Review Article

Hormonal Factors Affecting Teeth Development

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Abstract:

Hormones are one of the main mechanisms that control metabolic events in the human body. Growth and development are increasing in direct proportion to the regular release of hormones at normal limits. However, imbalances in the hormonal system affect growth and development negatively.

The purpose of this review is to examine the growth-development status of the patients in pedodontic and orthodontic treatment planning; acknowledging the dentists about the effects of hormones on dental and bone development in patients with hormonal disorders, and evaluating these factors in the light of the published studies released in recent years.

In the light these data reported by these studies, it will be more accurate and reliable when children's dentists and pediatricians consider the growth and developmental stages of children during the dynamic process of accurate diagnosis and treatment.

Keywords: Hormones, Dental development, Odontogenesis, Hormonal factors

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Introduction

Development of teeth includes epithelial-mesenchymal interactions that are essential for tooth development. Different hormones involved in these interactions have been identified. The purpose of this review is to examine the effects of hormones on dental and bone development in patients with hormonal disorders and evaluating these factors in light of the published studies released in recent years.

Growth Hormone (GH)

Growth hormone releases from the hypophysis are balanced with inhibitor and stimulator effects. It stimulates by the release of growth hormone release factor hormone (GHRH) and ghrelin from the hypothalamic peptide, and somatostatin (growth hormone release inhibiting factor) inhibits it (1). It is an important hormone affecting postnatal growth and is the main hormone of bone expansion during childhood and puberty and stimulates bone mineralization and accelerates the speed of potassium and phosphor metabolism. The highest release appears during puberty, and then gradually decreases (2,3).

In case it is released much from the Hypophysis and can cause gigantism in 0-6-year-old children, and acromegaly in grown-ups. In this type of disease, the dentition will be normal only, the size/shapes of the teeth will be different (4). It is considered that GH affects teeth development in patients who have hypophysis dwarfism due to low GH release and GH insensitivity (Laron Syndrome), hypodontia, microdontia, and delayed dentition (5,6).

Kosowichz and Rzymski studied hypophysis of dwarf people and reported that GH treatment stimulated the growth and development of chins, and accelerated the maturation of the teeth. On the other hand, Sarnat et al. reported that the success of the treatment depended on the age and duration of the disease (7,8). Leche et al. studied with children who had growth disorders and observed that the dentition times were delayed in children with genetically short height or who had GH deficiency. In children who had growth delays due to other reasons, the dentition was found normal (7,9).

Zhang et al. studied with rats and reported that although GH was released as of the 16th day in the embryonic period, GH and its receptors existed in tooth tissues in earlier periods (10). In addition, GH and its receptors existed in the embryonic cap and bell stages in a form that is specific to each cell type during tooth development. This shows that GH plays an active role in intrauterine tooth development (4,10).

Zhang et al. reported that GH receptors played roles in the development of odontoblast, ameloblast, and cementoblast in rats (7,11). Becks et al. examined the physiological changes of GH in serum and concluded that it had an accelerator effect on odontoblast and ameloblast lifecycle (7).

GH increases the proliferation of the internal dental epithelial cells, dental papilla cells, and HERS cells before the differentiation of the odontoblasts. In some in vitro studies, it was reported that GH had some properties like stimulating the reproduction of osteoblast and bone marrow and inducing bone marrow markers like Gla protein and a1-procollagen (12). Similarly, it was observed that GH might stimulate the proliferation of the epithelial root cells in molar teeth buds, the differentiation of ameloblasts, and dentin matrix formation (7,13).

It was also observed that GH is influential in the enamel layer and root formation; and it was reported that it affected the thickness, shape, and appositional growth of the dentin, enamel mineralization, crown width, and root size (4,7,14).

BMP-4, which exists in the early stages of tooth formation, and BMP-2, which exists in later stages and play roles in epithelial-mesenchymal interactions, are stimulated by GH (10).

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HERS determines the dimensions of the roots by inducing odontoblasts, which are among the adjacent dental papilla cells in the epithelial diaphragm. Excessive GH activities stimulate the mitotic activity in HERS and increase the root growth. Similarly, the deficiency in GH activities causes shorter dentine roots and smaller dentine root areas (4).

Young et al. reported that the molar teeth root development stopped when the hypophysis glands of the rats were removed and started again when GH treatment was started (7,15).

In a conclusion, GH participates in all stages of dental development and determines the size of the tooth and the crown/root ratio (4).

