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Effect Of Hormone on Orthodontic Tooth Movement: A Review

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ABSTRACT

Hormones have an important influence on the rate of tooth movement, and information on their consumption is essential to adequately discuss treatment planning with patients. Orthodontic tooth movement results from the response of the periodontal tissue to orthodontic force, which leads to modeling and remodeling of the surrounding alveolar bone. The response is considered to occur through the activation of specific signaling pathways, many of which are known, all acting to ultimately result in tooth movement. The rate at which tooth movement occurs is dependent upon the ability of these pathways to effect metabolism of bone by the two main cell types responsible for tooth movement: osteoblasts and osteoclasts. GH can affect craniofacial growth and tooth formation and eruption. Therapeutic administration of eicosanoids resulted in increased tooth movement, whereas their blocking led to a decrease. Corticosteroid hormones, parathyroid hormone, and thyroxin have all been shown to increase tooth movement. Estrogens probably reduce tooth movement, although no direct evidence is available. Vitamin D3 stimulates tooth movement, and dietary calcium seemed to reduce it. Bisphosphonates had a strong inhibitory effect. This article covers each aspect of hormonal influence on orthodontics

Keyword: *Hormone, Orthodontics, Tooth Movement, Craniofacial*

1. INTRODUCTION

Orthodontists increasingly see patients that use medication for prevention or treatment of various diseases on a regular basis. In the USA, the National Drug Early

Warning System (NDEWS) reports data and trends showing that prescription drug

abuse explodes. Among prescription medication users, about half used concurrently

over-the-counter medications and/or dietary supplements.[1] It is known that medication may have side effects intervening with orthodontic treatment. Orthodontists should be aware of that, as it may result in increase or decrease in the rate of orthodontic tooth movement (OTM) or other unwanted side effects that should be discussed with the patients .[2]

Recently, the effects of different types of medication on biological processes

related to orthodontic tooth movement have been reviewed [1 ,3,4].

Most of these reviews discuss the possible effects of medication on biological processesrelated to OTM. [4,5]Briefl y, they conclude that the principal trigger for OTM is probably strain of the periodontal ligament cells, the bone-related cells, and theextracellular matrix. This strain subsequently leads to multiple changes in gene

expression in the cells by interactions between cells and extracellular matrix,

whereby integrins play an important role. A variety of cell-signaling pathways is

activated, which ultimately leads to stimulation of periodontal ligament turnover as

well as localized bone resorption and bone deposition. Many of these processes can

be modulated by systemic or local application of medications and the intake of

dietary supplements, such as vitamins and minerals, suggesting that they may have

a stimulatory or inhibitory effect on OTM [5,6,7]. In most cases, these

authors distinguish two categories of effects: those related to general bone physiology in terms of bone density, bone mineralization, bone turnover rate, and osteoclastdifferentiation, on one hand, and on the other hand, clinical side effects

induced by medications, such as gingival hyperplasia, xerostomia, and external root resorption.[8\

The endocrine system constitutes endocrine glands which are situated in different parts of body.[9\The functions of these glands are mediated by chemical substances which are called chemical messengers or chemical mediators or first messengers or hormones. The endocrine glands are also called as ductless glands because the hormones secreted by them are directly release into blood.[3,9\

In June 1905, Ernest Starling, a professor of physiology at University College London, UK, first used the word 'hormone' . Starling (1905) defined the word, derived from the Greek meaning 'to arouse or excite', as “the chemical messengers which speeding from cell to cell along the blood stream, may coordinate the activities and growth of different parts of the body”.[10]

Orthodontic tooth movement results from the response of the periodontal tissue to theorthodontic force, which leads to modeling and remodeling of the surrounding alveolar bone. The response is considered to occur through the activation of specific signaling pathways, many of which are known, all acting to ultimately result in

tooth movement. The rate at which tooth movement occurs depends on the ability of these pathways to realize bone metabolism by the two main cell types responsible for tooth movement: osteoblasts and osteoclasts.[3,5,6,11,12]

Hormones have an important influence on the rate of tooth movement, and information on their consumption is essential to adequately discuss

treatment planning with patients. This is especially important in dentistry because many of the patients attending dental clinics face stressful situations.[7]

Awareness is therefore necessary on the risks and difficulties that may arise during the dental and orthodontic management of patients with endocrine disorders and most common oral manifestations.[2,3]

Hormones, calcium and calcium regul,ators such as exogenous parathyroid hormone

(PTH), and thyroxine stimulated OTM in a dose- dependent manner.

