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Role of hormones in bone formation and resorption: A literature review

[How hormones; adiponectin, angiotensin, cortisol, erythropoietin, insulin, parathyroid hormone, oxytocin, sex hormones, affect bone remodeling]

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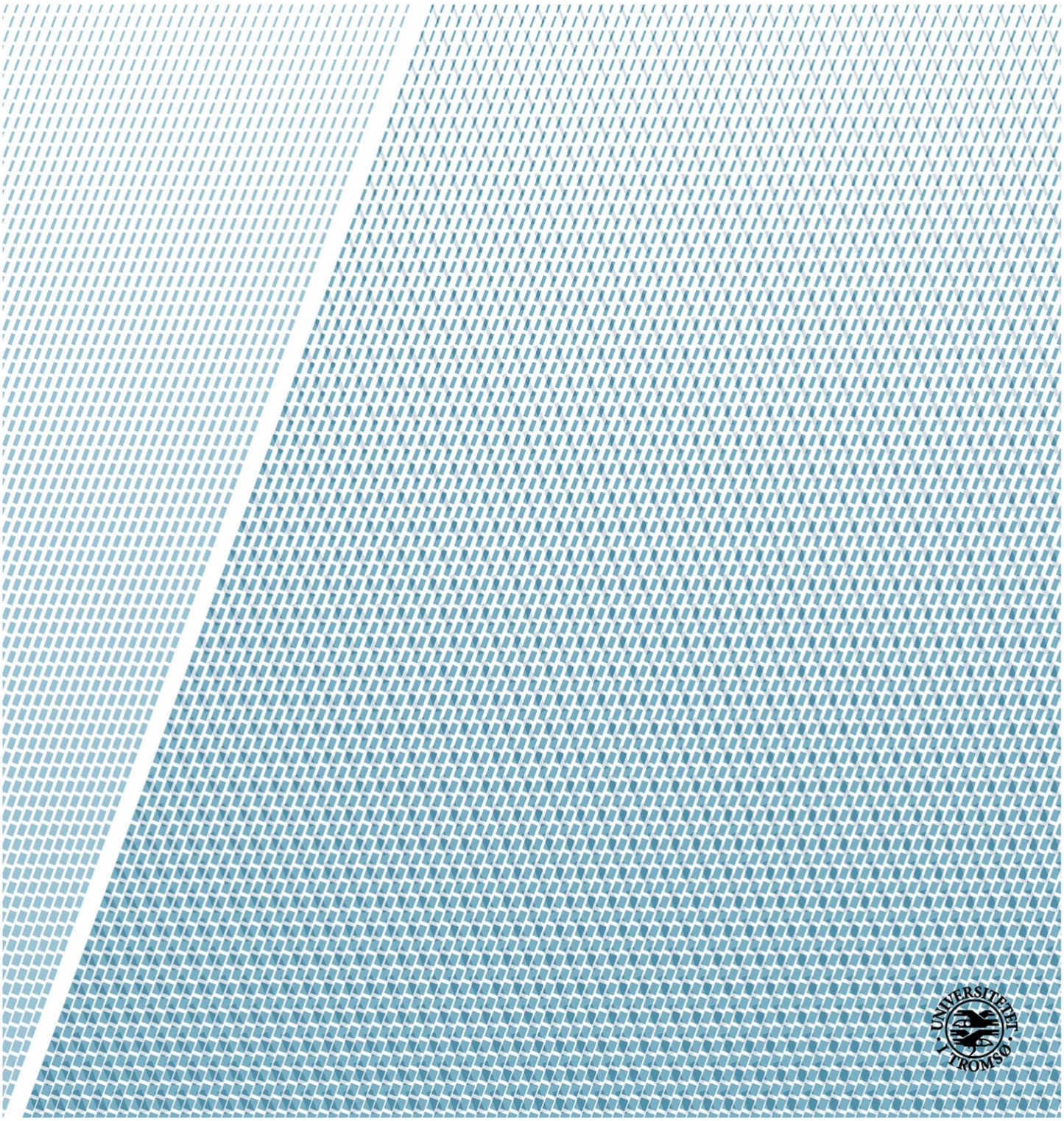

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Preface

This basis for my passion for this research derived from an experience I had after a tooth extraction, as I developed a post-ex complication. A question popped up in my head, and I wondered about the association between my female hormone replacement therapy and the complication. My interest began to grow ever since then. As the world is moving forward, more people can connect to the internet and search for the information they are passionate about. Therefore, I did sew together studies regarding this problem as well as I could. At the same time, I did explore how other hormones may impact similar problems. I hope this work will be of help to researchers and students.

I could not have achieved my success without strong advisors, support groups, and family. First of all, I would like to thank my advisors, who provided advice and guidance throughout the research process. Secondly, my mother and siblings provided me with understanding and love. Thank you for your unwavering support.

Contents

1 Abstract

Diseases causing bone resorption such as periodontitis and osteoporosis are expected to rise tremendously among older adults globally by 2050. These are multifactor diseases with hormonal involvement and may reduce quality of life. Bone formation and remodeling are complex processes which are influenced by various hormones. Studies on the role of hormones' influence on these processes are useful to develop methods for bone repair. This study aims to review various hormones that regulate the bone formation and resorption and present the role of hormones on bone remodeling and metabolism. Dry socket and bone related diseases such as periodontitis and osteoporosis are given emphasis. Herein, role of current literatures on bone formation and resorption are searched of nine hormones: adiponectin, angiotensin, cortisol, erythropoietin, estrogen, insulin, parathyroid hormone, oxytocin, and testosterone. This thesis will be a guide for the further study on specific hormone on bone metabolism in specific disease.

2 Background

Hormones are produced inside of us and dictate much of our growth, function and development. They are mentioned in advertisements, media and have been extensively researched over decades. Hormones make you stronger, exercise more efficient (1), to make you more feminine (2), regulate appetite (3), to make you happier, even change your behavior (4), to aid in birth (5) or to prevent pregnancy (6), regulate sexual, and so on (7). Hormones can even influence how you react to advertisements (8). Their functions are many and their utilizations apparently widening. Hormones seem to influence most aspects of human life and society in one way or another. The growing awareness and acceptance of gender transition has contributed to increased awareness of longtime hormone use, the need for thorough understanding of hormones' long-term effects is crucial. In the case of gender transition or certain conditions where certain hormones are lacking, it is implicated that correcting the hormonal imbalance will achieve desired physiology or restore health. A number of hormones are implicated to play a role in bone physiology, with changes in these hormones' levels, changes in bone can also be observed (9).

Bone changes, more specifically bone loss, are a limitation in dentistry as it influences treatment choices such as implant insertions and prognosis of teeth. Especially relevant may this be to periodontists and oral surgeons as they regularly deal with the most challenging cases involving bone defects. The number of dental implants placed is rapidly growing (10), and their success rate depends on available bone to be inserted into (11). Osteoporosis and periodontitis are global diseases affecting bone, with the latter one resulting in severe bone loss if left untreated, making implant placement challenging. Osteoporosis' impact on the survival of dental implants is debated, however, observations point toward these patients possibly having a slight disadvantage for their implants' survival (12, 13). The gold-standard technique to rebuild adequate bone levels is the autologous bone graft (14). This bone graft is the one with the most reliable success, however, it is invasive as the operator needs to harvest available bone from another location from the patient and relocate the graft to the desired location. Therefore, the graft's limitations involve increased morbidity and post-operative pain, as well as limited donor sites (15, 16). Researchers are continually developing new methods to prevent bone loss and to rebuild bone in the jaw. Hormones may be a direction to explore for such new methods as several hormones are implicated in bone growth and degradation.