Insulin-like Growth Factor-1 (IGF-1)

The bio-synthesis and release of IGF-1 are controlled by GH, it joins the circulation after it is produced in the front lobe of the hypophysis (adenohypophysis). It is transferred by binding to the carrier protein. IGF-1 is also produced in various organs like the liver, lungs, kidneys, skeleton muscle, and the spleen aside from adenohypophysis, and directly affects the growth cartilage (16,17).

IGF-1 release varies with the furthering age; it is low in babies and during the childhood period, at the highest level during puberty, and decreases with further age [18]. Juul et al. determined that average serum IGF-1 levels were 80-200 mg per liter in prepubertal children; increased 500 mg during puberty; decreased 500 mg after puberty until 25 years of age in a cross-sectional study (18).

IGF-1 is an important factor in the growth and development of the skeleton and many other tissues [1]. IGF-1 is produced in all of the cells that are responsible for re-modeling of bones like osteoprogenitors, osteoblasts, osteocytes, and osteoclasts (16).

In a cell culture study, it was reported that IGF-1 increased the proliferation, calcification, and mineralization of osteoblasts in all stages of tooth and bone development (1,19). Besides, IGF-1 also increased matrix production, mineralization, collagen Type-1 synthesis, and BALP activity (19,20).

Although it has not yet been clarified how IGF-1 affects the formation of the enamel and dentin, it was shown that it plays a role in the formation of mandibula and teeth (21–24).

IGF-1s have roles in the regulation and protection of proteins like collagen Type-1, osteonectin, osteocalcin, osteopontin, alkaline phosphatase (1,20,21). The majority of these proteins being present in the formation process of the teeth makes us think that IGF-1s may regulate the development of the teeth in a way that is similar to bone formation (19,21).

IGF-1 expression occurs simultaneously with the amelogenin, ameloblastin, and enamelin expression during late bell and excretion stages (16,24). IGF-1 receptor (IGF-1R) is localized in the early stages of tooth development in internal and external enamel epithelia in an immunohistochemical way, and several cells from the stellate reticulum and dental papilla are in contact with the enamel organ. In the late stages, IGF-1R exists only in several cells in dental papilla mesenchyme and dental follicle (16).

In animal studies, IGF-1 was expressed by excretive ameloblasts and odontoblasts and in mature ameloblasts, and odontoblasts (22,25).

Salih et al. showed the existence of IGF-1 in the dental lamina, oral epithelia, epithelial bud, dental mesenchyme, stratum intermedium, internal animal epithelium, and external enamel epithelium (22). IGF-1 was also observed to increase in vitro tooth volume, mitotic index, and cell differentiation (7,13,16,19,24). These data support the idea claiming that IGF-1 regulates the epithelial-mesenchymal interactions that affect growth and cell differentiation and play a role in embryonic dental development (21, 24).

The results obtained in immunohistochemical studies and in studies that were conducted within situ hybridization methods show that IGF-1 not only influences cell differentiation but also the physiological activities of

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ameloblasts and could act as an autocrine/paracrine system (21,22,24).

Thyroid Gland Hormones

The thyroid gland is located in the front side of the neck and excretes T3 (tri-iodo-trenin), T4 (thyroxin) and calcitonin hormone (26). The production of thyroid hormone is regulated by Thyroid Stimulating Hormone (TSH), which is excreted by the front hypophysis gland. When the levels of thyroid hormones decrease in blood, the hypothalamus releases Thyrotropin Releasing Hormone (TRH) and then stimulates TSH (24).

The thyroid gland regulates the metabolism speed of the body with the T3 and T4 it excretes. The thyroid gland excretes T4 at a rate of 80%, and T3 at a rate of 20%. Although T4 is the main excretion of the thyroid gland, the hormone that interacts with the cells is the T3 hormone. T4 hormone only exists in the circulation of the blood. For this reason, T4 may be converted into T3 with the help of some enzymes (27).

Calcitonin hormone is also excreted from the thyroid gland and its duty is to ensure that calcium is excreted to blood when the calcium amount decreases in the blood (22). Calcitonin affects the activity and metabolism of many cells and plays a very influential role in somatic growth (27).

