Review

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Neuro-Immuno-Endocrine Regulation of Bone Homeostasis

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Bone is an important connective tissue involved in the movement and mechanical support of the body. Its homeostasis refers to the equilibrium between bone formation by osteoblasts and bone resorption by osteoclasts. Hematopoietic progenitor cells are shared by bone and immune cells, and the skeletal system is extensively innervated by an extensive nerve network. The immune, endocrine and nervous systems synthesize and secrete cytokines, hormones and neurotransmitters, respectively, which regulate physiological processes involved in bone homeostasis. Hormones such as gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, testosterone, insulin, thyroxine, parathyroid hormone (PTH), calcitonin, etc., regulate bone formation and resorption. Tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin (interleukin (IL)-1,3,4,6,10,17,18,23,27) regulate the function of osteoblasts and osteoclasts as well as the bone microenvironment. The skeleton is innervated by sympathetic, parasympathetic and sensory nerve fibers that release neurotransmitters/factors such as serotonin, nerve growth factor, neuropeptide Y, substance P, norepinephrine and acetylcholine, which interact with various cells in the bone. Sclerostin, osteopontin, osteoprotegerin, osteocalcin, prostaglandin E2 and receptor activator of nuclear factor-kappa B ligand (RANKL)/receptor activator of nuclear factor-kappa B (RANK) are some of the important proteins released by osteoblasts, osteocytes and osteoclasts that regulate osteoblastogenesis, osteoclastogenesis and angiogenesis and are also involved in pathological conditions. Further research is needed to establish links between the skeleton and other tissues and to gain additional insights into the etiology of degenerative diseases and the drug development process. The aim of this minireview is therefore to understand the composition of bone and the maintenance of bone homeostasis through three coordinates, namely the endocrine, nervous and immune systems.

Keywords: bone cells; neuro-immuno-endocrine; hormones; cytokines; neurotransmitters; homeostasis

Introduction

The skeletal system is one of the largest organ systems in the body and accounts for approximately 15% of the total weight. The two main types of skeletal tissue are bone and cartilage. Bone consists of a matrix, vascular networks, stores calcium and phosphate, harbours bone marrow and four cell types such as osteoclasts, osteoblasts, osteocytes and bone lining cells [1]. Bones maintain homeostasis through continuous processes of bone formation and resorption [1]. Bone diseases such as osteoporosis, osteoarthritis and intervertebral disc degeneration are caused by a disturbance in the balance between osteoclasts and osteoblasts [2,3]. The delicate balance between bone formation and resorption is influenced by a number of local and systemic factors such as biomechanical factors, chemokines, hormones, neurohormones and cytokines [4,5].

Hormones that influence bone remodeling include pituitary hormones, calcitriol, thyroid, glucocorticoids, parathyroid and sex hormones, etc. [5]. G protein-coupled receptors (GPCRs) for growth hormone (GH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), oxytocin (OT) and arginine vasopressin are abundant in both osteoclasts and osteoblasts [6]. The thyroid gland is one of the most important endocrine organs, producing and secreting thyroid hormones (THs) and calcitonin. Parathyroid hormone (PTH) promotes osteoclast activity, which increases the concentration of calcium ions in the blood by releasing calcium from the bones into the bloodstream. The GH/insulin-like growth factor (IGF)-I axis is also important for bone homeostasis in adulthood. Long bones grow longer as a result of GH-induced chondrocyte proliferation in the epiphyseal plates. The sex hormones (testosterone and estrogen) play a role during puberty. They are also responsible for the growth spurt that often occurs during puberty and promote the activity of osteoblasts and osteoclasts and the synthesis of bone matrix [7,8]. Thus, there are many theories to explain the intricate

relationships between growth factors, hormones and their receptors, as well as the autocrine, paracrine and endocrine signaling pathways that control bone physiology.

There are important physical and functional relationships between bone and the immune system. The precursor cells of myeloid cells, specifically monocytes and macrophages, which are innate immune cells, are the source of these osteoclasts. During osteoclast differentiation, myeloid cells undergo transcriptional changes and receive signals from important cytokines. Ultimately, these cells develop into multinucleated adult osteoclasts. Transforming growth factor-β (TGF-β), prostaglandins, cytokines and certain morphogenetic proteins are examples of local factors. The onset and progression of osteoporosis depend on the interaction between the immune system and the skeletal system [9]. Bone resorption is traditionally regulated by cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), interferon-gamma-γ (IFN-γ) and IL-17α [10,11]. Numerous other cytokines, including TGF-β, IL-2 and interleukin-6 (IL-6), are also involved in the regulation of osteoclastogenesis [12]. The essential links between the innate and adaptive immune systems and the skeleton provide a unique perspective on the biology of new bone formation which will ultimately allow us to use immunomodulation to alter osteoclastogenesis to cure bone disease.

Reports from basic medicine, clinical medicine and biomaterial science have highlighted the interactions between the nervous system and bone. Numerous signaling channels, neuroendocrine variables and molecular mediators are part of the brain-bone axis which coordinates the interplay between the central nervous system and skeletal metabolism [13]. The functions of the sympathetic and sensory nerves in bone homeostasis, bone remodeling and development are also known. Neuropeptides, neurotransmitters, proteins, peptides and derivatives of amino acids are the means by which sensory and sympathetic nerves communicate with bone [14]. The peripheral and central nervous systems can use certain specific pathways to influence bone metabolism [15]. Osteoblastic osteoclastic cells have been shown to mediate neuronal regulation of bone metabolism [16]. Neuroskeletal regulation has received more attention in recent years and several novel hypotheses and concepts have been proposed.

In this minireview, we will address the cellular and biochemical components of bone. We will look at the influence of the central nervous system, the endocrine system and the immune systems on the regulation of bone physiology. We will also discuss the proteins secreted by bone that interact with other biomolecules in the regulation of bone homeostasis. This minireview will be extremely valuable to bone biologists, neurobiologists, endocrinologists and immunologists and will contribute to the corpus of knowledge in this field of study.

Cellular Organization of Bone

Four primary cell types are involved in the formation and breakdown of bone: osteoblasts, osteocytes, osteoclasts and bone lining cells (Fig. 1). During bone development, the mesenchymal stem cells of the bone marrow differentiate into osteoblasts, which release collagen fibres and bone matrix, gradually store calcium and finally form bone [17]. Osteoblasts, which are cuboidal cells derived from mesenchymal progenitor cells, are the main source and deposition site for the extracellular matrix that eventually forms mineralized bone [18]. The Runt-related transcription factors 2 (RUNX2), Distal-less homeobox 5 (Dlx5) and osterix (Osx) are required for osteoblast development [19]. RUNX2 has been shown to upregulate osteoblast-related genes such as collagen type I alpha 1 (ColIA1), alkaline phosphatase (ALP), bone sialoprotein (BSP), bone gamma-carboxyglutamic acid-containing protein (BGLAP) and osteocalcin (OCN) [19]. Osteoblasts synthesize bone matrix in two steps: deposition of organic matrix and mineralization. Some of the osteoblasts have cytoplasmic extensions to the bone matrix and eventually reach the osteocyte processes [20]. Mature osteoblasts can either apoptosis or differentiate into osteocytes, or bone lining cells [21]. These cells have the features of protein-producing cells, such as an abundant rough endoplasmic reticulum, a distinct Golgi apparatus and numerous secretory vesicles [4]. Bone morphogenetic proteins, angiogenic factors such as endothelin-1, growth factors such as fibroblast growth factor (FGF) and insulin-like growth factor (IGF), hormones such as PTH, microRNAs, connexin-43 and prostaglandin agonists are a few paracrine, autocrine and endocrine factors that influence osteoblast development and maturation [22]. FGF plays an important role in osteoblast differentiation [23].

Osteoclasts are specialized multinucleated giant cells that are required for high metabolic activity and efficient bone resorption. Factors that regulate osteoclast formation include macrophage colony-stimulating factor, secreted by osteoprogenitor mesenchymal cells and osteoblasts, and receptor activator of nuclear factor-kappa B (RANK) ligand, secreted by osteoblasts, osteocytes and stromal cells [24]. The cytoplasm of osteoclasts comprises a number of well-developed organelles, including mitochondria, the endoplasmic reticulum, the Golgi apparatus, transport secretory vesicles and microtubule arrays [21]. A distinguishing feature of osteoclast cytoplasm is the presence of a specific structure known as a ruffled rim. This is a strongly folded cell membrane that creates many microvilli-like projections that press against the bone surface. The polarization of osteoclasts during bone remodeling reveals four different types of osteoclast membrane domains: the basolateral and functional secretory domains, which are not in contact with the bone matrix, and the sealing zone and ruffled border, which are in contact with the bone matrix [25]. Osteoclasts perform their resorption activity in a particular region depending on their attachment mechanism to the bone sur-

face. The old bone created by necrotic and apoptotic osteocytes is broken down and reabsorbed by osteoclasts during bone resorption [26]. Thus, a normal, healthy bone mass is maintained by the interaction of osteoblasts and osteoclasts [27,28]. Numerous bone-related disorders are caused by a disturbance of bone homeostasis [29].