While hormones are used for a wide array of conditions in medicine, little is known about hormones in dentistry and their possible therapeutic applications. This review aims to provide an overview of available research on the topic of hormones and dentistry in regard to their effects on jawbone. Additionally, the authors have selected three diseases to discuss how they are influenced by hormones; osteoporosis, periodontitis and what is colloquially known as dry socket.

3 Introduction to bone

Bone is a unique organ as it functions as a scaffold for the attachment of muscles via the skeleton and as protection of vital organs (17). The skeleton consists of approximately 206 bones. Calcium phosphate is the main constituent of human bone (18). Calcium phosphate makes the bone a calcified and rigid tissue. Besides calcium phosphate, reinforcing collagen fibers; they armor the bones and make them resistant to stretching and bending (19).

Bone formation occurs during and after embryonic development. Bone formation occurs mainly by two mechanisms, intramembranous and endochondral ossification. Intramembranous ossification involves a direct formation of bone. This process results from the integration of mesenchymal cells, resulting in a number of tiny blood vessels, collagen fibers, fibroblasts, and stem cells. The stem cells (osteoprogenitor cells) will differentiate further and become osteoblast cells and later differentiate into osteocyte cells, ultimately resulting in ossification, bone formation (Figure 1) (20).

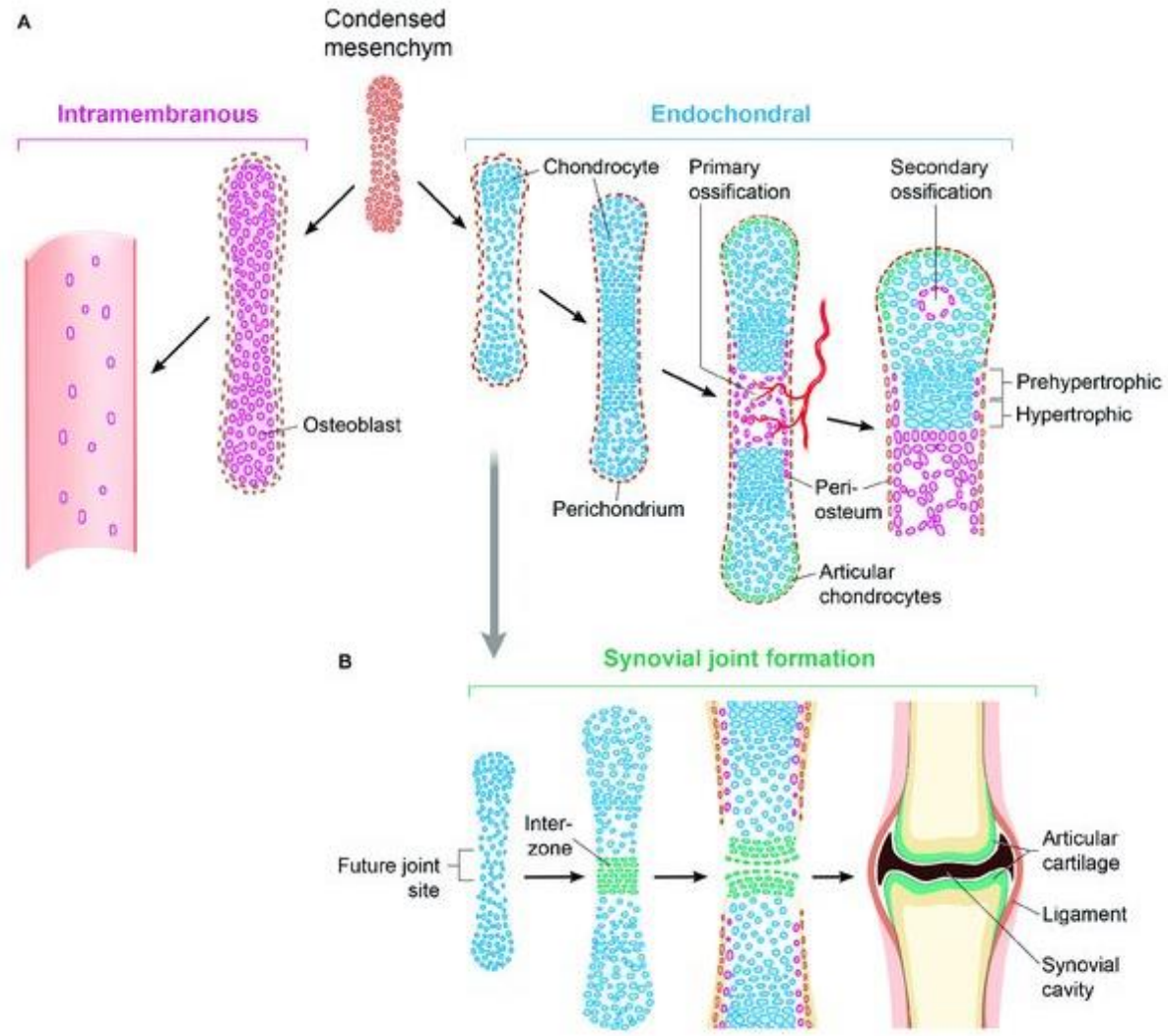

Figure 1. Intramembranous and endochondral ossification (21).

Intramembranous ossification is a process that occurs by a condensing of mesenchymal cells. Those cells will produce collagen fibers that contain tiny blood vessels, fibroblasts, and origin stem cells. Osteoprogenitor cells (origin bone cells) will differentiate more and change to osteoblasts cells. Osteoblast function is to cumulative organic substances and silt to the bone. And later, the osteoblast will change to an osteocyte. This process occurs during embryonic development. Later will most of the bone growth with a cover, periosteal new bone formation. This is important for the bone to grow wider. Intramembranous ossification occurs in flat bones, such as the mandible and parts of the skull. Intramembranous ossification doesn't occur in cartilages (Figure 1) (22).

Endochondral ossification occurs in all bones of the skeleton, except for parts of the skull, most of the mandible, facial bones, and the clavicle. A typical example is a long bone, such as the humerus or femur; their terminal ends consist of cartilage. The cartilage serves as a model for further ossification. The process begins in the cartilage, which is slowly replaced by bone tissue. This contributes to the longitudinal growth of bone as we age (23).

Bone is a living tissue richly vascularized and comprised not only of organic and inorganic substances, but cells as well. Osteoblasts, a type of cell resembling its dental counterparts the odontoblasts and cementoblasts, stem from the bone marrow's multipotent stromal cells and mesenchymal stem cells in the periosteum. The second type of bone cells are osteocytes, odontoblasts trapped in bone tissue during bone formation. The third kind of bone cells, the osteoclast, mature from hematopoietic stem cells, found in blood circulation and bone marrow, as do red and white blood cells (Figure 2). The osteoclasts are multinucleated giant cells present on the external surface of the bone (24). Thanks to these cells, bone is an ever-adapting organ with the remodeling of the skeleton to renew it and adapt to functional demands (24).