Treatment with insulin delayed OTM, while relaxin might have a positive effect

on relapse, following OTM, because it modulated collagen metabolism. Estrogen

supplementation used to overcome postmenopausal problems might slow down

OTM, but there was no experimental evidence. Progesterone, bisphosphonates

(BP), and local injection of vitamin D 3 delayed OTM. Medications may infl uence

OTM, and for this reason, adequate information on their consumption is essential

for orthodontic treatment planning.[12,13,14]

Close communication with the endocrinologist is essential to provide quality care to orthodontic patients. A complete understanding of the patient’s medical condition can help an orthodontist plan and execute treatment effectively6. Knowledge of the physiological processes and potential risks during orthodontic therapy can aid in planning mechanics and employing suitable appliances.[2,11,12]

This multidisciplinary approach to treatment can prove to be a significant benefit in terms of regular appointments and follow ups with monitoring of disease control or progression.[12,14,15]

Most of the functions of nervous system are executed by hormonal substances, and endocrine functions are controlled by nervous system. The endocrine system constitutes endocrine glands which are situated in different part of body.[12] The functions of these glands are mediated by chemical substances which are called chemical messengers or chemical mediators or first messengers or hormones. The endocrine glands are also called as ductless glands because the hormones secreted by them are directly release into blood.

This article covers each aspect of hormonal influence on orthodontics.

GLUCOCORTICOIDS

The adrenal cortex secretes steroidal hormones which have glucocorticoid, mineral ocorticoid and weakly androgenic activities. Conventionally, the term 'corticosteroid' or 'corticoid' includes natural gluco- and mineralo-corticoids and their synthetic analogues. By the middle of 19th century it was demonstrated that adrenal glands were essential for life. Later it was appreciated that the cortex was more important than the medulla. A number of steroidal active principles were isolated and their structures were elucidated by Kendall and his coworkers in the 1930s.[3]However, the gate to their great therapeutic potential was opened by Hench (1949) who obtained striking improvement in rheumatoid arthritis by using cortisone. The Nobel Prize was awarded the very next year to Kendall, Reichstein and Hench.[12]

The corticoids (both gluco & mineralo) are 21 carbon compounds having a cyclopentanoperhydrophenanthrene (steroid) nucleus. They are synthesized in the adrenal cortical cells from cholesterol. Adrenal steroidogenesis takes place under the influence of ACTH which makes more cholesterolavailable for conversion to pregnenolone and induces steroidogenic enzymes.[12,13,14,16,17]

Since adrenal cortical cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis. The circulating corticosteroids inhibit ACTH release from pituitary as well as CRH production from hypothalamus and thus provide negative feed back regulation of the hypothalamopituitary adrenal (HPA) axis.[18]The normal rate of secretion of the two principal corticoids in man is—Hydrocortisone—10–20 mg daily (nearly half of this in the few morning hours). Aldosterone — 0.125 mg daily.[19]

Corticosteroids form a class of steroid hormones, produced in the adrenal cortex. Some corticosteroids, the glucocorticoids (cortisone, cortisol, prednisolone, and methylprednisolone) are involved in the control of carbohydrate, fat, and proteinmetabolism. They are also participated in bone physiology, but their mode of action is not yet completely elucidated. Osteoblasts and osteoclasts can

expressglucocorticoid receptors under the influence of pro-inflammatory factors, such as IL-6 and IL- 113. Glucocorticoids are prescribed for a variety of inflammatory and(auto)immune conditions, including rheumatoid arthritis, dermatitis, allergies, and asthma. They are also used as immune suppressive medications after organ transplantation. Their anti-inflammatory function is based on the indirect blocking of phospholipase A2 and the suppression of the synthesis of both COX-1 and COX-2. This leads to an inhibition of the synthesis of prostaglandins and leukotrienes[17,18,19]

Their immuno suppressive action is due to the inhibition of interleukins and IFN-ã. Other

corticosteroids (mineralocorticoids), such as aldosterone, controlmainly electrolyte and water levels by promoting sodium retention in thekidneys.1-3Corticosteriods are drugs that are used in a wide range of medical conditions. They are known to affect the rate of tooth movement. When given in low doses of 1mg/kg of body weight it is seen that the orthodontic tooth movement is decreased as the osteoclastic activity gets suppressed and in high doses of 15mg/kg of body weight it is seen to increase and cause rapid tooth movement as the osteoclastic activity increases,. [17,18,19]

In 2004 Kalia and colleagues , had evaluated the affect of short and long term corticosteroid therapy on the orthodntic tooth movement in rats. The results of the study was found that in the group of acute administration of corticosteroids the rate of tooth movement had slowed down.]10,12,13] Thereby, patients who are on short term administration of corticosteroids it is better to delay or postpone the orthodontic treatment. However, the study also shows that in case of chronic treatment the rate thetooth movement increased. Thus, in patients who are on long term corticosteroid therapy like chronic asthmatics the orthodontic treatment can be done with minimal adverse effects and with a expectation of faster tooth movement.