Osteocytes are the most prevalent and long-lived cells, accounting for about 95% of all bone cells and having a lifespan of 25 years [30]. Osteocytes have a dendritic shape and are found in lacunae surrounded by mineralized bone matrix [31]. Osteocytes arise from the mesenchymal cell lineage through osteoblast differentiation. Osteocyte, preosteocyte, young osteocyte and mature osteocyte are the four distinct stages identified in this process [32]. Before the osteocytes have been enveloped by the bone matrix, the cytoplasmic process begins during the transition between osteoblasts and osteocytes [33]. The cytoplasmic processes of the osteocyte traverse microscopic tunnels called canaliculi that emerge from the lacuna space, creating the lacunocanalicular system of the osteocyte, although the cell body of the osteocyte is situated inside the lacuna [34]. The vascular supply that provides oxygen and nutrients to osteocytes is located near the lacunocanalicular system of osteocytes. It has been demonstrated that osteoclasts absorb apoptotic osteocytes during bone resorption. The expression of podoplanin (PDPN/E11/GP38), plastin 3 (PLS3) or cluster of differentiation 44 (CD44) determines the unique shape of osteocytes *in vivo* and in culture [32]. Proteins such as sclerostin and receptor activator of nuclear factor-kappa B ligand (RANKL) are produced by osteocytes, and osteoprotegerin (OPG) may have an autocrine or paracrine effect on other bone cells.

Quiescent, flat-shaped osteoblasts, known as bone lining cells, cover the surfaces of bone where neither bone growth nor resorption occurs [35]. These cells have a thin, flat nuclear profile; their cytoplasm runs along the bone surface and has some cytoplasmic organelles, including the Golgi apparatus and rough profiles of the endoplasmic reticulum [12]. Gap junctions between neighboring bone lining cells and between these cells and osteocytes are also seen, and some of these cells exhibit projections that extend into tubules [36]. The secretory activity of the bone lining cells depends on the physiological state of the bone; these cells can regain their secretory activity by becoming larger and assuming a cuboidal shape.

Biochemical Composition of Bone

A mature bone is characterized by the presence of inorganic minerals deposited on an organic framework. Bone is composed of water, hydroxyapatite and biological components such as type I collagen and non-collagenous proteins that support the mineralization of bone [37]. Due to its high density, the mineral component accounts for almost half of the weight of bone, although it makes up only about 25% of its volume. The organic bone matrix on which the mineral is deposited is called osteoid. At least 95% of the material in an osteoid consists of type I collagen. The base material consists of a variety of proteoglycans, high molecular weight compounds composed of several types of polysaccharides linked by a polypeptide backbone. Trace elements such as calcium, phosphorus, iron, zinc (Zn), copper (Cu) and magnesium also influence bone formation and metabolism [38].

Zinc is essential for tissue metabolism and bone formation and determines the differentiation and maturation of osteoclasts [39,40]. Zinc is not only a component of numerous enzymes, but is also present in the mineral fraction, especially in bone apatite, both in bones and in other tissues [41]. Bones lacking Zn are thin and brittle, leading to a progressive decrease in bone mass. Osteoporotic women were found to have less zinc in their bones than healthy women. Zinc cations are cofactors for collagenase, which is involved in the metabolism of bone tissue, and for ALP [42]. ALP is classified as a metalloenzyme and contains two zinc and one magnesium ion in its active core [43]. Zn has effects on osteoblast proliferation and ALP activity [40]. In substances such as phosphoethanolamine, pyrophosphate and pyridoxal phosphate, it acts by breaking the phosphate ester bond, releasing phosphate ions into the bone matrix and promoting its mineralization [43]. Together with IGF-I and TGF-β, zinc has a physiological role in promoting bone development [44]. By controlling the RANKL/RANK/OPG signaling pathway, zinc promotes bone remodeling. Zinc has been found to inhibit both RANKL activation and associated signaling pathways in preosteoclasts. Zinc has been reported to inhibit RANKL activation in osteoclast progenitor cells, which in turn inhibits TNF-α-induced osteoclastogenesis. Zinc has been shown to influence osteoblast development via induction of the BMP-2 signaling pathway. Tyrosine kinase and tyrosine phosphatase, which are part of the IGF-I signaling pathway, may interact with zinc to some extent [45]. It has also been demonstrated that 1,25-dihydroxyvitamin D3 (calcitriol) receptors have two zinc fingers at the DNA binding site. Thus, the effects of calcitriol on bone development and mineralization can be modulated by the availability of zinc [44].

Cu mainly plays a role in the structure of electron transfer enzymes and is therefore necessary for the energy metabolism of cells. Cu is important for bone formation and mineralization as it is a cofactor of various enzymes, including lysyl oxidase, which is responsible for the process of cross-linking collagen fibers, which, when disturbed, leads to bone fragility [46]. Cu is involved in bone tissue metabolism, but its main function is to act as a coenzyme in oxidation-reduction processes, where it regulates Fe metabolism, collagen metabolism and transport [47]. Low levels of Cu increased the viability and development of osteoblast cells, while high levels of Cu were found to be cytotoxic [48]. Cu is also involved in collagen harden-

