.[47]

Alcohol abuse (Table 3)
Alcoholism may lead to liver cirrhosis, neuropathies, osteoporosis and spontaneous bone fractures. Circulating ethanol inhibits hydroxylation of vitaminD3 in liver, impeding calcium homeostasis. Parathyroid hormone is secreted, causing resorption of mineralized tissues.

Chronic alcoholics receiving orthodontic treatment may develop severe root resorption.[48]

Echistatin and RGD peptides (Table 3)
Dolce et al. reported that integrin inhibitors like echistatin and RGD peptide agents perturb bone remodelling, reduce tooth movement.[49] Echistatin also decreases root resorption.[50]

Relaxin (Table 2)
A pregnancy hormone released just before childbirth for widening birth canal. It regulates vasotonus, plasma osmalility, angiogenesis, collagen turn over, and renal function.[51] Relaxin influences soft tissue remodelling and mediators stimulating osteoclast formation.[52]

Administration of human relaxin on rats accelerates early stages of OTM.[53]

Relaxin promotes remodelling of gingival tissue during extraction space closure, orthopedic expansion in non-growing patients (reduces tension of stretched soft-tissue) and after orthognathic surgery.[54]

Relaxin causes disorganization of PDL, tooth rnobility, and reduced yield load, strain, and stiffness.

Fluorides

Fluoride is one of the trace elements having an effect on tissue metabolism. Fluoride increases bone mass and mineral density, and because of these skeletal actions, it has been used in the treatment of metabolic bone disease, osteoporosis. Caries treatment with sodium fluoride may delay orthodontic tooth movement and increase the treatment time.[55] Sodium fluoride has been shown to inhibit osteoclastic activity.[56]

CONCLUSION

It can be seen that orthodontic treatment responses may be drastically modified due to systemic consumption of various medications by the patient. It is extremely important for the orthodontist to be aware of the effects of each of these drugs before deciding to accept these individuals for orthodontic correction. Careful documentation of the history helps the orthodontist to precisely plan treatment for a successful outcome. The dictum should be "*RECORD, MONITOR AND PROCEED WITH CAUTION"*

Table 1: Published studies on Prostaglandins and NSAIDs with their orthodontic inferences

Medication	Author	Inference
Exogenous PGE 2	*Yamasaki K et al JDR 1982*[4]	Increases the rate of OTM
	Leiker BJ et al AJODO 1995[5] *Kale S et al AJODO 2004*[6]	Rate of OTM increased significantly in a dose-dependent manner
	Seifi M et al EJODO 2003[57]	Stimulated the mesial molar movement
	Kokkinos PP et al 1995[7]	Omega -3 fatty acids lower the concentrations of arachidonic acid and PGE2, lower the rate of OTM
Exogenous PGE 1	*Kehoe MJ et al Angle Orthod 1996*[8]	Misoprostol (synthetic analogue of PGE1) increases the rate of OTM
	Yamasaki K et al AJODO 1984[58]	Multiple local injections of PGE1 increases the rate of OTM - Human study
Thromboxane	*Gurton AU et al Angle Orthod 2004*[3]	Increases the rate of OTM
Prostacyclin	*Gurton AU et al Angle Orthod 2004*[3]	Prostacyclin analogue iloprost and the Thromboxane analogue U 46619 increases the rate of OTM
Leukotriene	*Mohammed AH et al AJODO 1989*[2]	Leukotriene inhibitors such as zileuton, montelukast, zafirlukast decrease the rate of OTM
Salicylates	*Wong A et al AJODO 1992*[10]	Low dose salicylates along with mild forces does not affect OTM
	Arias OR et al AJODO 2006[11]	High dose salicylates along with high forces decrease the rate of OTM
Indomethacin	*Giunta et al AJODO 1995*[13]	Causes reduced bone turn over, so a decreased rate of OTM
	Kleber BM et al 1991[12]*; Zhou D et al 1997*[14]*; Chumbley AB et al AJODO 1986*[15]	Reduces the rate of OTM
Diclofenac sodium	*De Carlos F et al AJODO 2006*[16]	Diclofenac injection completely stopped the OTM
Ibuprofen	*Vayda P et al JDR 2000*[17] *Arias OR et al AJODO 2006*[11]	Reduces the rate of OTM
Flurbiprofen	*Sandy JR et al EJODO 1984*[18]	At low dose no inhibitory effect on the rate of OTM
Coxibs	*De Carlos F et al AJODO 2006* [16]	No OTM occurred with a mild force, at higher forces induced OTM ,that also less than control with no medications
Paracetamol	*Arias OR et al AJODO 2006*[11] *Roche JJ et al Angle Orthod 1997*[21]	Does not affect the rate of OTM. Analgesic of choice for managing pain associated with orthodontic therapy