GLUCOCORTICOIDS

Cortisone

Acts rapidly but has short duration of action. In addition to primary glucocorticoid, it has

significant mineral ocorticoid activity as well.

Used for:

-Replacement therapy—20 mg morning + 10 mg afternoon orally.

-Shock, status asthmaticus, acute adrenal insufficiency— 100 mg i.v. bolus + 100 mg 8 hourly I. v.infusion.

The effect of cortisone on OTM was investigated in rabbits. Cortisone acetate was injected at a dosage of 15 mg/kg/day for 4 days before, as well as during the application of an orthodontic force of approximately 100 cN for a period of 14 days. Compared to controls, this regime led to a significantincrease in the rate of OTM. Also, the relapse rate was faster in the

experimental than in the control animals .. [13,17,18,19]

Prednisolone

Methylprednisolone

Mineralocorticoids

Triamcinolone

It is 4 times more potent than hydrocortisone, also more selective glucocorticoid, but fluid

retention does occur with high doses. Has intermediate duration of action: causes less pituitaryadrenal suppression when a single morning dose or alternate day treatment is given. Used for allergic, inflammatory, autoimmune diseases and in malignancies: 5–60 mg/day oral, 10–40 mg I. m., intra articular; also topically.4-5In a rat study was tested the effect of two dosages of prednisolone (0.13 and 0.67 mg/kg/day) administered through the drinking water over a period of 14 days. It show eda dose- dependent suppression of OTM2. In another study, prednisolone was administered at 1 mg/kg/day in rats for an induction period of 12 days, followed by a subsequent experimental period of 12 days.

During the latter phase of the study, the first molar was moved mesially with a force of 30 cN. This therapy had no significant effect on the rate of OTM .. [14,18,19]

Methylprednisolone

Slightly more potent and more selective than prednisolone: 4–32 mg/ day oral.

Methylprednisolone acetate has been used as a retention enema in ulcerative colitis. Pulse therapy with high dose methylprednisolone (1 g infused i.v. every 6–8 weeks) has been tried in non responsive active rheumatoid arthritis, renal transplant, pemphigus, etc. With good results and minimal suppression of pituitary adrenal axis.6The initial effect of methylprednisolone pulse therapy (MPPT) is probably due to its anti inflammatory action, while long term benefit may be due to temporary switching off of the immuno damaging processes as a consequence of lymphopenia and decreased I g synthesis. 6 In one of the experimental groups, an induction period of 7 weeks was used, where upon OTM was performed for 3 weeks with a force of 25 cN in which methylprednisolone was given at a dosage of 8 mg/kg/day. This led to an increase in the rate of OTM. However, in another experimental group where the induction period was omitted, methylprednisolone had no effect on the rate of OTM. [19,20,21]

Triamcinolone

Triamcinolone is a synthetic corticosteroid. It is used to treat various ophthalmologicand skin

conditions or to relieve mouth sores. The derivative triamcinoloneacetonide is one of the ingredients of Ledermix, used during root canal treatment. 7The effect of triamcinolone acetonide on OTM has recently been studied in rabbits. The drug was injected at a dose of 1 mg/kg/day for 21 days, and the incisors were moved by a force of 50 cN for the same period. A significant increase in OTM was found. The differences in the results of the studies on glucocorticoids probably reflect the combined effects of the applied dosages, the induction periods, and the relative anti-inflammatory activity of the glucocorticoids tested. [19,21,22,23]

GROWTH HORMONE

GH is a protein hormone, secreted by the acidophils of the anterior pituitary. GH secretion is pulsatile, and the secretory bursts occur especially at early hours of sleep and throughout the night. GH has no specific target organ. It's an anabolic hormone to which every organ system responds. It doesn't show any direct action on bones, but acts through a substance called somatomedin. GH stimulates liver to secrete somatomedin.[11,12]

Humans have 2 types of somatomedin. These are:

1.Insulin like growth factor I (IGF-I), also called somatomedin-C.