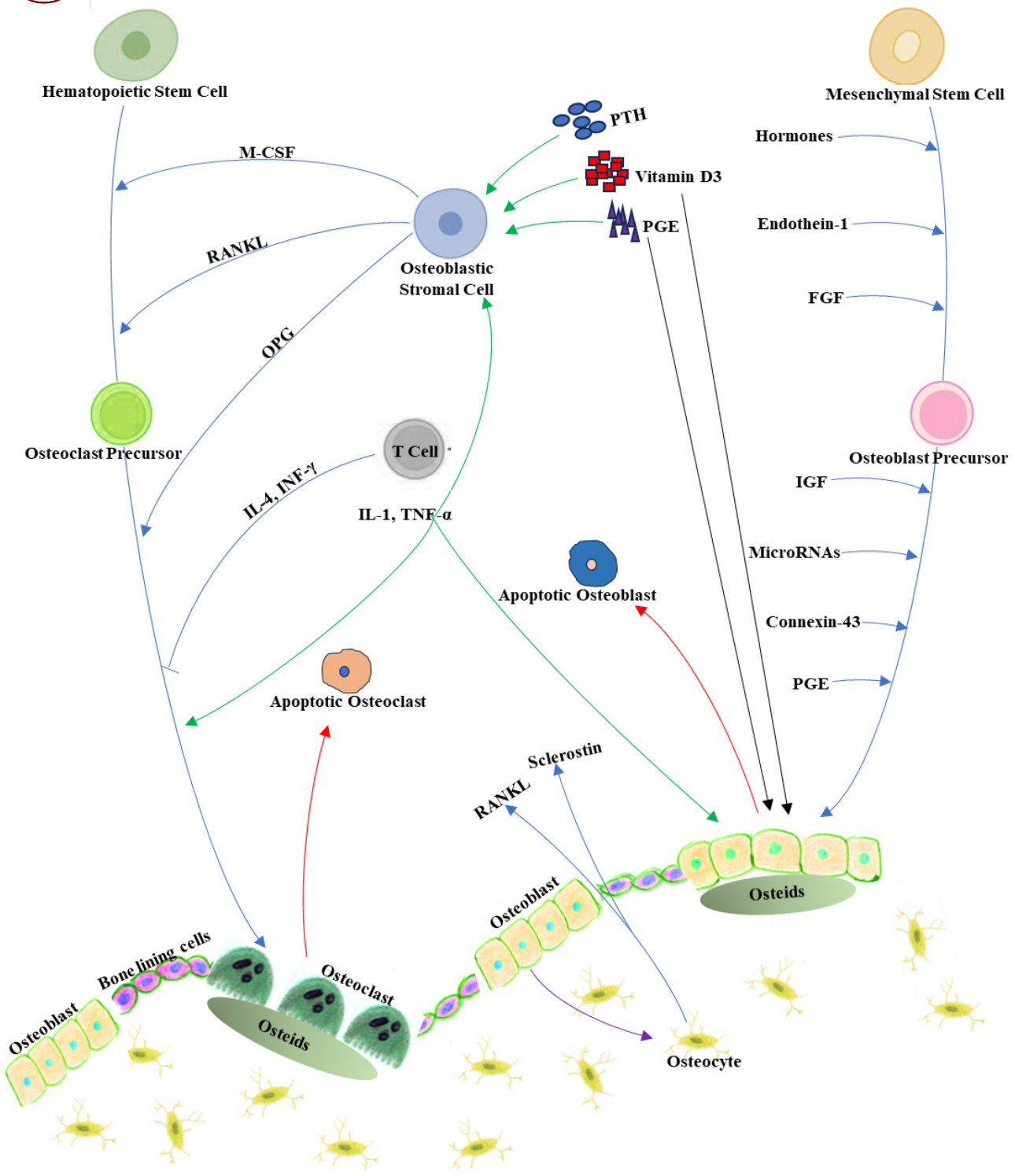

Fig. 1. Schematic representation of bone cell differentiation. Mesenchymal stem cells differentiate into osteoblast precursor cells and then become osteoblasts. Osteoblasts can either remain on the surface as bone lining cells or differentiate as osteocytes and integrate into the bone. Before they fuse to form a mature, multinucleated osteoclast, a common precursor of the myeloid lineage develops into a preosteoclast. Hormones, cytokines, endothelin-1, growth factors such as fibroblast growth factor (FGF) and insulin-like growth factor (IGF), microRNAs, connexin-43 and prostaglandin regulate the osteoclast. As soon as osteoblasts and osteoclasts have completed their task, they undergo apoptosis. The image was created with Adobe Photoshop 7.0 (Adobe, San Jose, CA, USA) and Microsoft Office 2016 (Microsoft, Redmond, WA, USA). M-CSF, macrophage colony-stimulating factor; PGE, prostaglandin E; INF-β, interferon-β; RANKL, receptor activator of nuclear factor-kappa B ligand; OPG, osteoprotegerin; PTH, parathyroid hormone; IL-4, interleukin-4; TNF-α, tumor necrosis factor-α.

ing, keratinization of hair and fur, and proper calcium and phosphorus deposition in bone [49]. Cu deficiency is mediated by a number of enzymes that use Cu as a cofactor, including amine oxidase, ceruloplasmin, cytochrome oxidase, dopamine monooxygenase, extracellular superoxide dismutase, lysyl oxidase, Cu/Zn superoxide dismutase and tyrosinase. In addition, Cu promotes the development of MSC in the osteogenic lineage [50]. The Cu content in human bones has been found to decrease with age [51]. Excess Cu can produce reactive oxygen species (ROS), causing lipid peroxidation and impairing bone metabolism. Cu, like Fe and Zn, has various functions in the human body, but excess Cu can have disastrous consequences. The most important negative consequence of a Cu deficiency is the reduced activity of lysyl oxidase [52]. Reduced activity of superoxide dismutase can potentially contribute to the suppression of osteoblast activity, as it is sensitive to free radicals generated by osteoclast activity [53].

Growth, development and maintenance of bone as well as the stability of the cellular cytoskeleton depend on calcium, which influences numerous extracellular and intracellular processes [54]. PTH, FGF-23 and 1,25-dihydroxyvitamin D3 ($1,25(OH)_2$ D_3) are the most important regulators of phosphorus and calcium levels in the blood [55]. In addition to calcium and phosphate, bones also contain considerable amounts of magnesium, salt and carbonate from the body. Magnesium is essential for bone cell activity, mineral and bone homeostasis as well as for the development and proliferation of hydroxyapatite crystals. Bones store about 60% of all magnesium in a fixed and dynamic pool [56]. Bone density is directly affected by magnesium deficiency. Magnesium insufficiency affects bone by regulating PTH and $1,25(OH)_2$ D_3, which in turn influence Ca homeostasis. Phosphoproteins and hydroxyapatite crystals account for up to 85% of the phosphorus deposited in bones and teeth [57]. For osteoblasts and osteocytes to be active during the mineralization process of the matrix, the right amount of inorganic phosphorus is essential [56]. Phosphorus deficiency leads to abnormalities in mineralization, unmineralized osteoid, which is a hallmark of bone disease, rickets, stunted growth in children and osteomalacia in adults. By promoting osteoblast activity and proliferation, fluorine also promotes bone formation. The increase in bone mass is the result of fluoride's stimulation of osteoblast growth and inhibition of osteoclast activity [58]. Ion exchange in mineralized tissue leads to the incorporation of fluoride into apatite crystals and the formation of fluorapatite.

Hormones and Bone Homeostasis

The balance between bone production and resorption and the maintenance of calcium and phosphate homeostasis is constantly controlled by the endocrine system. Gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), FSH, insulin, calcitonin, thyroid hormones, PTH, GH, IGF-I, vitamin D and sex steroids are some of the most important hormonal systems associated with bone health (Fig. 2).

Calcitonin normally promotes calcium deposition in bone, and its production by gastrointestinal tract hormones provides an additional means of optimizing the absorption of calcium into bone after food intake [59]. Vitamin D3 is essential for the regulation of plasma calcium levels. Vitamins D2 and D3 undergo a series of modifications in the liver and kidneys that convert them into powerful hormones that control calcium levels [60]. One of the main regulators of plasma calcium concentration is PTH, which is produced by the parathyroid glands after a decrease in ionized calcium concentration. As a classic calciotropic hormone, parathyroid hormone can rapidly mobilize calcium from the skeletal exchangeable calcium pool. When levels are elevated over time, it increases the frequency of activation and the depth of resorption, leading to an initially reversible bone loss comparable to the situation in thyroid hormone excess [61]. An increase in renal calcium excretion, which can lead to nephrocalcinosis and stones, and a decrease in bone mass and strength are the final consequences of persistent PTH excess. The extent of bone mass increase caused by hypoparathyroidism depends on the site of the skeleton and the duration of the disease [62]. In subjects with hypoparathyroidism, both an increase and a decrease in bone mineral density (BMD) were observed after substitution with PTH and PTH analogs.

Thyroid hormones are essential for maintaining proper bone mass, structure and strength in adulthood and for controlling skeletal growth and development. While thyroid receptor beta (TRβ) is responsible for the hypothalamic feedback loop controlling TSH secretion, thyroid receptor alpha (TRα) is the primary receptor for T3 activity in the osteoblast nucleus [63]. Regulation of bone turnover can be influenced by local expression of an alternative splice variant of TSH in the bone microenvironment [64]. However, when TSH signaling is sufficiently replaced by normal levels of T3 and T4, this alone has no effect on skeletal growth or maturation in children with loss-of-function mutations [65]. Severe hypothyroidism with low T3 and T4 levels leads to reduced tooth eruption and reversible arrest of bone growth in the developing child. However, due to faster skeletal maturation with the closure of the epiphyseal joints, hyperthyroidism in growing children also leads to short stature and reduced growth of long bones [66]. The main feature of hyperthyroidism, which causes reversible bone loss in the adult skeleton, is an increased activation frequency. Thus, as long as patients do not have chronic over-substitution with thyroid hormones, there is no evidence that hypothyroidism has a deleterious effect on bone [65]. It has been found that the bone mass density and structure of hypothyroid patients who are not over-substituted with T4 is the same as that of euthyroid control subjects [67]. TSH decreases within the euthyroid range and may