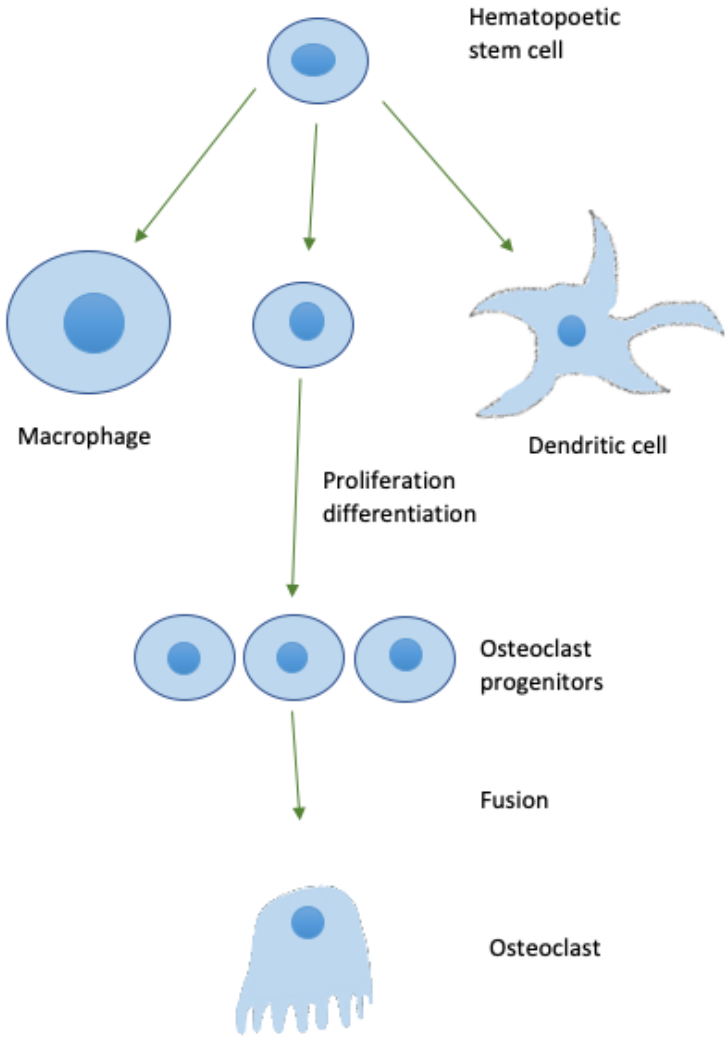

Figure 2. Overview of white blood cells derived from hematopoietic stem cells in the bone marrow (24). All blood cells are formed from the hematopoietic stem cells in bone marrow, including a subset of leukocytes, which can differentiate into macrophages, dendritic cells, or osteoclast progenitors.

The most rigid tissues in the body, namely bone tissue, enamel, and dentin, all have calcium phosphate in common (24). The calcium phosphate is formed as crystals, hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] (25). The most rigid human tissue is the tooth enamel, where the primary component is indeed the inorganic hydroxyapatite (90-92%). The organic part of the enamel consists of proteins, proteoglycans, and lipids, which represent only 1-2% of the entire weight

(26). Teeth are attached to the periodontal ligament, an apparatus of attachment between the bone of the jaw and the surface of the teeth (27). The bone of the jaw, much like most bones in the body, is structured of mainly two types of bone, compact and cancellous bone (Figure 3). Compact bone is the harder outer shell. Cancellous bone is sponge-like and makes up the inner part of the bone (28). The upper and lower jaw, the maxilla, and the mandible, together form the framework of the oral cavity containing the teeth. Only the mandible is movable and makes it possible to chew by moving up and down to crush and cut food (29).

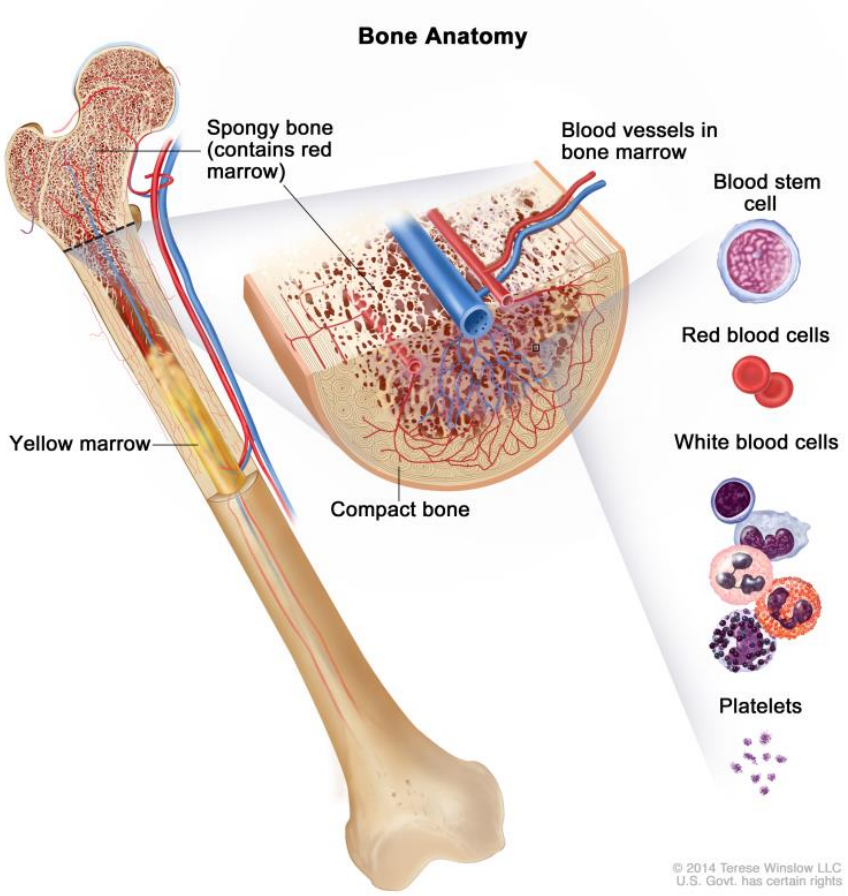

Figure 3. Anatomy of cancellous and compact bone (30).

3.1 Bone formation and resorption

Bone formation occurs when osteoblasts produce bone matrix, which later mineralizes into mature bone tissue. Osteoblasts are thus the bone-forming cells, and as paradoxically it may

seem, they are responsible for the differentiation of osteoclasts, the bone-resorbing cells. A lifelong process known as bone remodeling involves a continuous breakdown and buildup of bone tissue. The remodeling is crucial to adapt to external physical stresses and to not only repair macro-fractures but, to repair microfractures as well. The osteocytes work as load sensors, telling the other bone cells when and where to resorb and when to form (31). Remodeling may also be influenced by osteotropic hormones, such as sex hormones (24). About ten percent of the total bone mass is renewed annually (24). Alveolar bone resorption occurs typically when a tooth is lost; as stimulus sensed by receptors in the periodontal ligament is lacking, the bone does not receive any stimulation to form new bone (32). Wolff's law states that during repeated mechanical loading, the bone adapts to this loading in order to become stronger and resistant to the loading over time. Lack of loading will make the bone resorb (33). Being the bone housing the teeth gives an idea of how adaptable the teeth and surrounding bone have to be. Teeth are constantly on the move, and chewing forces are considerable. This makes jaw bone quite unique due to its high rate of remodeling (34).