2.Insulin like growth factor II (IGF-II)

Among these two IGF-I act on the bones and cause the growth and other affects on bones. GH carries out most of the metabolic functions through the somatomedin IGF-I.GH is the main regulator of childhood and adolescent growth. GH pulse amplitude is increased in growth spurt with simultaneous increase in plasma IGF-I concentrations.[11,13]

Dental delay is always less pronounced than delay in height or bone age. The dentition seems to be harmoniously delayed, so that all studied components of dental development (primary root resorption, secondary tooth formation, and eruptive movement) display the same degree of retardation. GH influence on growth starts after 9 months of age so their effect on growth of primary teeth is very little known.[24]

It is suggested that individuals undergoing orthodontic treatment and who use GH, require longer intervals between the

applications of light orthodontic forces, since

the new bone formation process is delayed, and because they present more intense bone resorption, particularly in the initial stages of administration of the drug. Another recommendation would be to begin orthodontic treatment after the initial stage of GH administration, since it stimulates bone formation only after 12 to 24 months. Radiographic control must be frequently made to assessthe status of bone resorption.[25]

2. HYPERSECRETION OF GROWTH HORMONE;

Gigantism

A cephalometric study was done on two female patients suffering from gigantism, due to excess of GH. Anterior facial heights were relatively the largest cephalometric dimensions, followed by posterior facial height. Posterior cranial base were long, but anterior cranial base were normal. Face was broad with pronounced zygomatic arches but relatively normal dental occlusion.[11,12]

Acromegaly

Serum levels of IGF-I in these patients were very high; mean value 10-fold higher than normal adults. Mandibular growth is gradual and often noted by the dentist when crossbite has developed. The calvarium, hands and feet grow by bone apposition. The tongue grows, and general visceral growth has been documented. Cartilaginous tissue enlarges, ribs thicken and costochondral cartilage has been shown to be hypertrophic.9.10 Hypertrophic articular cartilage and the growth of chondrocytes in the articular cartilage may give rise to acromegalic arthropathy. Mandibular growth in acromegaly results from both appositional growth and hypertrophic changes in the condylar cartilage.[12,25-29]

GH Deficiency

Children gave big skull with babyish face, but in contrast their intelligence is normal for their age. Cephalometric studies in such children have shown small size of anterior and posterior cranial bases and smaller mandibular dimensions, small posterior facial height, and small posterior mandibular height. This has been shown in a study done over 13 untreated patients with pituitary deficiency the cephalometric findings were low as compared to normal, N-ANS being the lowest.[11-13,26,28]

Thyroid Hormones

Thyroid hormones are recommended for the treatment of hypothyroidism and used after thyroidectomy in substitutive therapy. Thyroxin administration lead to increased bone remodeling, increased bone resorptive activity, and reduced bone density.[30] Effects on bone tissue may be related to the augmentation of interleukin-1 (IL-1B) production that thyroid hormones induce at low concentrations, cytokine stimulate osteoclast formation and osteoclastic bone resorption.

The speed of orthodontic tooth movement increased in patients undergoing such medication. Low-dosage and short-term thyroxin administrations are reported to lower the frequency of “force induced” root resorption. Decrease in resorption may be correlated to a change in bone remodeling process and a reinforcement of the protection of the cementum and dentin to “force induced” osteoclastic resorption.

Calcitonin has the opposite effects. It is a peptide hormone secreted by the thyroid, which decreses the intestinal calcium and renal calcium reabsorption. In bones, calcitonin inactivates osteoclasts and hence inhibits bone résorption. It also stimulates the bone forming activity of osteoblasts.[31-33]

The thyroid hormone increases the speed of orthodontic tooth movement in patients undergoing such medication. Low dosage and short-term thyroxine administration are reported to lower the frequency of "force-induced" root resorption. Decrease in resorption may be correlated to a change in bone remodeling process and a reinforcement of the protection of the cementum and dentin to "force-induced" osteoclastic resorption.[34]

Parathyroid Hormone

The function of parathyroid is to maintain a normal level of diffuse calcium and phosphorus in the blood plasma and to keep constant the ratio of these minerals to each other. [10]The act as a check on the thyroid gland parathyroids are important organs in ca metabolism and play a leading role in calcification of teeth. However, once the teeth are formed, there is no evidence found of calcium withdrawal from teeth due to parathyroid disturbances.[12] The parathyroids are important in regulating blood ca level, but have little or no direct effect on growth or tooth eruption.[10-13]