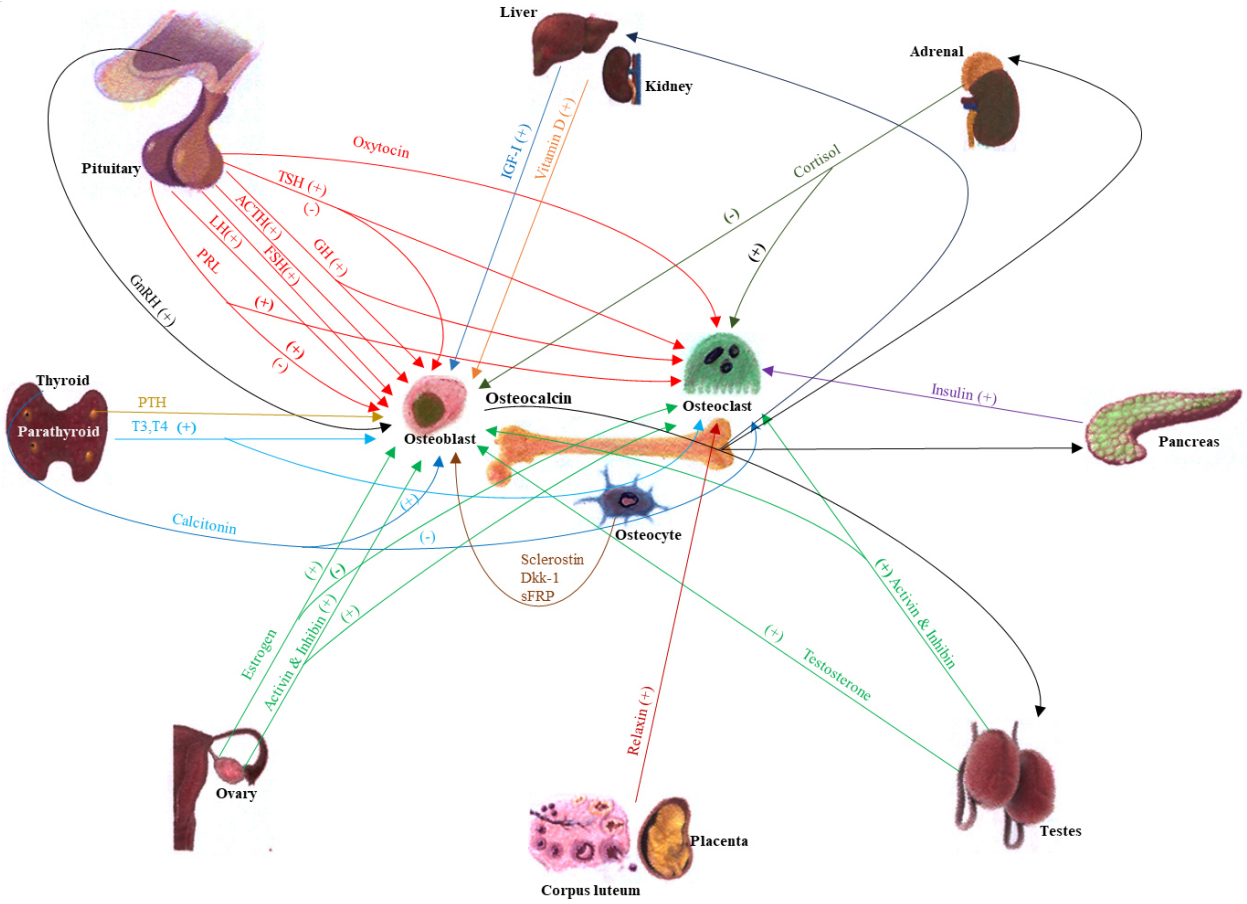

Fig. 2. Schematic representation of the effect of various hormones on bone cells and bone-derived proteins on organs. Gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), insulin, calcitonin, thyroid hormones, parathyroid hormone (PTH), growth hormone (GH), IGF-I, vitamin D and sex steroids regulate bone cell differentiation and osteoclastogenesis. The hormones also maintain calcium and phosphate homeostasis. Osteocalcin regulates steroidogenesis in the testes and adrenal glands. It regulates energy metabolism via the pancreas and liver. The image was created with Adobe Photoshop 7.0 (Adobe, San Jose, CA, USA) and Microsoft Office 2016 (Microsoft, Redmond, WA, USA). Dkk-1, Dickkopf-1; sFRP, secreted frizzled-related protein; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin; IGF, insulin-like growth factor.

have some effect on fracture risk, but subclinical hyperthyroidism increases the risk much more [68].

Skeletal growth and bone remodeling are significantly regulated by growth hormone (GH) and IGF-1, as evidenced by longitudinal bone growth through these two factors [69]. GH receptors and the activation of hepatic IGF-1 synthesis are the primary and indirect mechanisms by which GH influences bone. Patients with untreated GH deficiency had a lower bone turnover rate, a lower BMD and a higher fracture risk [70]. GH and other hormones such as PTH, estrogen and T3 regulate local IGF-1 production. Both GH and IGF-1 are essential for postnatal longitudinal bone growth, with a gradual increase in bone size and mass during childhood, with a more rapid increase at puberty. However, GH and IGF-1 appear to be generally anabolic and stimulate bone formation in preclinical studies [71]. Systemic IGF-1, which is produced in the liver by circulating GH, and local IGF-1 in bone are the main tools by which GH influences bone. Short stature, reduced bone size, reduced bone mass and reduced bone mineral content are associated with untreated GH deficiency (GHD) in childhood and adolescence. Both osteoblast differentiation and bone formation [72] as well as osteoclastogenesis and bone resorption [73] are promoted by local IGF-I signaling. The GH/IGF-1 axis is an important trigger for bone remodeling due to its simultaneous effect on osteoblast and osteoclast activity.

The two most important molecules that connect energy metabolism and bone remodeling are insulin and osteocalcin. According to the findings, there is an endocrine loop between bone and pancreas that controls insulin sensitivity and pancreatic insulin secretion. Osteoblasts bind to insulin and regulate their own growth through the expression of insulin receptors. Thus, bone remodeling and glucose metabolism are linked by complex interactions between the pancreas and bone [74]. By modulating bone

resorption, insulin signaling and action on bone-forming osteoblasts promote their activation and enhance the synthesis of osteocalcin. Therefore, osteocalcin is activated and glucose metabolism is promoted by insulin signaling in osteoblasts. Insulin signaling in osteoblasts ensures osteoblastic development and promotes the synthesis of osteocalcin. The results show that insulin signaling in osteoblasts integrates bone remodeling and energy consumption [75]. Insulin signaling in osteoblasts is important for the maintenance of glucose homeostasis throughout the body by upregulating the expression and activity of osteocalcin [76]. Reports have also demonstrated that postnatal bone formation and body composition are regulated by insulin receptor signaling in osteoblasts [76]. Osteoblasts possess the insulin receptor, and the development, survival and proliferation of osteoblasts depend on insulin signaling [77]. Adults with type 1 diabetes (T1D) have a slightly lower BMD, but those with type 2 diabetes (T2D) have a normal or even higher BMD. Meta-analyzes have demonstrated that diabetes in T2D increases the risk of hip fractures [78]. Energy-dependent activities, bone development and remodeling depend on adequate nutrition and substrate availability. Glucagon Like Peptide-1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP) are two gut hormones that have been shown to be effective in preclinical and evolving clinical studies [79,80]. As incretins, GLP-I and GIP increase postprandial insulin production, which in turn enhances the effect of insulin on bone. Although the immediate effect on bone formation is less obvious, clinical studies have shown that infusion of GLP-1 and GIP or the use of GLP-1/GIP receptor agonists can acutely inhibit bone resorption [81]. Overall, analyses of these agonists in clinical trials demonstrate that they stop bone resorption and increase fracture risk that often occurs after significant weight loss.

Adrenocorticotropic hormone (ACTH), a melanocortin peptide hormone produced from proopiomelanocortin (POMC), can influence the differentiation of osteoblasts and chondrocytes [82]. ACTH directly increases bone markers associated with adrenocorticotropic receptor expression on the surface of mesenchymal stem cells (MSCs) and osteoblasts formed from MSCs [83]. Although it is well known that excess glucocorticoids (GCs) are bad for bone, optimal bone formation depends on physiological levels of GCs. The development of mesenchymal progenitor cells into the osteoblast lineage depends on GCs [84]. Osteoblasts from mice showed slightly lower bone size and density when the glucocorticoid receptor was specifically switched off [85]. There is clear evidence that GCs act directly on bone cells both *in vitro* and *in vivo*. The RANKL/osteoprotegerin and Wnt signaling pathways in osteoblasts are specifically affected by GCs. It is difficult to fully understand how GCs affect osteoclasts; it probably involves both direct toxicity to the osteoclast and indirect effects through the osteoblast and osteocyte.

The effects of OT and PRL on bone have been linked to bone loss and bone recovery that occur during pregnancy, lactation and weaning. Elevated PRL levels during pregnancy and lactation are known to place the mother in a state of bone resorption, which provides the calcium necessary for fetal and neonatal skeletal growth and development [86]. By promoting intestinal calcium absorption during pregnancy, breastfeeding and the associated lactation process, PRL acts in part as a hormone that regulates calcium balance. Given the information from *in vitro* and *in vivo* studies, PRL appears to directly influence bone remodeling by stimulating bone remodeling with increased bone resorption and possibly decreased bone formation during periods of hyperprolactinemia [87]. Osteoblasts can respond to elevated PRL associated with lactation because they express PRL receptors (PRLR), whereas osteoclasts do not [88]. In mice lacking PRLR, bone production is lower [89]. On the other hand, PRLR-deficient female mice had significantly lower blood progesterone and estradiol levels, while both sexes had significantly higher parathyroid hormone levels [90]. The reduction in bone mass observed in PRLR-deficient animals could be due to a more complex change in the hormone profile and not just the lack of direct effects of PRL on bone cells. However, in adult animals, PRL has been shown to reduce the number of osteoblasts by reducing proliferation [91]. Weanling rats increased calcium release, resulting in net bone loss in adult animals, while young rats responded to PRL by increasing the rate of calcium deposition, resulting in net bone growth [92]. To some extent, PRL enhanced bone resorption by decreasing OPG expression and increasing RANKL. OT, a primitive neurohypophyseal hormone, has been shown to be an anabolic regulator of bone mass and is used in bone formation therapies. It has been suggested that OT may have both direct and indirect effects on bone metabolism because lactation causes increased calcium release from bone and because functional oxytocin receptors (OTRs) were first reported in primary osteogenic and osteosarcoma cells [93]. Postmenopausal women with osteoporosis showed significantly lower OT plasma levels compared to their healthy counterparts [94]. OT has been shown to suppress adipocyte differentiation while altering the fate of human bone marrow-derived mesenchymal stromal cells toward the osteoblastic lineage. The initial *in vitro* discovery that OT is pro-osteogenic and promotes the increase of a substance known to be associated with an increase in bone formation, prostaglandin E2, was the basis for the first proposal to use OT as a new class of bone-building drugs. Deletion of OT or OTR has been shown to impair bone development in young mice, and it has been postulated that OT is essential for the maintenance of basic skeletal homeostasis in both sexes [95]. Increases in Ca^{2+} levels and pre-osteoclast numbers *in vitro* are responses of functional OTRs to osteoclasts and their precursors to OT administration [96]. Intramuscular OT injection has been found to promote bone development in adult male albino rats [97]. OT promotes osteoclast development in-

directly by upregulating RANKL through cocultured stromal cells and directly by inducing nuclear factor-κB and mitogen-activated protein kinase.