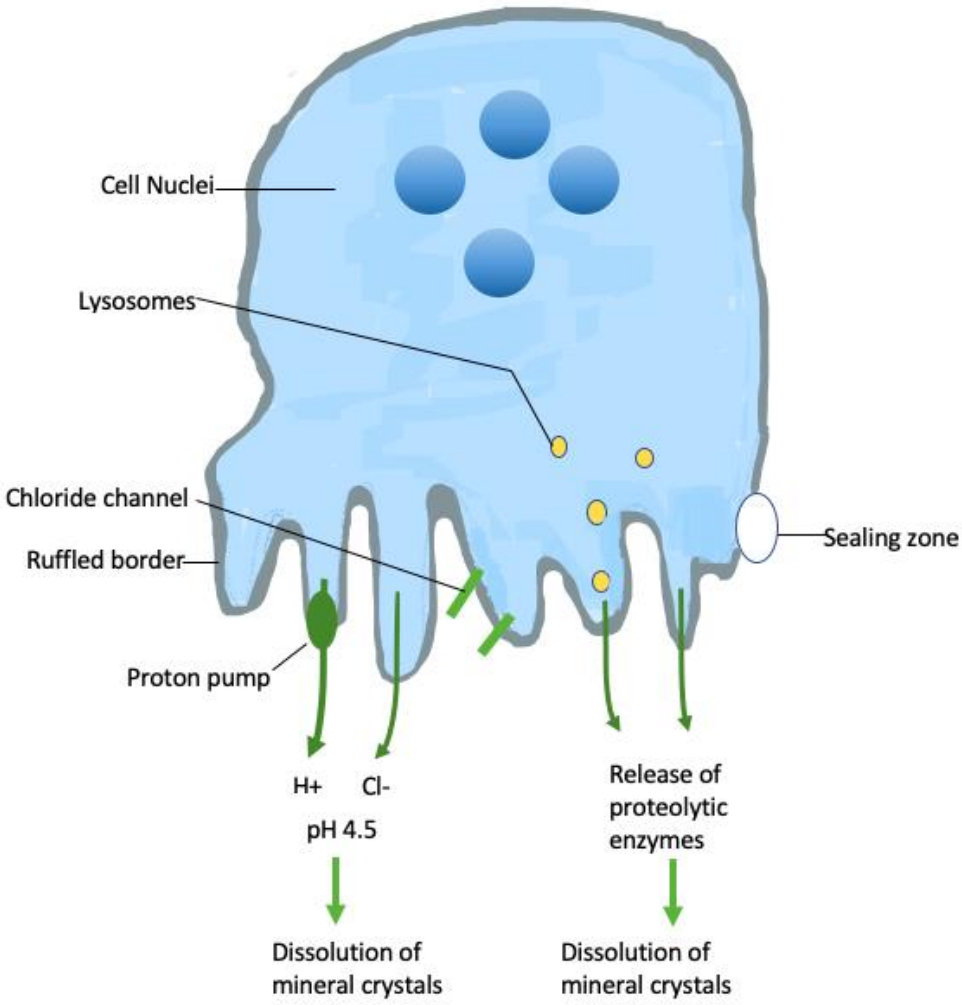

Figure 4. A multinucleated osteoclast adhering to bone tissue using a sealing zone on the cell membrane. The sealing zone is a self-organized structure on the bone. The membrane develops a ruffled border which constitutes a unique environment where the resorption takes place. Protons and chloride ions are secreted, the low pH dissolves the hydroxyapatite crystals. Proteins become accessible to proteolytic enzymes (24).

Receptor activator of nuclear factor-kappa-B ligand, or RANKL, is a protein at the surface of a number of cell types, including osteoblasts. Together with its receptor, RANK (receptor activator of nuclear factor κ B), expressed on osteoclast progenitor cells and mature osteoclasts, it is essential for bone remodeling. RANKL and RANK are regulated by several factors, including the female sex hormones; estradiol and progesterone (35). Osteoblasts can influence osteoclast differentiation, osteoclastogenesis through the pathways of RANKL and RANK (36). RANKL can be secreted, and when it binds to RANK on the osteoclast progenitor cell's surface,

it will result in further differentiation of the osteoclast, a mature osteoclast. A mature osteoclast is able to adhere to the bone by a sealing zone, a self-organizing structure of adherence to the bone, and then secrete bone-resorbing enzymes (Figure 4) (7]. As a response, osteoclasts will release a decoy receptor, osteoprotegerin (OPG). This creates a negative feedback loop (Figure 5), regulating the bone-resorbing activity. OPG will merge with RANKL to prevent its binding to RANK. This will lead to a reduced amount of mature osteoclasts. Other factors that may affect osteoclastogenesis include hyperthyroidism, lack of certain hormones, inflammatory cytokines-related syndrome, such as increased production of interleukin-1 (IL-1) or tumor necrosis factor-alpha (TNF-alpha).