PTH affects osteoblasts’ cellular metabolic activity, gene transcriptional activity, and multiple protease secretion. Its effects on osteoclasts occur through the production of RANK-L Recepor activator of nuclear factor kappa -B ligand), a protein playing a crucial role in osteoclasts’ formation and activity. In 1970s, animal studies demonstrated that PTH could induce an increase in bone turnover that would accelerate orthodontic tooth movement. More recently, an increased rate of tooth movements has been observed in rats treated with PTH, whether administered systemically or locally.[35[These results

indicate that orthodontists should take note of patients being treated with PTH, as for example, in cases of severe osteoporosis.[36]

Parathyroid hormone affects both bone resorption and formation process. If PTH appears around bone cells, the effect of bone will be resorption. By contrast, low level of PTH results in bone formation. When the calcium level in blood decreases, PTH will stimulate osteoclastic activity to increase calcium and phosphate absorption in the gut, and decrease calcium excretion and tubular phosphate reabsorption in the kidney. This plays a role as regulator of calcium homeostasis by PTH .[10,12,13,35]

Insulin

Insulin is a polypeptide hormone secreted by the beta cells of the Langerhans islets of the pancreas. A normal non-obese man secretes approximately 50U/day, with a basal plasma insulin concentration of 10-50 microns/ml. Its main function is to maintain the blood glucose level.[10] Insulin deficiency produces a clinical state called diabetes mellitus, while its excess leads to hypoglycemia. Diabetes mellitus is diagnosed in 3-4% of the population treated in our day-to-day orthodontic practice. The orthodontic practitioner should have a basic knowledge and understanding of this disease and of its impact on the oral cavity, as well as of its consequences upon the dental treatment.[10-13]

Informed on the oral complications induced by diabetes mellitus, the dental practitioner should consider them when treating a DM patient; the key to any orthodontic treatment is a good medical control. No orthodontic treatment should be performed in a patient with uncontrolled diabetes. There is no treatment reference with regard to fixed or removable appliances [37]

A good oral hygiene is especially important when fixed appliances are used, as they may increase plaque retention, which could more easily cause tooth decay and periodontal breakdown. Daily rinses with fluoride-rich mouthwash can provide further preventive benefits. Candida infections may also occur in the oral cavity, so that they should be well monitored. Diabetes related microangiopathy can occasionally appear in the periapical vascular supply, resulting in unexplained odontalgia, percussion sensitivity, pulpitis, or even loss of vitality in sound teeth. Especially in orthodontic treatments involving force application for moving teeth over a considerable distance, the practitioner should regularly check the vitality of the teeth involved. It isadvisable to apply light forces and not to overload the teeth .[13]

Holtgrave and Donath, who studied the periodontal reaction to orthodontic forces, evidenced retarded osseous regeneration, weakening of the periodontal fibers and microangiopathies in the gingival areas. In adults, before starting the orthodontic treatment, the orthodontist should obtain a full-mouth (periodontal) examination and evaluation of the need for periodontal treatment. [13,37-40]

The periodontal condition should be improved before staring the treatment and should be monitored regularly. Maintaining a strict oral hygiene is important, by a proper use of toothbrush, interdental toothbrush and chlorhexidine mouthwash. [10-13]

To minimize the neutralizing effect of toothpaste on the chlorhexidine molecule, an at least 30-min interval should be left between tooth brushing and chlorhexidine rinse As no upper age limit for orthodontic treatments is any longer valid today, the practitioner will see both type1 and type2 DM patients. Type2 patients can be considered more stable than type1 ones, as hypoglycemic reactions are more frequent in these patients. If a patient is scheduled for a long treatment session, he or she should be advised to eat a usual meal and take the medication as usual.{66.67} At each appointment, the orthodontist should confirm the meal and medication, to avoid a hypoglycemic reaction in the office. DM patients with good metabolic control, without local factors, such as calculus, and with a good oral hygiene, have a similar gingival status as the healthy ones, consequently they can be treated orthodontically [37-41]

Diabetes was induced by weekly intraperitoneal injections of 120 mg/kg of streptozotocin.