Although there is limited data from primary cell cultures, a recent study has provided possible evidence for direct effects of GnRH on osteoblast-like cells. Expression of GnRH and gonadotropin-releasing hormone receptor (GnRHR) was found in canine osteosarcoma cell lines and to a lesser extent in normal canine osteogenic progenitor cells [98]. GnRH and kisspeptin may have osteoblastic proliferative effects on osteosarcoma cells, as the serotonergic system has been shown to control bone mass through recruitment and proliferation of osteoblasts [99]. Previous findings show that increased serum levels of the hormone follicle-stimulating hormone (FSH) are associated with bone loss. There is an ongoing debate about the possible function of FSH as a direct modulator of bone physiology [100]. *In vitro* and *in vivo* studies in animals have yielded conflicting results suggesting a direct involvement of FSH in the control of bone turnover. Mature osteoblasts do not express FSH receptor (FSHR) mRNA, whereas human and mouse osteoclasts and bone marrow-derived skeletal stem cells do [101]. In addition, FSH promotes the production of tartrate-resistant acid phosphatase, a hallmark of differentiation. This suggests that FSH has a selective effect on differentiation and not on the proliferation of osteoclast precursors [102]. To mimic osteoclast formation, FSH increases the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα) and protein kinase B [103]. In addition to the aforementioned direct enhancement of osteoclast formation, FSH is also associated with modulating the activity of many proinflammatory cytokines that regulate osteoclastic bone resorption. In bone marrow preparations from mice exposed to recombinant FSH, the pool of osteoclast precursors increased because it enhanced the formation of TNF-α [104]. Increased bone mass and increased FSH-induced bone formation were found to be independent of GnRH or LH activity, but dependent on ovarian function [105]. Higher FSH levels have been associated with an increase in indicators of bone turnover in premenopausal and early menopausal women. Bone physiology may be directly influenced by LH and human chorionic gonadotropin (hCG). Extracts from primary human osteoblasts and osteoblast-like cell lines (SAOS2 and MG63) have been found to contain the LH receptor (LHR) [106]. Furthermore, it is not yet known whether LH/hCG has a direct effect on the biology of osteoclasts or osteocytes.

Males and females build bone at roughly the same pace before puberty. After puberty, when estrogen and testosterone levels increase, young men build more bone mass than young women; this is probably related to sex hormones. Throughout postpubertal life, estrogen plays a crucial role in the accumulation and maintenance of bone mass [64]. An imbalance of bone remodeling units leads to a decrease in bone mass; a net loss of bone occurs when bone resorption by osteoclasts exceeds osteoblast-induced bone synthesis. According to another preclinical study, estrogen has a direct effect on the survival and activity of the three major bone cells-osteocytes, osteoclasts and osteoblasts [107]. Estrogen also acts directly on osteoclasts; in animal models, deletion of estrogen receptor-α (Erα) leads to a loss of trabecular bone mass, most likely due to a decrease in osteoclast death and an increase in RANKL-induced osteoclast differentiation [108]. Recent research shows that estrogen deficiency decreases osteogenic differentiation and bone matrix synthesis by osteoblasts, which also possess ERα receptors. It is well known that a decrease in bone mass increases fracture risk through weakening, disorganization and thinning of bone trabeculae [109]. Most clinical studies demonstrating the efficacy of pharmaceutical therapies for osteoporosis have been conducted in postmenopausal women. Even though estrogen levels are significantly lower in postmenopausal women, they can still be detected and contribute to the maintenance of bone mass. As in women, the higher fracture risk associated with androgen deprivation emphasizes the importance of these hormones in maintaining bone health [110]. Oestradiol has been shown to reverse the increase in bone turnover indicators that occurred following GnRH agonist treatment in men to a significantly greater extent than testosterone. Although the progesterone receptor (PR) is expressed by both osteoblasts and osteoclasts in the bone microenvironment [111], the effects of progesterone on osteoclasts and osteocytes have not been thoroughly investigated. It has been reported that estrogen can induce PR expression on osteoblasts, suggesting that some of the effects of estrogen on bone physiology may be mediated in part by enhanced progesterone signaling [112]. Progesterone has been shown to support bone production through its effects on osteoblastic cells, although estrogen's function of reducing bone resorption is critical for maintaining bone health. Although it is now known that progesterone and estrogen interact, postmenopausal estrogen insufficiency is a significant risk factor for osteoporosis [113]. Studies in healthy premenopausal women have shown that levels of indicators of bone production and resorption fluctuate during the menstrual cycle, with osteoblastic activity being higher and markers of bone formation being more pronounced in the luteal phase.

The placenta and corpus luteum secrete relaxin during pregnancy. Early evidence for the involvement of relaxin in osteoclast formation was provided by several studies showing that relaxin may induce peripheral blood mononuclear cells to differentiate into mature osteoclasts [114]. Relaxin stimulates the expression of conventional stimulators of osteoclastogenesis such as RANK, nuclear factor-kappa-B (NF-κB), nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) and tartrate-resistant acid phosphatase, which are involved in osteoclast differentiation, survival and activation [115]. The production of the cysteine protease cathep-

sin K (CTSK), which is produced by mature osteoclasts, is primarily induced by relaxin. By upregulating RUNX2 expression and activity, relaxin has been demonstrated to synergistically enhance bone morphogenetic protein-2 (BMP-2)-induced osteoblast development and bone formation *in vitro* [116]. In an undamaged control bone (femur), relaxin appeared to promote trabecular bone formation [117].

Despite structural similarities, the regulating glycoprotein hormones inhibin and activin have very different physiological effects on reproductive function. Activin stimulates both osteoblasts and osteoclasts in primary mouse bone marrow cells, while inhibin has the opposite effect [118]. However, the inhibitory effect of inhibin produced by the gonads is not overridden by the stimulatory effect of locally produced activin on the formation of osteoblasts and osteoclasts [119]. Both inhibin A and inhibin B inhibit osteoblastogenesis and osteoclastogenesis in human skeletal and hematopoietic progenitor cells [120]. Reports show that inhibins directly affect the formation of osteoblasts and osteoclasts, and these effects apply to both human and animal *in vitro* models. Numerous studies show that activin has stimulatory effects on bone development *in vivo*. Activin administered daily to the fracture site improved callus development in a dose-dependent manner in a rat fibula fracture model [121]. The mechanical strength of the healed fracture improved after three weeks of treatment, and histologic examination showed that activin promoted the formation of new bone [87].

Thus, research has made progress in shedding light on the various hormones involved in the regulation of bone formation and resorption. Here we provide an overview (Table 1, Ref. [7,8,60,71,75,82,91,96,105,107,108,114,118,120,122–129]) of the most important hormones that influence bone homeostasis, either alone or in combination with other hormones or factors.

Nervous System and Bone Homeostasis

Although the peripheral nervous system and the central nervous system are thought to have different effects on the skeletal system, much research has uncovered coordinated mechanisms operating between them in the regulation of skeletal homeostasis (Table 2, Ref. [130–142]).

Involvement of the Central Nervous System

The central nervous system consists of the brain and spinal cord, which processes and integrates information to generate responses to stimuli [143]. Reports show that the central nervous system and the autonomic nerves, which are located in the bones, are interconnected [144]. The likelihood of heterotopic ossification is increased by damage to the central nervous system or spinal cord [145]. A reduction in bone mineral density following spinal cord injury due to compression, trauma or overextension may be related to the increase in Wnt signaling [146]. Our understanding of the role of the central nervous system in the control of bone metabolism has greatly expanded since the discovery of the regulatory effects of many neural circuits and neuropeptides [147]. Neurotransmitters or neural factors mediated modulation of bone homeostasis is summarized in Fig. 3.