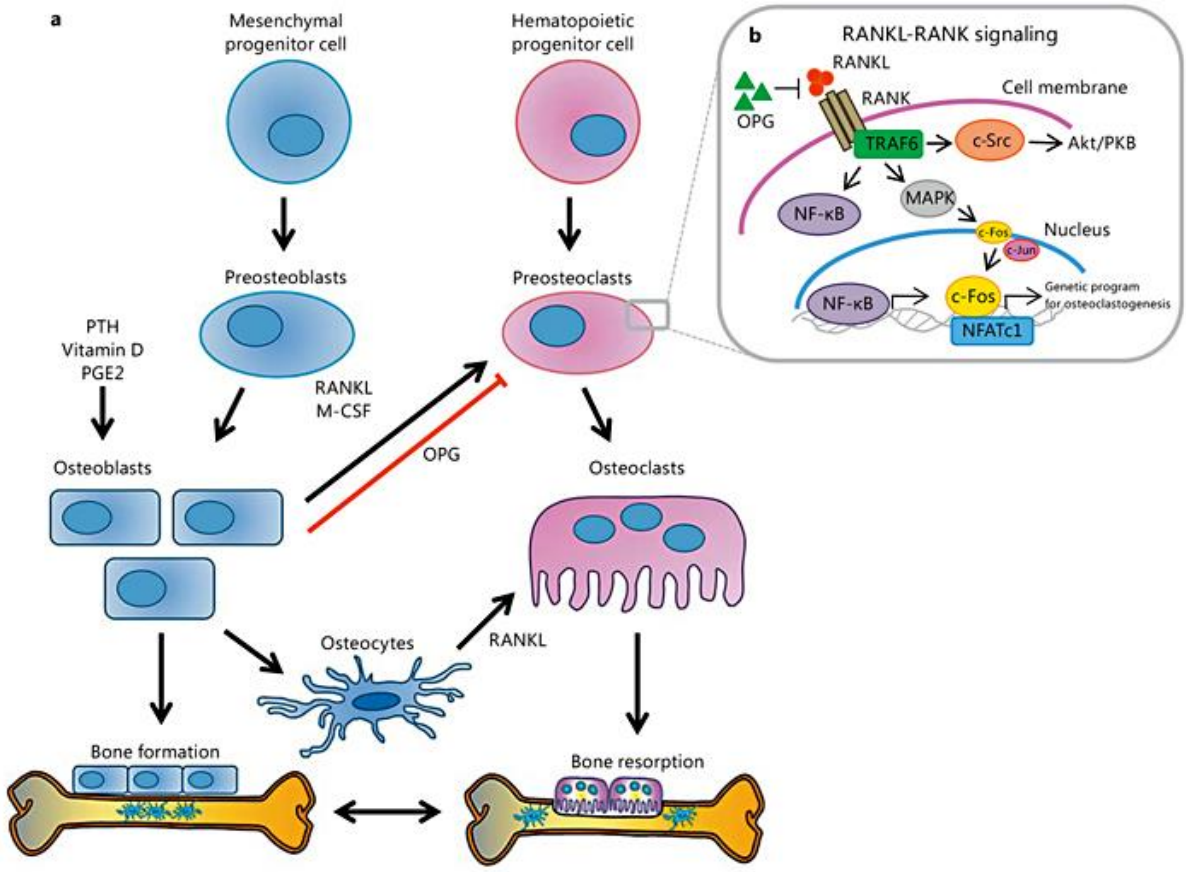

Figure 5. RANKL-RANK signaling (35). RANKL/RANK-ligand also controls the process. RANK is a member of the family tumor necrosis factor (TNF). RANKL is a member of the family TNF-receptor (37). Cytokine plays a key role in osteoclast development and functions and increases bone resorption (38-40).

3.2 Diseases involving bone

To limit the scope of this review, it was decided to focus on three diseases involving bone—namely, periodontitis, dry socket, and osteoporosis. As they will be discussed somewhat later in this review, a short introduction of each of them are provided in this section.

Periodontitis (PD) is typically characterized by increasing tooth mobility and may eventually lead to loss of the tooth if left untreated. Over time, this may result in a significant loss of masticatory function. PD is an inflammatory process initiated by local factors, such as bacterial plaque, immunological and systemic factors may play essential roles in pathogenesis. Risk factors involve smoking, diabetes mellitus, and age (41). Because of the disease process, the surrounding bone of the tooth is resorbed. Additionally, PD is associated with an increased risk of cardiovascular disease (42) aspiration pneumonia (43) and severe outcome of COVID-19 (44). Adequate function and status of the teeth and mouth are necessary to maintain quality of life. Poor oral health may lead to low quality of life, social withdrawal, and weight loss due to difficulties eating. By 2040, the prevalence of PD is expected to have increased by 50% among older adults 65 years and older (45).

Dry socket, or alveolar osteitis (AO), is a painful post-operative complication after tooth extraction. AO clinically shows an empty tooth socket, devoid of any blood clot, with exposed bone. This causes severe pain; the patient often has to visit the clinic repeatedly for treatment (46). AO may delay healing and challenge tooth brushing and food intake. The cause of AO is not entirely understood (47). However, AO is ten times more likely to occur in the mandible than the maxilla (48) and may affect, interestingly, females more often than males, with a ratio of 5:1 (49). AO typically occurs in mandibular third molar extractions (50).

Osteoporosis (OP), the disease's etymology, is of Greek origin meaning "porosity of bone." OP is characterized by low resistance to fracture. Typically, the patient is an older adult or postmenopausal female presenting a hip fracture. The strength of the bone depends mainly on two factors, bone mass, and bone quality. Osteoporosis occurs because of an imbalance of osteoblast and osteoclast-activity, favoring the resorption. The most typical cause is reduced

estrogen, as this causes a reduced expression of OPG. Consequently, reduced inhibition of osteoclast activity occurs (24). OP is not only caused by physiological estrogen decline experienced by postmenopausal in females but also by anorexia, excessive physical training, or cytostatic drugs. It has been reported that the prevalence of OP is 15% to 33% among postmenopausal in Brazil in 2015 (51). In Norway, it was estimated periodontitis to be 49,5% among patients in the age range of 20-79 years, and 9,1% had severe periodontitis (52). It is expected that the prevalence of bone-related diseases, most typically OP, will increase with the aging population. Globally, the number of older adults may be expected to reach 1.5 billion by 2050. That is a fivefold increase from 1990 (53). While OP is a systemic bone disease, it affects the jaw as well, however, its impact on dental implant survival is debated. OP has been reported to have a direct, but not significant, influence on implant failure (12). Preclinical studies also suggest a lower rate of implant integration in OP-like bone (54).

4 Methods

A literature search was conducted on PubMed and Google Scholar for studies related to hormones and jawbone. Search strategies included the combinations ("name of hormone" + "dental term") of the following terms: "hormones", "oxytocin", "estrogen", "adiponectin", "parathyroid hormone", "testosterone", "insulin", "angiotensin", "cortisol", and "erythropoietin", combined with a dental term "jaw bone", "alveolar bone", "dental implant", "jaw + bone regeneration, healing or repair", "saliva", "dentistry", "periodontitis", "dry socket", "osteoporosis" or "alveolitis". Search results were screened for relevance; publications describing or investigating hormone(s) effects on jawbone in relation to dentistry. The publications' cited papers were screened for relevance, as well, and included if fitting inclusion criteria. Additional inclusion criteria included full text availability, English language, publication date from January 1st 2000 to March 31st 2021. Publications included reviews, book chapters and original research papers; *in vitro* studies, *in vivo* animal, or human studies, including clinical studies, and meta-analyses. Where no studies could be found on jawbone specifically, we included studies to elucidate the basic mechanisms and relevant medical studies, by removing "jaw" from the search words. Case studies, letters, viewpoints, editorials,

publications providing irrelevant or unusable data, lack of full text availability, and non-English language articles were excluded.

5 Hormones related to bone formation and resorption

Hormones are substances produced in the endocrine glands of the body and released to the bloodstream and further carried to specific target cells, where their effects are exercised. Such endocrine glands include the pituitary gland, adrenals glands, and parathyroid glands, and more (55). Hormones may act as messengers or something as complex as coordinators of various essential processes such as blood volume and blood pressure regulation, development and reproduction, and more (56). Following nine hormones were found to be involved in the bone formation and resorption in human (57-65).

5.1 Adiponectin

Adiponectin (AN), a hormone produced by adipose tissue, is typically implicated in the regulation of blood glucose and the oxidation of fatty acids. However, the hormone has many additional biological functions (66). Recently, AN has been found to play a potential role as a positive bone mass regulator (67), as an angiogenesis stimulator, and an osteoclast suppressor (68).