Another group was treated with insulin after diabetes induction. Tooth movement was evoked by a mesial force of 35 cN. OTM in the diabetic animals was faster than in the controls7-8.Treatment with insulin resulted in slower OTM than in the normal animals. One other study was performed in rats with a comparable experimental design. However, in this study, OTM itself was not measured, but the presented histomorphometric data point in the same direction: increase in bone remodeling indiabetic animals and return to about normal values after insulin treatment.[10,12,13,42]

Sex Hormones

Sex hormones play a role of bone metabolism. Estrogen has a direct effect on bone. It preserves calcium in bone by suppressing the activation frequency of bone remodeling. The remodeling activation will increase when menopause starts and the result is rapid bone loss leading to symptomatic osteoporosis.

Estrogen directly stimulates the bone-forming activity of osteoblasts, so it is reasonably to expect a slower rate of orthodontic tooth movement.[13]

Androgens also inhibit bone resorption and modulate the growth of the muscular system. Thus, the excessive use of these

drugs by athletes, in an attempt to achieve better athletic scores, may affect the duration and results of the orthodontic treatment[7,12].

These are female sex hormones that present in three forms; estradiole, estrone and estriole. Estrogens enhance bone formation by stimulating bone forming activity of osteoblasts and inhibit tumour necrosis factor,[43] interleukin 1and 6 which are involved in bone resorption.[44,45] Thereby these are going to affect orthodontic tooth movement. Celebi et al reported orthodontic tooth movement association with ovarian activity. PGE2 and interleukin 1 are increased in ovariectomized and anestrous cat groups resulting in greater tooth movement.[46] Orthodontic tooth movement is faster and root resorption is less in ovariectomized female rats and orchiectomized male rats.[47] Xu X et al also found that tooth movement is faster when estrogen levels are low. Therefore orthodontic treatment should be planned according to menstrual cycle.[48] Another study showed association of tooth movement with ovulation and menstruation. Orthodontic tooth movement would be faster if orthodontic force applied during menstruation as estrogen levels are low at this time and tooth movement would decrease during ovulation. So this study suggested that orthodontist may accelerate tooth movement by doing activation of orthodontic appliances during menstruation. This method will be safer and effective for female patients.[49]

Vitamin D

Vitamin D (cholecalciferol) is a pleiotropic steroid hormone and is the prohormone

of 1,25-dihydroxycholecalciferol (1,25(OH) 2 D 3). Vitamin D is rarely

found in food as D 3 in animal sources and as D 2 in vegetal sources. It regulates

calcium and phosphate serum levels by promoting their intestinal absorption and

reabsorption in the kidney. Vitamin D defi ciency is also associated with periodontal

disease, rickets, and osteomalacia as well as other autoimmune, cardiovascular,

and metabolic disorders [50]. Therapy for 1,25(OH) 2 D 3 defi ciency

involves dietary changes or taking 1,25(OH) 2 D 3 supplementation. Active vitamin

D compounds are used against osteoporosis. Hypervitaminosis D causes hypocalcemia and may lead to conditions such as anorexia, nausea, polyuria, and

eventually renal failure. It can be treated with a low-calcium diet and corticosteroids.

Several animal studies are available on the effect of topical injections of

1,25(OH) 2 D 3 on OTM. The studies vary largely in the application regimes.

Repeated injections are given in all studies, but the dosages vary. Injections of

10-100 pg/ml showed a dose-dependent increase in OTM in cats [51].

Bone remodeling, following the application of orthodontic forces, includes resorptive and bone formation phases at the alveolar process.[50] A correlation has been shown between vitamin D receptor polymorphisms and periodontitis andbone metabolism.[51]Researchers have shown that vitamin D, parathyroid hormone, and calcitonin regulate calcium and phosphorus levels.[50]In various studies, vitamin D stimulated bone resorption by inducing the differentiation of osteoclasts from their precursors and increasing the activity of existing osteoclasts.[35] One of the earlier attempts was made by Boyce and Weisbrode,56 who evaluated the effects

of calcium-rich diets and vitamin D metabolite injection on bone formation in rats. On day 1, osteoclasts in treated rats increased in comparison to controls. On days 3 and 4, the researchers observed a decrease in the number ofosteoclasts. This sequela continued through days 6, 8, and 10. Meanwhile, in the same experimental period, there was a substantial increase in the number of osteoblasts in treated rats compared to controls. As anticipated, the calcium and phosphorus levels were increased. Boyce and Weisbrode[56] concluded that the experimental group experienced a net increase in bone formation. Collins and Sinclair[57] demonstrated that intraligamentary injections of vitamin D metabolites cause an increase in the number of osteoclasts, and consequently in the rate of bone resorption, leading to an