As a neurotransmitter, serotonin is important for memory, learning and concentration [148]. There is great interest in learning how serotonin receptors regulate bone metabolism as they are present in major bone cell types such as osteoblasts, osteocytes and osteoclasts [130]. Several studies have confirmed that peripheral serotonin has a negative effect on bone production by promoting bone resorption [131]. Few reports suggest that increased peripheral serotonin causes structural damage and decreased bone density. It is possible that serotonin directly prevents bone formation and promotes resorption via bone tissue receptors by delaying osteoblast growth and differentiation [130]. The effect of serotonin on the modulation of bone tissue in the central nervous system is related to leptin and the sympathetic nervous system. By suppressing sympathetic nervous system activity, central serotonin can indirectly prevent bone resorption and promote bone growth [149]. Leptin can also suppress central serotonin, increase sympathetic activity and negatively influence bone formation. In addition, selective serotonin reuptake inhibitors have been associated with decreased bone density and increased fracture risk [150].

Brain-derived neurotrophic factor (BDNF) is found in the neurons of the dorsal root ganglia (DRG) and is essential for the development of the nervous system [132]. BDNF and its receptor TrkB have been found in fracture tissues during inflammation and early bone development, particularly in osteoblast and endothelial cells [132]. In an *in vivo* cortical osteotomy study, BDNF was observed to promote osteosclerosis, and osteocytes showed strong TrkB expression. BDNF also stimulates RANKL synthesis by hBMSCs, thereby promoting osteoclastogenesis. BDNF stimulates the proliferation and differentiation of hBMSCs by increasing the expression of integrin β1 via TrkB-mediated activation of ERK1/2 and AKT signaling pathways.

Semaphorin3A (Sema3A) is abundantly expressed in the hypothalamus and promotes healthy development of the nervous system [151]. The abundant expression of its receptor, neuropilin-1 (Nrp-1), in bone tissue suggests that Sema3A contributes to the bone-nerve connection. Sema3A and Nrp-1 have been shown to interact and activate the Wnt/β-catenin signaling pathway in osteoblasts, which suppresses osteoclast formation and adipogenesis. Studies in mice with an osteoporotic phenotype lacking Sema3A and Nrp-1 showed a reduction in osteoblasts and poor bone production, suggesting that Sema3A stimulates osteoblast development [152]. When mice were administered Sema3A intravenously, they showed faster bone regeneration and greater bone accumulation. In addition, neurospecific Sema3A-deficient animals exhibited a strikingly low bone mass phenotype, demonstrating a link between neuron-derived Sema3A and the observed skeletal abnormalities [153].

Table 1. Table showing the effect of hormones on bone homeostasis.

Hormones	Effect	Function in bone homeostasis	References
Gonadotropin-releasing hormone	Osteoblast	Osteoblastic proliferative	[122]
Growth hormone	Osteoblasts Osteoclasts Chondrocytes	Up-regulates osteoblast, chondrocyte, and osteoclast activity	[71,123]
Thyroid-stimulating hormone	Osteoblast Osteoclast	Enhances osteoblast differentiation Inhibit osteoclast formation and survival	[124]
Follicle-stimulating hormone	Osteoclast	Enhances osteoclast proliferation	[105]
Luteinizing hormone	Osteoblasts	Enhanced proliferation	[105]
Oxytocin	Osteoclasts	Bone formation	[96]
Prolactin	Osteoblasts	Bone resorption	[91]
Adrenocorticotropin hormone	Osteoblast	Differentiation of osteoblasts and chondrocytes	[82]
IGF-I	Osteoblast Chondrocytes	Up-regulates osteoblasts and chondrocytes	[71]
Calcitonin	Osteoblasts Osteoclasts	Down-regulates osteoclasts Up-regulates osteoblasts	[125]
Cortisol	Osteoblasts Osteoclasts Chondrocytes	Down-regulates osteoblasts and chondrocytes Up-regulates osteoclasts	[126,127]
Insulin	Osteoblasts Chondrocytes	Up-regulates osteoblasts and chondrocytes	[75]
Estrogen	Osteoblasts Osteoclasts Chondrocytes	Up-regulates osteoblasts Up-regulates chondrocytes at moderate levels Down-regulates chondrocytes at high levels Down-regulates osteoclasts	[8,107,108]
Testosterone	Osteoblast Chondrocytes	Up-regulates chondrocytes and osteoblasts at moderate levels	[7]
Vitamin D	Osteoblast Chondrocytes	Up-regulates osteoblast and chondrocytes	[60]
Thyroid hormone (T3 and T4)	Osteoblast Osteoclast	Up-regulates osteoblasts and chondrocytes at normal levels Up-regulates osteoclasts at high levels Acts on bone resorption and formation	[128]
Parathyroid hormone	Osteoblasts	Up-regulates osteoblasts	[129]
Relaxin	Osteoclasts	Promotes osteoclastogenesis	[114]
Activin	Osteoblast Osteoclast	Up-regulates osteoblasts Up-regulates osteoclasts	[118]
Inhibin	Osteoblast Osteoclast	Down-regulates osteoclasts Down-regulates osteoblasts	[118,120]

Involvement of Peripheral Nervous System

The peripheral nervous system (PNS), which serves as a transmitter of information, is the link between the central nervous system (CNS) and the skeleton. Nerves that originate at various points innervate the cranial bones and the long bones. The sensory neurons in the limbs originate in the DRG next to the spinal cord and have a pseudo-unipolar shape. The peripheral nerves that innervate the human bones are largely sensory and motor nerves that send stimuli or responses via action potentials or chemical signals. Neurons are found in sensory and autonomic ganglia in the PNS, which are groups of nerve cell bodies with axons that reach the target tissue. The majority of motor nerves in bone are autonomic nerves, which are classified as sympathetic or parasympathetic depending on their pharmacological properties. Innervation by sensory nerves is essential for bone restructuring and healing [154]. Reduced trabecular thickness and increased bone fragility are the consequences of damage to sensory innervation, which slows down bone production and increases bone resorption. Prior to vascular ingrowth and bone mineralization, the hyperplastic periosteum, callus, and fibrocartilage rim of a tibial fracture had multiple sprouting nerve fibers [155]. The autonomic nervous system is responsible for maintaining bone homeostasis and controlling the internal environment [156].

The influence of the peripheral nerves on bone is significantly influenced by neurogenic substances such as Calcitonin gene-related peptide (CGRP), Substance P (SP),

Table 2. Table showing the effect of neurotransmitters/factors on bone homeostasis.

Neurotransmitters/Factors	Effect	Function in bone homeostasis	References
Serotonin	Osteoblasts Osteocytes Osteoclasts	Promote bone resorption	[130,131]
BDNF	Osteoclasts	Promote osteoclastogenesis	[132]
NGF	Osteoblast	Promotes osteoblast differentiation Inhibits osteoblastic apoptosis for bone remodeling	[133]
CGRP	Osteoblasts Osteoclasts	Inhibit osteoclastogenesis	[134,135]
Neuropeptide Y	BMSCs	Promotes proliferation and differentiation of BMSCs into osteoblasts Facilitate bone repair after fractures	[136]
Substance P	Osteoblasts Osteoclasts	Promote osteogenesis Promote osteoclastogenesis	[133,137]
Semaphorin 3A	Osteoblast	Promote bone remodeling Promote bone mass	[138]
Norepinephrine	Osteoclast	Promote bone resorption	[135,139]
VIP	BMSCs Osteoclast	Enhance the osteogenic development Temporarily limit osteoclast activity and bone resorption; block osteoclast development	[140,141]
Acetylcholine	Osteoblast	Minimal impact on osteoblast differentiation Enhances osteoblast proliferation	[142]

BDNF, Brain-derived neurotrophic factor; NGF, Nerve growth factor; VIP, Vasoactive intestinal peptide; CGRP, Calcitonin gene-related peptide; BMSCs, Bone marrow stromal cells.

Vasoactive intestinal peptide (VIP) and Neuropeptide Y (NPY) as well as by neurotransmitters such as acetylcholine (Ach) and noradrenaline (NA). These substances influence angiogenesis, macrophage polarization, bone production and bone resorption by binding to specific receptors in bone tissue. Tropomyosin receptor kinase A (TrkA)-expressing sensory nerve fibers innervate bone and are necessary for the proliferation of osteochondral progenitor cells during skeletal development in mammals [157]. Nerve growth factor (NGF), which was identified as the first neurotrophic factor, mainly controls the development, survival and regeneration of neurons [158]. In addition to initiating TrkA+ sensory neurons to transmit injury signals, NGF also determines the type and amount of innervation required for recovery and controls the development of TrkA+ neurons in the long cartilage membrane of bone during development, which is necessary for progenitor cell differentiation and bone mineralization [144].