"Hyperthyroidism" occurs when thyroid hormones are excreted more. In this case, increases are observed in the metabolism speed. On the other hand, the dental development is also accelerated. "Hypothyroidism" is the situation in which the thyroid hormones are excreted less due to structural or functional reasons. Hypothyroidism causes that the development of bones is paused. There are 3 types of Hypothyroidism:

Cretinism: It is the thyroid hormone deficiency in early stages of childhood. Bone development is inadequate. Shortness in height, mental retardation, rough fascial bones are observed in it.

Juvenile Myxedema: It is the hormone deficiency observed in school period children.

Myxedema: This is the Hypothyroidism observed in adulthood. It is characterized by shortness in height, increases in weight, and mental retardation that develops later (Table 1).

It was revealed that thyroid hormones have effects on endochondral ossification. It was also determined that there are further-level organization disorders in Hypothyroiditis, and the chondrocyte differentiation is inadequate. These effects are related to the increases in the mNRA expression of Parathyroid Hormone-Related Protein (PTHrP). It was also reported that the histology is mostly normal in thyrotoxic growth plaques; however, the mRNA of the PTHrP receptor has not been found yet (28–30).

Risinger and Proffit examined the human premolar teeth and observed that the eruption had a daily rhythm. The authors observed that the dentition occurred at very late hours, and teeth were inclined to be intruded at early hours in the morning. They determined that the reason was related with the status of the GH and thyroid hormones in the blood, and was not related to hemodynamic changes or functional activity (31–34).

Parathyroid Hormone (PTH)

PTH is a parathyroid hormone and is excreted from parathyroid glands. The parathyroid glands are located behind the thyroid gland and work in a way that is sensitive to the calcium levels in the body (27). When the amount of calcium decreases in the blood, parathyroid glands are stimulated; PTH is excreted and the transition from bones to blood is ensured. In addition to this, the amount of the calcium that is removed from the body in kidneys is also reduced, and thus, the calcium level in the blood is increased (35,36).

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PTH affects osteoclasts directly and increases the conversion of mesenchymal cells into osteoclasts (27).

The conversion of D vitamin into the active form in the kidneys also occurs with the PTH release. The calcium re-emission of calcium increases in the intestines with the synthesis of active D vitamin, and the level of calcium is increased in the blood (36).

When the level of calcium in the blood is high at excessive levels, less PTH is released, and the release of calcium from bones is also decreased and the removal of calcium in the kidneys is also decreased to the normal level (35).

PTH plays roles in the appositional growth of the bones. Vitamin D plays an auxiliary role in establishing the balance between module skeleton and calcium balance in enchondral bone development (36). Vitamin D is more active than parathormone in dentin and alveolar bone formation (35).

The excessive release of the parathyroid hormone is called “hyperparathyroidism”, and the insufficient release of it is called “hypoparathyroidism” (Table 2).

Furthermore, there are many effects of PTH on tooth movement. Drazek examined the changes that occurred in the alveolar bone that surrounded the incisors after the application of orthodontic force in the hyperparathyroid medium in rats. He reported that there was a destruction at a further level, atypical wide osteoclasts, increased vascularity in the neighboring area where osteoclastic activity was observed, and hyalinize bone islets in the bone to which hormone and force combination was applied together, and concluded that PTH, when applied together with orthodontic force, increased bone resorption (37). Kamata conducted a study on rats and found that osteoclastic activity decreased depending on the decrease in the PTH release; and on the other hand, the increase in the PTH level caused that there were increases in the osteoclastic activity, and decreases in the osteoblastic activity (27,38).

Parathormone-related Protein (PTHrP) is a protein from the parathormone family. It is released by cancer cells (it is the most common reason for hypercalcemia in malignity); however, it also has functions in growth-development. It regulates the enchondral bone development. It has active duties in epithelial-mesenchymal interaction (35,36,39).

Kindblom et al. reported that PTHrP increased in early puberty stages, and was released less in the stages after puberty (40).

PTHrP has critical roles in dentition. When it is not released, dentition does not occur because the bone surrounding the tooth follicle is not resorbed. PTHrP, which is excreted from tooth germs, controls the expression levels of RANKL/OPG in PDL cells and plays roles in the dentition of temporary teeth, and in the process in which the temporary teeth are resorbed and the dentition of permanent teeth occurs (35,39).

Liu et al. reported that PTHrP played anabolic roles in bones that were produced with enchondral ossification. They reported that this selective role of PTH occurred due to the differences that were specific to the area in the expression of IGF-1 and PTH receptors (35).