increase in the rate of tooth movement during canine retraction(. Later, in 2004, Kale et al[58] compared the effect of the administration of prostaglandin and 1,25-dihydroxy cholecalciferol (1,25 DHCC) on tooth movement. Both were found to increase the amount of tooth movement significantly when compared to controls. An increase in the number of Howship lacunae and capillaries on the pressure side was

found in the experimental group. In addition, the number of osteoblasts on the external surface of the alveolar bone was

increased following the administration of 1,25 DHCC in comparison to prostaglandin administration. Thus, the authors outlined the role of 1,25 DHCC in facilitating tooth movement through the regulation of bone deposition and the resorption processes.[13,35,59]

Some investigators have suggested that in addition to faster teeth movement, localized administration of vitamin D enhances tooth position stability. Kawakami and Takano- Yamamoto50 hypothesized that calcitriol may improve bone formation and periodontal tissue remodeling by increasingosteoblastic activity, which in turn would improve the stability of the teeth position after orthodontic movement. In this

experiment, the authors divided a sample of 16 Wistar rats into experimental and control groups. In the experimental group, orthodontic elastics were inserted around the upper molars bilaterally. Every 3 days, calcitriol was injected locally and palatally to the upper molars on the right side. In the control group, calcitriol was injected locally but orthodontic elastic was not applied. The researchers found an increase in the mineral appositional rate on alveolar bone after they applied an orthodontic force and injected calcitriol in the submucosalpalatal area of the rats, who were subjected to tooth movement. On day 7, researchers reported a significant increase in the number of osteoblasts and osteoclasts at the mesial side of the interradicular septum, and on day 14 an increase in osteoblasts only. In so doing, they showed that calcitriol has a potent effect on bone formation. The authors concluded that

the use of calcitriol may promote the reestablishment of tissue

supporting the teeth after orthodontic treatment .[59,60]

Similar findings were shown by Boyce and Weisbrode,[56] who found a temporary rise in the rate of bone resorption on the first 2 days followed by a progressive rise in bone formation after 14 days of calcitriol adminstration.[50]

1, 25-dihydroxy cholecalciferol is the active metabolite of vitamin D and vitamin D plays an important role in maintainence of calcium in the body. Injection of 1,25-dihydroxy cholecalciferol into the PDL of intraligementously was done in cats for canine retraction by Collins and Sinclair [59-60]in 1988. After 21 days the teeth that had received the injections had moved 60% more than the control teeth. Well balanced bone turnover can also lead to enhanced tooth movement and this is induced by local application of vitamin D according to Kale and colleagues 200425. According to Noor Hasani and colleagues26, the canine retraction of patients who received 25pg/0.2 ml calcitriol diluted with 10% of dimethylsulfoxide (DMSO) the rate of tooth movement was 51% faster compared to the control

side.241,25(OH)2D (now known as the D hormone) has multiple biologic effects. Vitamin D (cholecalciferol) is a pleiotropic steroid hormone and is the prohormone of 1,25- dihydroxycholecalciferol (1,25(OH) 2 D 3). Vitamin D is rarely found in food as D 3 in animal sources and as D 2 in vegetal sources. It regulates calcium and phosphate serum levels by promoting their intestinal absorption and reabsorption in the kidney.25 Vitamin D deficiency is also associated with periodontal disease, rickets, and osteomalacia as well as other autoimmune, cardiovascular, and metabolic disorders. Therapy for 1,25(OH) 2 D 3 deficiency involves dietary changes or taking 1,25(OH) 2 D 3 supplementation. Active vitamin D compounds are used against osteoporosis. [59]

Hyper vitamin osis D causes hypocalcemia and may lead to conditions such as anorexia, nausea, polyuria, and eventually renal failure. It can be treated with a low-calcium diet and corticosteroids.26Several animal studies are available on the effect of topical injections of1,25(OH) 2 D 3 on OTM. The studies vary largely in the application regimes. Repeated injections are given in all studies, but the dosages vary. Injections of10-100 pg/ml showed a dose-dependent increase in OTM in cats. 26A study in young and adult rats used 20 ìl 10 ?10 or 10 ?8 mol/l in the young animals, which leads to a significant dose-dependent increase in OTM, while the same regime in adult animals showed more increase in OTM with the lowest dose (20 ìl 10 ? 10 mol/l) than with the higher dose (10 ? 8 mol/l). Also another rat study showed a stimulation of OTM after repeated injections with 20 ìl 10 ?10 mol/l vitamin D 3. [59,60]