Administration of AN in rabbits has resulted in increased mineral content, increased mechanical strength, and a coarser bone morphology locally, suggesting new and accelerated bone formation (69). The rabbits in the study were undergoing a procedure known as distraction osteogenesis, a surgical method of elongating bone by cutting it and slowly pulling the pieces apart using a mechanical device over time. It was evaluated that the key steps of AN-induced bone regeneration in the surgically made gaps involved the recruitment and clonal expansion of bone-forming cells under mechanical stimulation (57, 70, 71). In addition, two AN-receptors have been identified to be expressed by osteoblasts, suggesting AN’s direct functions in bone

metabolism (72), by promoting proliferation and stimulating bone formation (69), Bone tissue is dependent on adequate blood circulation; therefore, angiogenesis is an important component of bone regeneration and function, as well. AN has proven to influence cellular responses in endothelial cells in an ischemic state to promote angiogenesis (73).

Indeed, Ouchi and collaborators reported increased angiogenesis mouse and rabbit models following administration of AN (68). Repeated local administration of AN in rats showed the potential of AN as a potential therapeutic to prevent orthodontic treatment relapse. Haugen et al. reported that AN submucosal injection prevented tooth movement in rats (74).

5.2 Angiotensin

The human body controls blood pressure and fluid volume by an endogenous hormone system known as the renin-angiotensin system (RAS). Hypertension is a pathological consequence that may occur due to RAS dysfunction. Angiotensin is formed in the liver and released in an inactive state, which is then split by the enzyme renin and converted to angiotensin I, and further split into angiotensin II by the angiotensin-converting enzyme (ACE) (75). Angiotensin is important in volume and blood pressure control (76).

Angiotensin can be generated by endothelial cells outside of the renin-angiotensin system, as well. Researchers reported that in co-cultures of osteoclasts with osteoblast-cells, angiotensin I activated bone resorption. This finding may show that RAS could play a role in bone resorption control (77). Saravi and collaborators concluded that inhibition of RAS in an animal model could lead to a reduction in periodontal bone loss and reduction in inflammation intensity (78). Whether or not various tissues and organs of rats are capable of generating angiotensin independently of circulating RAS has been reported (58). Interestingly, gingival tissue of rats express RAS locally, making it possible to produce angiotensin II *in vitro* (58). It is suggested that increased renin production may increase the risk of periodontitis. Santos et al., discussed the mechanism behind the increased risk to involve bacteria stimulating the expression of the gingival RAS, resulting in a proinflammatory environment by increased angiotensin II-levels which could contribute to the bone loss experienced in periodontitis (58). Understanding the

inflammatory effect of RAS can provide a unique perspective for clinical research and treatment of periodontitis.

5.3 Cortisol

Cortisol is a steroid hormone produced by the adrenal glands. Like other steroid hormones, it is released into the bloodstream, passes through the cell membrane, and translocated to bind to the cell nucleus receptor proteins, triggering changes in gene expression. Stress triggers the release of cortisol. Typical examples of stress triggers include fear, anxiety, hemorrhage, pain, low blood glucose, illness, and starvation. To endure stress, muscle, liver, and adipose tissue empty their storage of nutrients as a response to cortisol. Chronically elevated cortisol levels cause muscle and bone damage, impaired endocrine and immune function (56). Stress is a factor leading to the onset of illness (79).

Experimental models involving the periodontium of rats have shown that stress increases susceptibility and worsens periodontitis, PD (80). Numerous studies have indeed shown the potential of the association of stress markers, inflammation, and PD (81, 82). Tissue repair is reportedly impaired by chronic and acute stress in rats (83). Previous studies have reported that chronic stress worsens healing (84) and the formation of the bone matrix and collagen fibers, and a decreased number of osteoblasts (59). As cortisol disturbs healing, it has also been found that chronic stress has been proven to disturb the initial repair process in the rat mandible following implantation. If this is true also in human patients, if patients' chronic stress levels affect the initial phases of osseointegration, it is left for future research (85).

Cortisol levels express diurnal variation, with a fall in the early morning, rise in the afternoon and a peak at night. Therefore, time of sample collection should be considered (86), on the other hand, Marie et al measured progression of periodontitis with stress as a factor in mind. They indicated that stress appears to be associated with microbial colonization between highly stressed patients and non-stressed patients. However, the salivary cortisol concentration is not associated with stress. Therefore, stress and subsequent cortisol increase may contribute to the progression of periodontitis (87).

5.4 Erythropoietin

Erythropoietin (EPO) is a well-known hormone released from the kidneys for its red blood cell-producing effects (88). Furthermore, EPO can increase bone formation indirectly by increasing vascular endothelial growth factor (VEGF) expression (56, 89).

Through osteoblast-osteoclast communication pathways, the EPO often indirectly activates osteoblast differentiation. These experiential findings are important in the understanding of mediated bone remodeling and may contribute to the treatment of bone defect growth (90). EPO can contribute to bone formation both directly by communication pathways and indirectly by VEGF (89) (91).

Holstein et al. experimented by delivering EPO to dental extraction sockets and observed that EPO significantly promoted new bone formation. Suggestively by the mechanisms of inhibiting pro-inflammatory pathways and apoptosis, improved vascularization, and enhanced osteoblast formation (60). Hoori et al evaluated the effect pf EPO on the improvement after phase I periodontal treatment, and they found that there was a significant reduction in calculus and periodontitis in test group. They suggest that EPO gel can improve clinical inflammation and calculus in periodontitis (92).

5.5 Estrogen and testosterone

Estrogen (ES) is a group of female sex hormones responsible for the development of female sexual characteristics and the reproductive system. ES is produced in a lesser amount in males, where androgens (AD), the male sex hormones, dominate. ES comprises a group of steroid hormones, typically estradiol, estrone, and estriol (93), and AD; testosterone, dihydrotestosterone, and androstenedione. Steroid hormones are synthesized in several endocrine tissues, such as the ovaries in females and in the testicles of males. They can bind to the receptors in the plasma membrane of cells and cause rapid effects. Through nuclear

receptors in the cell nucleus, ES can cause changes at the level of gene expression, though these effects are slow (56).

5.6 Estrogen

In both sexes, steroid hormones regulate skeletal preservation and maturation, and the impact of gonad insufficiency on skeletal integrity has been widely recognized (94). Ovariectomy and orchiectomy have been shown to cause condylar bone loss in mandibular condylar bone (95). The role of ES in osteoporosis is well-known; however, Ayed et al. investigated the association of osteoporosis and progression of PD in postmenopausal females and concluded that OP is a risk factor for PD (96). Sundeep et al. reported that estrogen inhibits bone resorption by direct action on osteoblasts, through estrogen modulation of osteoblasts and osteocyte and T-cells regulation of osteoclast differentiation and activity (97).

It has been observed a higher ratio of females being affected by AO, dry socket (49). It has been proposed that EO may promote the degradation of the protective blood clot that would facilitate proper healing (98). Interestingly, the incidence of AO shows a positive correlation with the use of oral contraceptives, which usually contain EO (99). Fibrinolysis, the degradation of blood clots, can be inhibited by plasminogen activator inhibitor type 1 (PAI-1). A greater rate of fibrinolysis has been noted in postmenopausal women, associated with a lowered PAI-1 concentration (100). Majid et.al suggested that the menstrual cycle could be a risk factor for AO, as EO levels do fluctuate with the cycles. However, he did not find a significant difference in the timing of a menstrual cycle and incidence of AO (101). Previously, there has been debate among researchers whether oral contraceptives may increase the risk of or worsen PD. According to Preshaw, evidence suggests that oral contraceptives on the market today no longer place users at any risk of PD (61).