Gonadal Hormones

Gonadotropin- Releasing Hormone (GnRH) is excreted by neuroendocrine cells in the hypothalamus, binds to GnRH receptors, and stimulates the excretion of gonadotropic hormones (FSH, LH). It also controls the Gonad hormones and fertility. This ligand/receptor interaction stimulates the signal transfer mechanisms that perform gene transcription and also stimulates the entry of calcium into the cells through plasma membrane channels (41).

Tiong et al. reported that GnRH and its receptor were excreted during dental development in rats. GnRH participants in the enamel formation and mineralization in the tooth

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epithelia differentiates the positive cells; and fills the dental structures including ameloblasts and papillary layers (41).

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In recent studies, it was reported that GnRH existed in the development of incisors in rodents; however, it was not detected in molar teeth. Morphological changes were observed in the papillary layer in rats that did not have GnRH (41). Although it is known that GnRH is expressed from teeth, the function and signal pathway in this tissue have not been clarified yet.

Estrogens inhibit the production of several cytokines like interleukin-1 (IL-1), tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6). These cytokines play roles in bone resorption by stimulating the osteoclast formation and osteoclastic bone resorption (43).

There are studies showing that estrogens do not have anabolic effects in bone tissues, as well as some other studies claiming that these hormones directly stimulate the bone-formation activity of the osteoblasts (27,44). Although its effects on decreased bone quality in osteoporosis, the increase in the risk of breaking of long bones, and on vertebra are well-known, the regional-variational specific effects of it on oral bone quality has not been revealed clearly yet.

Estrogen deficiency increases bone resorption, and thus, leads to resorption being more than bone formation, and eventually leads to disproportional bone remodeling (45). Haruyama et al. reported that the dental activity in rats, which received the force in estrous cycles, was more than the rats which received the force in pro-estrous cycles at a rate of 33%. As a conclusion, it was determined that the estradiol hormone level in serum and the amount of dental activity were reversely proportional (46).

Yamashiro et al. investigated the effects of ovariectomy (which result in estrogen hormone deficiency) in a group of rats on orthodontic dental activity and alveolar bone formation (47). They reported that estrogen hormone deficiency accelerated orthodontic dental activity at a clear level, and this acceleration was dependent on the activation in alveolar bone transformation (27).

Sexual Dimorphism

Many authors support the hypothesis claiming that “The dental type formation in early childhood period must be less dimorphic when compared with the late childhood period”. The differences between the concentrations of the gender hormone between girls and boys increase gradually during childhood; and it was considered that this would affect the size of the teeth (48).

Guatelli-Steinberg (49) and Alvesalo (50) examined the enamel formation starting time and the mesio-distal sizes of the permanent teeth and reported that the sexual dimorphism in the teeth stemmed from the supportive effects of Y chromosome for growth and that the gender hormones had minor effects. However, their hypothesis is based on postpartum testosterone levels, they ignored the intrauterine testosterone effect (49). Since all the other teeth -except for third moral teeth- undergo morphogenesis and differentiation stages in intrauterine period, the testosterone levels before birth must be considered (49).

Zilberman et al. reported that the thickness of the dentine was more in males than females during childhood because of the effect of ychromosome on teeth development. This difference becomes clearer during puberty. However, this difference did not show any dimorphism in the size of the teeth after the tooth form was completed. This finding shows

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that gender hormones affect the tissues of the teeth (48).

Hietela et al. observed that the dentine formation was increased in the molar teeth of rats whose ovaries were removed. In this context, it is hypothesized that estrogens prevent odontoblasts, and testosterone stimulates (51).

Dempsey et al. examined the effects of prenatal diffused hormones in twins on the crown sizes of the tooth. Their study group consisting of twins from different genders, twins from the same gender, and children who were the only children in their families. They reported that there were no significant differences between the girls who had twin siblings from the opposite gender when compared with the male children, and determined that the sizes of the teeth were bigger at a significant level when compared with the twin girls and the girls who were the only daughters (52).

The measurable differences in tooth crown size between two genders show that gender hormones have effects on tooth tissues. However, Alvesalo et al. examined the tooth sizes of women who had 46xy androgen insensitivity syndrome, and reported that the sizes of the tooth were equal to those of male control group in 46xy women, and bigger when compared with the 46xx female groups (50).