BISPHOSPHONATES

Bisphosphonates (BPNs) have strong chemical affinity to the solid-phase surface of calcium phosphate; this causes inhibition of hydroxyapatite aggregation, dissolution, and crystal formation. Bisphosphonates cause a rise in intracellular calcium levels in osteoclastic-like cell line, reduction of osteoclastic activity, prevention of osteoclastic development from hematopoietic precursors, and production of an osteoclast inhibitory factor. Studies have shown that BPNs can inhibit orthodontic tooth movement and delay the orthodontic treatment .[61[Topical application of BPNs could be helpful in anchoring and retaining teeth under orthodontic treatment..[4,5,6[

The study of Igarashi et al showed that after giving of subcutaneousbisphosphonates for 3 weeks in rats, tooth movement was decreased by 40%. In addition, the alveolar bone adjacent to the periodontal ligament showed the reducing of osteoclasts after giving a single dose of intravenous bisphosphonate (pamidronate) during tooth movement. [61,62]Marx et al stated that bisphosphonate osteonecrosis showed the decrease of microcirculation of bone until the stage of necrosis happened. Because the osteoclast cannot absorb the mineral matrix of bone, and the capillary formation in new bone cannot be stimulated

completely, acellular and avascular bone will occur.) The typical osteonecrosis in patients who received intravenous bisphosphonate appeared as painful abscess teeth. When they are extracted, the underlying necrosis bone will be exposed, and abnormal healing causes bone loss in the future. [63]

At the present, there should be concerned about orthodontic treatment in the patients who received bisphosphonates High intravenous doses of bisphosphonates can inhibit tooth movement more than lower oral doses. Orthodontic tooth movement may increase the uptake of bisphosphonates locally, so it decreases osteoclastic activity. The result of this process shows as slower tooth movement.[5,7,18.47,48,49]

The mandible contains a large amount of cortical bone, whereas the maxilla contains

more marrow, and thus the micro circulation is more extensive. [64,65] Most early experimental research on the effect of bisphosphonates on the rate of OTM has been performed by the Mitani group. A similar model and protocol were used consistently throughout their experiments. [64,65]

They induced lateral or mesial movement in rat molars with a force of approximately 15 cN. A considerable number of studies have been published in which topical or systemic administration of bisphosphonates resulted in a dose-dependent decrease in the rate of OTM. [64,65]

This has been shown in mice, rats, and rabbits. Only few studies have been performed in orthodontic patients. They comprise case reports, case series, and retrospective cohort studies. They are rather uniform intheir conclusions, namely, the orthodontic tooth movement under bisphosphonate medication is possible, especially in low-risk patients (low dose and short period of intake). The final outcome of orthodontic treatment in these patients showed longer treatment

duration, incomplete space closure, poor root parallelism, poor incisor alignment, sclerotic areas, and wide PDL with tooth mobility in some cases. [64,65]Therefore, the altered bone metabolism and higher extent of side effects should be considered in treatment planning, especially in extraction cases or high- risk patients.

On the other hand, bisphosphonate therapy might be beneficial for orthodontic anchorage control, skeletal relapse after maxillary expansion or mandibular distraction and similar procedures. Further long-term prospective randomized controlled trials are required to assess possible benefits and adverse effects of bisphosphonate treatment, before bisphosphonates can be therapeutically used in orthodontics. [65]

A complicating factor is the increasing off-label use of bisphosphonates in children for the treatment of primary osteoporosis in conditions like osteogenesis imperfect a and Ehlers–Danlos or Marfan syndrome or even for the treatment of secondary osteoporosis associated with cerebral palsy, cystic fibrosis, anorexia nervosa, idiopathic juvenile arthritis, diabetes mellitus, and childhood cancer . [64,65]

The use of bisphosphonate therapy in pediatric patients remains controversial because of inadequate long-term efficacy and safety data. Therefore, limiting the use of bisphosphonates to those children with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass is advocated. More research is needed to define appropriate indications for bisphosphonate therapy in pediatric patients and the optimal agent, dose, and duration of use. [65-68]

3. CONCLUSION

Hormones have a great importance in the growth of the face and craniofacial structures, also they affect tooth movement during orthodontic treatment, so orthodontists must have a background of knowledge about these hormones and their impact on the movement of the teeth before starting treatment because any defect in these hormones may negatively affect orthodontic treatment. .

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Conflicts of interest

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