Table 2: Published studies on Steroids, Hormone, Calcium regulators and Fluorides with their orthodontic inferences

Cortisone	*Ashcraft MB et al AJODO 1992*[59]	Due to defective remodelling significant increase in the rate of OTM with a faster relapse rate
Prednisolone	*Kalia S et al Orthod Craniofac Res 2004*[60]	Has no effect on rate of OTM
Estrogen	*Schwartz JE et al AJODO 2005*[24]	The rate of OTM was inversely related to the estrogen serum level
Dietary calcium	*Midgett RJ et al AJODO 1981*[25] *Goldie RS et al AJODO 1984*[26]	Increases in the number of osteoclasts and osteoblasts with a low-calcium diet resulting in increased bone remodeling phenotype in which excessive bone resorption prevailed over deposition which in turn increases the OTM
Parathyroid hormone	*Soma S et al J Bone Miner Res 1999*[29]	Significant stimulation of rate of OTM in dose depended manner by exogenous PTH
	Fan Li et al AJODO 2013[28]	Increases the rate of OTM by increasing the number of osteoclast and growth factors
Vitamin D3	*Takano-Yamamoto T et al JDR 1992*[27] *Kale S et al AJODO 2004*[6]	Stimulated the rate of OTM in a dose-dependent manner favoring the coupling of formation and resorption in alveolar bone remodeling during orthodontic tooth movement
Thyroxin	*Verna C et al EJODO 2000*[30]	Increases the rate of OTM
	Shirazi M et al J Clin Pediatr Dent 1999[31]	Dose dependent stimulation of OTM
Calcitonin	*No experimental data on OTM*	
Relaxin	*Gameiro et al., 2007*[52] *Liu et al 2005*[53] *Nicozisis et al. 2000*[54]	Influences soft tissue remodeling, stimulate osteoclast formation and accelerating the early stages of OTM
Fluorides	*Hellsing E et al EJOD0 1991*[55]	Decreases the rate of OTM

Table 3: Published studies on Anti arthritic and Anti cancer drugs, Alcohol abuse and Echistatin with their orthodontic inferences

Bisphosphonates	*Adachi H et al. J Dent Res 1994*[32] *Liu L et al EJODO 2004*[33] *Igarashi K et al, AJODO 1994*[34]	Decrease the rate of OTM in a dose depended manner, riserdronate : most effective in inhibiting OTM
	Rinchuse DJ et al. AJODO 2007[36]	Bisphonates (zoledronate): complete cessation of OTM
	Igarshi K et al. JDR 1996[61] *Adachi H et al, JDR 1994*[32]	Dose- depended reduction of the root resorption
Doxycycline	*Mavragani M et al EJODO 2005*[37]	Low doses reduces the resorption of bone and roots, ultimately slowing down the bone remodelling and thereby reduces the pace of tooth movement
Rheumatoid arthritis Drugs Leflunomide TNF alpha antagonists Anakinra	*Bartzela et al AJODO 2009*[40]	Influence the inflammatory response following force application, reducing the pace of bone remodeling, thereby tooth movement.
Anticancer drugs	*Davidovitch Z et al 2000*[43]	Damage to precursor cells involved in bone remodeling process thereby complicating tooth movement.
Alcohol abuse	*Davidovitch Z et al 1996*[48]	High risk of developing severe root

		resorption during the course of orthodontic treatment
Echistatin	*Dolce C et al JDR 2003*[49]	Perturb bone remodeling and reduce tooth movement at a local level.
	Talic NF et al AJODO 2006[50]	Decrease in root resorption following orthodontic force application

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