5.7 Testosterone

Testosterone, the most well-known androgen, is mainly anabolic of effect (102). Testosterone can be reduced, by a cytoplasmic enzyme called 5-alpha-reductase, to dihydrotestosterone (DHT). DHT binds to the same androgen receptor 2.5 times stronger than testosterone and thus shows increased androgenic potency (103). Testosterone is responsible for the development of

male reproductive organs and sexual characteristics, including increased bone and muscle mass (104).

Administration of sex steroid hormones, such as testosterone, has been shown to affect the human gingiva by increasing the growth rate of oral bacteria, which is causally considered to be related to periodontal inflammation. It has been reported that human gingival tissues metabolize testosterone (105) with conversion to DHT (106). Interestingly, inflamed tissue, including inflamed gingival tissue, has a two to three-fold increase of DHT receptors (107). Testosterone deficiency in older men is one of the risk factors for OP. Androgens can be converted to ES through a process known as aromatization (108). It has been shown in previous *in vitro* studies that androgen can promote pre-osteoblast proliferation and converted ES can suppress osteoclast development. Human studies among elderly men, both androgen and ES, are necessary for the formation of bone. ES is required for the suppression of bone resorption. while androgens are essential for older men in the prevention of OP and its complications (62). According to Sergio V. K., there were four studies that showed no correlation between serum testosterone and chronic periodontitis and two studies with a positive correlation. However, their limits of the evidence and further longitudinal studies are needed (109).

5.8 Insulin

Insulin is a peptide hormone developed secreted by beta cells in the Langerhans islets of the pancreas. The hormone is essential in maintaining normal blood glucose levels by facilitating the absorption of glucose into cells. Insulin is, therefore, a vital component of anabolism (110).

Diabetes mellitus (DM), a disease of reduced production or sensitivity to insulin, reports delayed bone formation and impaired fracture healing. DM increases and prolongs inflammation-promoting osteoclast differentiation. Subsequently, the balance of bone remodeling shifts towards a resorbing tendency. Indeed, it has been reported that insulin activates osteoblast differentiation, reduces apoptosis of osteoblasts, and reduces osteoclast activity (63).

Kido et al. performed an experiment in diabetic rats and reported that an association between periodontitis and diabetes is evident (111). They also reported that diabetes can induce abnormal proliferation of gingival fibroblasts. Insulin resistances plays a role in the progression of periodontitis in diabetic patients. They concluded that delayed gingival wound healing in diabetic rats was caused by impaired proliferation and migration of fibroblasts. Dysfunction of fibroblasts may be caused by high glucose-induced insulin resistance via oxidative stress (111).

A growth factor so similar to insulin in structure that is has been named insulin-like growth factor-1 (IGF-1) can be secreted from the liver by the stimuli of human growth hormone, but also by bone cells (112). IGF-1 is critically involved in bone growth during puberty and throughout life (113). IGF-1 has also proved to, in combination with other growth factors, to accelerate bone formation around dental implants in rabbits (114, 115). Perhaps due to their structural similarity, insulin itself has bone promoting properties with osteoblasts actually expressing insulin-receptors – possibly promoting osteoblast differentiation (112). An animal study explored the role of insulin in the integration of titanium implants in rat tibias. Three groups of rats were involved: diabetes-induced rats, insulin-injected rats, and healthy controls. Up to three weeks after implant insertion, it was found that a delayed healing was evident in the diabetes rats, which showed improvement after insulin injection. While the controls and insulin-treated rats had similar amounts of bone healing (116). It would be of interest to conduct a similar study in jawbone. Insulin is involved in bone healing, although the mechanisms are not entirely elucidated. Understanding the mechanisms more thoroughly may contribute to a better understanding and possibly a future local insulin treatment of periodontitis worsened by DM.

5.9 Parathyroid hormone

Parathyroid hormone (PTH) regulates the calcium homeostasis of the body (117). PTH is secreted from four glands located behind the thyroid gland, where they monitor and regulated serum levels of calcium. When levels are low, PTH is released to the bloodstream to release calcium from the body’s largest reservoir, the skeleton, by bone resorption (118).

Recent clinical and pre-clinical studies indicate that PTH increases the bony density of the jaw and enhances soft tissue healing and bone fill after tooth extraction (119). In rat models with PD, PTH was reported to have an anti-inflammatory effect (120). Inflammation in the gingiva was significantly reduced, and bone loss was suppressed by PTH.

Ji-Hye Kim intermittently administered parathyroid hormone (PTH) DM-rats with periodontitis and found that such an administration regimen of PTH reduced alveolar bone loss and increased bone formation (121). This finding suggests that PTH administration counteracted bone loss, as promoted by DM, by inducing bone formation. A combination of the protein SDF-1alpha and PHT showed enhanced bone formation , SDF-1alpha also plays a promoting role in the regeneration of PDL (121). Several studies have examined the impact of PTH on dental implant stability and integration in bone. Bellido et al induced artificial osteoporosis in rabbits and measured a general bone loss and reduced mineral content in their jaws (122). However, administration of PTH almost completely reversed these negative findings, and restored the jawbone to almost normal levels. A study on mongrels found increased levels of bone remodeling around dental implants inserted in the mandible, in the group administered PTH (64). An application perhaps close to clinical utilization is presented in a paper investigating PTH-coated titanium dental implants in rats (123). The results were promising, with increased bone formation around the PTH-coated implants. Therefore, these results together suggest that PTH might represent a future therapy for improving the integration of dental implants in humans. However, the frequency of PTH-administration varies among studies, therefore a priority should be to find the optimal frequency and dosage to improve bone growth (117).

5.10 Oxytocin

Oxytocin (OT) is produced in the hypothalamus and excreted via the pituitary gland (124). The hormone acts on the mammary gland and uterine muscles. The hormone can induce uterine contractions during pregnancy, contributing to childbirth. During lactation, OT causes milk release (56). OT may also be involved in the process of bone remodeling (125), as it has been

reported to reduce resorption of bone and cause a relative increase in the formation of bone (126).

Reduced levels of OT in plasma have been reported in postmenopausal women (127) and have been found to play a role in skeletal homeostasis (126). In addition, intramuscular injection of OT has been shown to promote bone growth in rats, with consequent alterations in serum levels of calcium, RANKL, and OPG (128). OT-treated rats have shown increased levels of osteocalcin and a significant increase in alveolar bone formation (129). Osteocalcin is synthesized by osteoblasts and can be used as an indicator of bone remodeling and mineralization of the bone matrix (130, 131).

Treatment with OT is shown to result in an increase in levels of intracellular calcium and to regulate stimulation of osteoblast formation and thus bone formation in rats. Additionally, deletion of the OT-receptor in mice resulted in the development of OP (126). Systemic OT has been investigated regarding the OP with positive results, such as improved peri-implant bone healing in the distal femoral metaphysis (132). In OP, the favored osteoclast activity has been suggested to be an implication of a lack of OT (131). According to the study done by Jee and collaborators, it showed that OT stimulates a reduction of bone resorption and yields a positive bone balance during the process of alveolar bone healing in female rats (65).