To control the activity of bone cells, CGRP is mainly produced in the DRGs and released to synaptic vesicles. The periosteum, which is essential for the formation of new bone, has a higher density of CGRP-positive nerve fibers than the trabeculae and bone marrow [159]. Studies have shown that CGRP has dose-dependent effects on the upregulation of osteogenesis-related genes and the mineralization of osteogenic cells [160]. CGRP, which is produced by sensory nerve endings, induces osteogenic differentiation in periosteal-derived stem cells via the cAMP-CREB signaling pathway by binding to the RAMP1-CLR complex. Through its interaction with inflammatory factors, CGRP can increase vascular permeability and promote vasodilation, thereby regulating blood flow in blood vessels [161]. In addition, CGRP released by DRGs is associated with bone defect regeneration and angiogenesis during osteoporotic fracture healing, both of which have a significant impact on nutrient delivery during fracture healing [162].

Substance P (SP), a neuropeptide, is widely distributed throughout the neurological system. The periosteum, joints, long bones and epiphyseal growth plates are among the areas of the skeletal system with high metabolic activity where SP-positive nerve fibers are most abundant. Recent research has shown that high levels of SP upregulate osteogenic genes in bone marrow-derived mesenchymal stem cells (BMSCs), possibly by modifying reactive oxygen species production and autophagic activity [163]. Low SP levels allow BMSCs to proliferate further and prevent them from undergoing osteogenic differentiation. SP has also been shown to enhance the recruitment of endogenous mesenchymal stem cells in the repair of cranial bone defects. Capsaicin-induced inactivation of sensory neurons with decreased SP expression during osteoporosis has been associated with an increase in osteoclasts. A known neuropeptide that is mainly produced and expressed in the nervous system is neuropeptide Y. In addition, NPY is essential for bone metabolism and the control of bone remodeling [136]. Mice with a genetic deletion of NPY showed an improved development of the bone cortex, a higher mineral content and a higher bone density. In addition, the aging process and the occurrence of osteoporosis are directly related to the promotion of adipogenesis by NPY and its in-

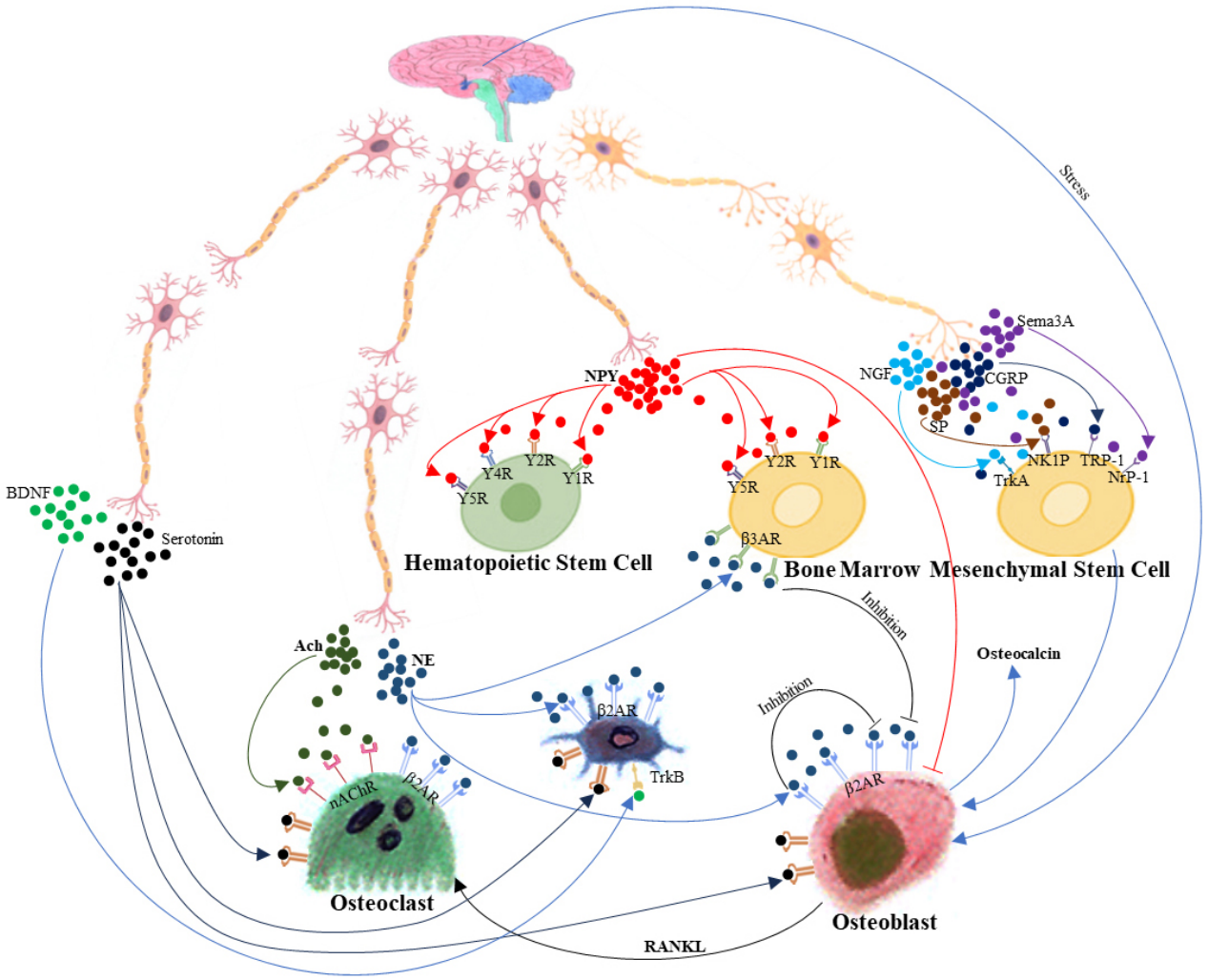

Fig. 3. Schematic diagram showing the involvement of the nervous system in the regulation of bone metabolism. Sema3A, NGF, CGRP and SP promote BMSC mobilization and bone formation. NPY modulates BMSCs and HSCs. Serotonin regulates the activity of osteoblast, osteoclast and osteocytes. NE modulates the activity of osteoblast and osteocytes through β2AR and BMSCs through β3AR. BDNF regulates osteocytes through TrkB. The image was created with Adobe Photoshop 7.0 (Adobe, San Jose, CA, USA) and Microsoft Office 2016 (Microsoft, Redmond, WA, USA). Sema3A, Semaphorin3A; BMSC, Bone marrow stromal cell; HSC, Hematopoietic Cell; NE, Norepinephrine; NPY, Neuropeptide Y; SP, Substance P; Ach, Acetylcholine.

hibitory influence on the osteogenesis of BMSCs. In rat experiments, it was discovered that NPY activates the Wnt/β-catenin signaling pathway, which in turn promotes the proliferation and differentiation of bone marrow stromal cells into osteoblasts [164]. By influencing central and peripheral noradrenergic neurons via the Y2 receptor, NPY also reduces excessive, stress-induced bone resorption. By activating the Y1 receptor, NPY has also been shown to facilitate bone repair after fractures [136].

The periosteum contains a high concentration of vasoactive intestinal peptide (VIP), and VIP-containing nerve fibers are widely scattered throughout the Haversian system and in Volkmann's canal, which runs from the diaphysis to the epiphysis [165]. VIP is usually released together with Ach from cholinergic nerve terminals and activates vasoactive intestinal peptide receptors (VPAC1 and VPAC2) to exert its physiological effects [166]. VIP has evolved into a multipurpose molecule with a variety of physiological functions, such as its involvement in bone tissue regeneration and homeostasis [140]. By activating the Wnt/β-catenin signaling pathway, VIP can promote osteogenic development of BMSCs according to *in vitro* studies [165]. In addition, a decrease in VIP levels in bone has been observed after ovariectomy, which is associated with the occurrence of postmenopausal osteoporosis [167]. Further studies have shown that VIP increases the expression of osteogenic markers and facilitates fracture repair in mice that have undergone sympathectomy [168]. In addition, a recent study demonstrated that VIP can transiently limit osteoclast activity and bone resorption and block osteoclast development [141].