Leptin and Ghrelin

It was reported in previous studies that leptin has an important role in the development of the skeleton and craniofacial structure (53). The effect of leptin on bone metabolism occur either through indirect inhibitor to bone formation or direct stimulator. It was shown in previous empirical studies that leptin inhibits bone formation over hypothalamus with the mediation of Sympathetic Neural System (54,55).

It is considered that leptin has a role in decreasing the bone mass. Increased bone mass was determined in obese patients and rats. In this context, it is considered that the cells of obese individuals resist to leptin function and disrupt the effects of leptin on bone mass (56).

The release of ghrelin is regulated by nutrition and hormonal factors. The levels of ghrelin vary according to the hours of the meals during a day, and increase before the meals, and decrease within the first two hours after meals. The inhibitor signals that decrease ghrelin release are leptin, interlökin1, and GH. Serum ghrelin level reaches peak levels between 02.00-03.00, in the morning, which is similar to GH. Aydın et al. determined the existence of Ghrelin in odontoblast and tooth pulpal tissue, and reported that it was expressed by odontoblasts (56). Ghrelin and leptin work with the "Ying-Yang" mechanism. The levels of this hormone in the blood are adjusted according to age, gender, weight, blood glucose, insulin resistance and diabetes, GH deficiency, acromegalia, hypothyroidism and hyperthyroidism, and to gastrointestinal status (56).

The fact that leptin is influential on bone metabolism makes us consider that ghrelin participates in tooth development (56,57). It is known that ghrelin have effects on common findings of hypothyroidism, hyperparathyroidism, Seckel syndrome, Turner syndrome, Bardet Biedl syndrome, Laron syndrome, rachitism due to D-vitamin, hypophysis dwarfism, osteogenesis imperfecta, premature birth and similar diseases in which developmental tooth anomalies are observed (56–58); however, there are no studies conducted to determine the relations with ghrelin (57).

Based on the participation of ghrelin in pre-dentin and dentin formation by interacting with proteins excreted by odontoblasts, its roles in bone formation and turnover, and on the similarities between anatomical, functional and developmental stages, Aydın et al. reported that ghrelin might play roles in dentinogenesis and mineralization process (56).

The saliva and plasma values of ghrelin were examined for the purpose of investigating the

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levels of the hormones that played roles in developmental tooth anomalies. Blood and saliva samples were taken from children who had amelogenesis imperfecta, dentinogenesis imperfecta and common enamel hypoplasia, and it was determined that ghrelin might form a preventive effect for mineralization; participate in enamel and dentine formation through various receptors and mechanisms; and play more than one role in tooth development (57).

Conclusion

In the light of the data reported by these studies, it will be more accurate and reliable when children's dentists and pediatricians consider the growth and developmental stages of children during the dynamic process of accurate diagnosis and treatment. Skeletal bone age, dental age, and growth development hormones must be assessed in all stages that are important for the growth and development of individuals. In planning the pedodontic and orthodontic treatments, examining the growth and development of the patient, and knowing the effects of hormones on tooth and bone development in patients who have hormonal disorders by the dentist are important for the prognosis of the treatment.

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Tables

Table 1: Oral Findings; Thyroid Hormones are not Excreted Normally (26).

Hyperthyroidism	**Hypothyroidism**
1. Accelerated eruption in children 2. Maxillary and mandibular osteoporosis 3. Growth in thyroid tissue 4. Increase in the sensitivity to cavities 5. Periodontal diseases 6. Burning mouth syndrome 7. Development of muscle tissue diseases Sjögren Syndrome and systemic lupus erythematosus	**Cretinism and Juvenile Myxedema:** 1. Delayed eruption 2. Enamel hypoplasia in dentition 3. Lack of dentition of lower chin second molar teeth 4. Front open-closure 5. Macroglossia 6. Micrognathia 7. Malocclusion **Myxedema:** 1. Thick lips 2. Disguise 3. Mouth respiration

Table 2: Oral Findings; Parathyroid Hormones are not Excreted Normally (26)

Hyperparathyroidism	**Hypoparathyroidism**
1. Dental anomalies Expanded pulpal chamber Developmental defects Changes in dentition Malocclusion 2. Brown tumor	1. Dental anomalies Artificial enamel hypoplasia Weakly calcified dentine Expanded pulpal chamber Pulpal calcifications Short roots

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3. Bone density loss 4. Soft tissue calcifications	Hypodontia Delays in dental development 2. Mandibular torus 3. Chronic candidiasis 4. Paresthesia in the tongue and lips 5. Changes in the fascial muscles

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