6 Discussion

There is plenty of available research about hormones in the medical literature, however, the literature is scarce in the field of dentistry. This review aims to shed light on available research on the topic of hormones and dentistry in regard to their effects on jaw bone. Additionally, the authors have selected three diseases to discuss how they are influenced by hormones: osteoporosis, periodontitis, and dry socket.

Reviewing the literature has revealed several hormones that beneficially impact bone healing, by a variety of mechanisms. Oxytocin, estrogen, testosterone, adiponectin, parathyroid hormone, insulin and erythropoietin, all of them influence the bone balance positively, except for cortisol and angiotensin where an increase results in bone loss. In general, all of them may have therapeutic potential in the clinical setting. Not all of the hormones had available research on jaw bone specifically, however, one may argue that the basic mechanisms may be translated to involve jaw bone as well despite some differences such as remodeling rate and growth(34), and thus a therapeutic effect could be possible also in jaw bone as in other investigated bones, and vice versa.

In regards to research, in terms of novel development of therapeutic hormone based treatment to combat bone loss in the jaw, PTH-coated implants (123, 133) and adiponectin for orthodontic treatment (74), are both animal studies and the ones that are the closest to human clinical trials. The authors' next step could be human clinical trials. PTH is interesting as it is safely used in the treatment of osteoporosis in medicine already and therefore has an established safety profile for that use (134, 135). The transition to develop a well-functioning application of PTH to dentistry in a way of local administration may therefore be quicker than with the other reviewed hormones. Adiponectin is promising as it may be able to prevent post-treatment movement of orthodontically treated teeth, although human clinical trials with long follow-up times are necessary to evaluate this potential usage. As any treatment, hormone treatment is not free of risk. Future research needs to focus on finding the optimal therapeutic dosage for bone healing with as few side effects as possible. For example the use of estrogen carries risks of (136), breast cancer(137), and thromboembolism (138). As estrogen illustrates, hormones are agents with systemic effects, able to affect several different tissues in a variety of ways. Local treatment with hormones may therefore be more advantageous than systemic administration. The dream scenario would be the possibility of "naturally" enhancing your hormone levels to achieve a clinical outcome. For example, oxytocin levels increase by hugging or physical contact; what if one could hug away their bone loss? In reality, the hormone levels needed to achieve desired clinical outcomes may be much higher than what is produced physiologically, and administration would perhaps still be necessary. Another disadvantage to keep in mind is that hormones are relatively slow acting agents, meaning that the patient may not experience immediate clinical improvement. Additionally, the patient needs frequent administration to achieve desired clinical effects. Thus, with long treatment times and frequent administration,

hormone treatment may not be cost efficient, although there are still insufficient data to consider this aspect as of now. Some possible benefits include hormone levels can be conveniently measured in the blood (109). Thus monitored and the dosage individually regulated for optimal effect, and it gives the body the tools to solve challenges on its own, for example without the need for invasive surgery. However, a maintenance dose may be necessary. Hormone treatment may be especially suited for individuals with conditions resulting in hormonal imbalance, such as osteoporosis. Therefore, finding the optimal dosage and frequency of hormone administration for bone repair is necessary to avoid suboptimal therapeutic effect or side effects of hormones in a clinical setting, as hormones may affect a magnitude of tissues and processes, and should require regular follow-up.

The role of estrogen in osteoporosis is well-known, however, more surprising was the influence of hormones in periodontitis and dry socket. Suggested correlation of estrogen and dry socket (98) has been reported with a plausible mechanism of estrogen degrading the healing blood clot in the postoperative alveolus. This is debated as somewhat conflicting reports exist (61, 99). Oral contraceptives and possibly menstruation where higher levels of female sex hormones, predominantly estrogen may increase the risk for dry socket. The risk of AO may not be apparent with today's contraceptives (61). However, with the increasing number, or rather the awareness of them, of gender transitioned men-to-females, a group we know little about may indeed require attention. This group of transgenders require regular injections of estrogen, at much higher levels than that found in commercial contraceptives (139). One may speculate that a much higher risk of post-operative complications such as dry socket exists if estrogen is injected around the same time as a dental extraction. Little research exists on this group of patients in dentistry and warrants further research. Dentists may consider asking this group of patients about their injection schedule as to not risk possible post-operative complications.

Some evidence existing suggest a link between low testosterone levels and risk of osteoporosis (62). A link between testosterone and periodontitis has been suggested by some authors, however, conflicting results exist in the literature with some showing a positive correlation of low testosterone levels and periodontitis, while others do not (109). No studies report fracture incidence on specific bone sites, such as the mandible, however, an increased risk of bone

fractures in men with testosterone deficiency, usually older adults, is apparent (140). Whether testosterone supplementation can prevent this could not be concluded based on a meta-analysis (140), however, sexual function and quality of life could improve. Out of curiosity, the author did explore another aspect of male sexual function and dentistry. Low-grade inflammation by periodontitis has been reported to be associated with erectile dysfunction. Interestingly, patients with erectile dysfunction also experienced improvement after periodontal treatment (141). The mechanism is unknown; however, the field of periodontitis and the male sex seems to contain more mysteries than expected.

Hormones and dentistry are very much a field one could call uncharted waters. Little research exists, and most assumptions and knowledge are extrapolated from the medical literature where hormone research is more abundant. Some diseases of the oral cavity that dentists commonly encounter, such as periodontitis and dry socket are possibly influenced by hormones. Groups requiring hormone replacement therapy, such as transgenders, and the dental consequence of such therapy is something we know very little about in dentistry. Further research is recommended, as it strengthens the relationship of dentistry and the rest of the body and may open new therapeutic techniques. Hormone treatment in dentistry is far away from common practice, however, some hormones are well researched, and some are regularly used in other medical settings, and may be implemented into dental related treatment.

7 Conclusion

Bone formation and remodeling is a complex continuous process involving many hormones. Bone volume reduction following tooth extractions and bone diseases such as periodontitis and osteoporosis causes serious problems and require a great understanding of the process. Hormones are with us all the time, shape our development and regulate our homeostasis. Newly discovered effects of hormones influencing bone healing opens the possibilities of using hormones as therapeutics to combat bone-related diseases. As the hormones may have a multitude of differing effects, the safety and regimens of administration regarding dosing, location, and frequency need to be assessed and more studies and clinical trials are needed.

However, there is no doubt how imbalance of cortisol and estrogen, can result in disease, and the control of hormones may be a cure for many diseases.

Adiponectin, intermittent administration of Adiponectin, can accelerate the new bone formation and mineralization following distraction osteogenesis and prevent orthodontic tooth movement. **Oxytocin** promote bone growth and show increased calcium level in bloodserum and regulate stimulation of osteoblast formation in rats. **Parathyroid** promote tooth extraction wound healing by improving bone fill, suppressing ridge resorption, and encouraging collagen deposition in soft tissue. **Testosterone** may be implicated in periodontitis when in low levels. **Insulin** activates osteoblasts and leads to the bone-forming process. **Angiotensin** inhibition may lead to reduced periodontal bone loss. **Cortisol** and stress increase susceptibility for periodontitis and lead to bone resorption. **Erythropoietin** facilitates bone formation directly by promoting osteoblast activity and indirectly by VEGF. This thesis will be a guide for the further study on specific hormone on bone metabolism in specific disease.

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