The major neurotransmitters of the sympathetic nervous system, noradrenaline (NE) and acetylcholine (Ach), act mainly through the widely distributed β-adrenergic receptors (β-AR) in bone tissue [142]. It is well known that increased sympathetic activity increases urinary epinephrine levels, which in turn inhibits osteogenic activity. The increased bone loss associated with glucocorticoid use may be explained by the effect of NE on BMSCs, which may inhibit bone formation [169]. In addition, NE promotes the production of RANKL by osteocytes, which is essential for osteoclast differentiation and ultimately enhances osteoclast maturation [170]. By promoting intracellular ROS production, NE also directly enhances osteoclastogenesis. β-AR inhibitors, including propranolol, have been shown to have corresponding negative effects on this process. As a primary neurotransmitter produced by cholinergic nerve fibers, ACh binds to muscarinic acetylcholine receptors (mAChRs) or nicotinic acetylcholine receptors (nAChRs) on cells to exert its biological effects. Reports indicate that although ACh has minimal effects on osteoblast differentiation, it promotes osteoblast proliferation. Reduced bone mass and increased bone resorption are observed in mice lacking the α(2)nAChR subunit [144]. Through reduced Ca^{2+}-NFATc1 communication, nAchR activation suppresses RANKL-induced Ca^{2+} oscillation, which in turn negatively regulates the process of osteoclastogenesis. These findings have demonstrated the importance of cholinergic processes in skeletal embryo development.

Immune System and Bone Homeostasis

The lymphoid progenitor cells differentiate further into T lymphocytes, B lymphocytes or natural killer cells, while all other myeloid lineages and preosteoclasts arise from common myeloid progenitor cells. Multipotent stem cells differentiate into mesenchymal precursors, chondrocytes and adipocytes [171]. These precursors then differentiate into preosteoblasts and finally into mature osteoblasts that produce matrix. Preosteoclasts and multinucleated osteoclasts fuse to form activated osteoclasts. Numerous proinflammatory cytokines produced by immune cells are involved in bone damage (Table 3, Ref. [11,172–188]). It should be noted that most cytokines thought to be involved in bone cell control are produced by both immune and non-immune cells, such as fibroblasts, and have pleiotropic effects on many cell types [189].

TNF-α and IL-1, -3, -6, -7, -11, -15 and -17 enhance bone resorption by either promoting the differentiation and activation of osteoclasts or by inducing the expression of RANKL on osteoblasts. On the other hand, IFN-α, -β and -γ as well as IL-4, -5, -10, -12, -13 and -18 prevent osteoclastogenesis by either directly or indirectly inhibiting RANKL signaling [190]. TNF-α, IL-1 and IL-4 are soluble cytokines that also influence osteoblast-mediated bone formation. Tumor necrosis factor receptor associated factor 6 (TRAF6) expression is stimulated by interleukin-1, which enhances the RANKL-RANK signaling cascade and induces mature osteoclasts to become bone resorbing. Through proteosomal degradation, interferon gamma suppresses TRAF6 expression, thereby halting osteoclast development [191]. In osteoclast progenitor cells, the receptor activator of NF-κB triggers the production of IFN-β, which inhibits RANKL-induced c-FOS expression and acts as a negative feedback regulator of osteoclast development [191]. Tumor necrosis factor-alpha mainly interacts with TRAF2 to promote the activation of NF-κB. TNF-α plus TGF-β leads to osteoclastogenesis even in the absence of RANK or TRAF6, although TNF-α alone cannot cause osteoclastogenesis and TNF-α overexpression cannot reverse RANKL deficiency. In general, osteoclastogenesis is inhibited by activated T cells. Most Th1 cytokines and some Th2 cytokines such as IL-4 and IL-10 prevent osteoclastogenesis even when T cells express RANKL. Th17 cells can directly contribute to osteoclast formation as they express RANKL to a higher degree than Th1 or Th2 cells [192]. In addition, Th17 cells do not produce much IFN-γ, which inhibits osteoclastogenesis. In addition, Th17 cells stimulate local inflammation, leading to the production of proinflammatory cytokines that enhance RANKL expression on cells supporting osteoclastogenesis and RANKL-RANK signaling transduction in osteoclast progenitor cells. Th17 cells produce interleukin-17, which triggers the production of matrix-degrading enzymes such as matrix metalloproteinases that promote the breakdown of bone and cartilage [193]. Through a cytokine-dependent process mediated by TGF-β, IFN-γ, IL-4 and IL-10, regulatory T cells counteract the effects of Th17 cells on osteoclast formation by suppressing osteoclast formation.

In osteoporosis, periodontal disease and rheumatoid arthritis, IL-1β promotes osteoclast production and bone resorption [194]. Another such cytokine is IL-6, which can promote the conversion of osteoclast precursors into mature osteoclasts and is pathogenetic for inflammatory bone loss in some situations. IL-6 is known to play a key role in the pathophysiology of bone loss in both acute and chronic inflammation by promoting osteoclastic bone resorption. The increased bone loss observed in postmenopausal and idiopathic osteoporosis is caused by IL-1 [4]. The production of IL-1, IL-6 and/or TNF-α by peripheral blood monocytes was positively related to bone resorption and spinal bone loss in healthy pre- and postmenopausal women [195]. IGF-1, which is produced in substantial amounts by osteocytes, has been shown to regulate osteoblasts and osteoclasts in either a paracrine or autocrine manner. By activating the ERK and Jun N-terminal kinase and mitogen-activated protein kinase (JNK-MAPK) pathways, IGF-1 can promote osteoblast proliferation via the MAPK and Akt pathways and also trigger osteogenic differentiation of periodontal ligament stem cells. In addition, ephrin B2/EphB4-mediated cell-cell communication controls IGF-1-induced differentiation of osteoblasts and osteoclasts. *In vitro*, os-

Table 3. Table showing the effect of different immune cells/cytokines on bone homeostasis.

Immune cells/Cytokine	Effect	Function in bone homeostasis	References
CD4+ Treg cells	Osteoclast	Inhibit osteoclast differentiation Suppress osteoclastogenesis	[172]
CD8+ Treg cells	Osteoclast	Promote bone loss	[172]
T_H17 cells	Osteoclast	Stimulating bone resorption Induce osteoclastogenesis	[173]
NKT cells	Osteoclast BMSCs	Increases development, maturation and activity of osteoclasts Promote osteoclastogenesis	[174]
B Cells	Osteoclast	Promote osteoclastogenesis	[175]
Neutrophils	Osteoblasts Osteoclasts	Activate osteoclastic bone resorption	[176]
Osteomacs	Osteoblast	Mineralization and maintenance of osteoblast	[172]
IFN-γ	Osteoclast	Promote osteoclastogenesis	[11]
TNF-α	Osteoclast	Induces osteoclastogenesis	[177]
TGF-β	Osteoclast	Promotes osteoclast differentiation	[178]
GM-CSF	Osteoclast	Inhibit osteoclastogenesis	[179]
IL-1	Osteoclast	Promote osteoclastogenesis	[180]
IL-3	Osteoblast	Inhibit osteoclastogenesis	[181]
IL-4	Osteoclast	Inhibit osteoclastogenesis	[182]
IL-6	Osteoclast	Promote proliferation of osteoclast Inhibit osteoclastogenesis	[183]
IL-10	Osteoclast	Suppress bone resorption	[184]
IL-17	Osteoclast	Induce osteoclastogenesis	[185]
IL-18	Osteoclast	Inhibit osteoclast	[186]
IL-23	Osteoclast	Activation of osteoclast Supports osteoclastogenesis	[187]
IL-27	Osteoclast	Inhibit osteoclast	[188]

Abbreviations: CD4+ Treg cells, CD4+ regulatory T cells; CD8+ Treg cells, CD8+ regulatory T cells; T_H17 cells, T helper 17 cells; NKT cells, Natural killer T cells; IFN-γ, Interferon-gamma; TNF-α, Tumor necrosis factor alpha; TGF-β, Transforming growth factor beta; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IL, Interleukin; BMSCs, Bone marrow stromal cells.

teoblast activity is inhibited and osteoblast death is triggered when various cytokines such as IL-1 and TNF-α activate the inducible NO production pathway. TNF-α has a strong proapoptotic effect and prevents the differentiation of osteoblast cells [29]. In osteoblasts, collagen production is inhibited by IL-1, TNF-α and IFN-γ. In inflammatory bone resorption areas, IL-10 suppresses the production of pro-inflammatory cytokines. It also inhibits bone resorption and osteoclast development. IL-4 and IL-13 have been reported to be chemoattractants for osteoblasts and to inhibit prostaglandin synthesis in bone [29]. In an osteoblastic cell line, IL-4 directly promotes proliferation and inhibits differentiation. The animals overexpressing IL-4 show reduced bone production and differentiated osteoblasts at the bone surface. The main effects of fibroblast growth factor 23 (FGF23) on mineral homeostasis include lowering parathyroid hormone levels, serum phosphate and $1,25(OH)_2D_3$ [12]. Reports show that vascular endothelial growth factor (VEGF) is secreted by chondrocytes and osteoblasts in bone and is essential for skeletal formation. VEGF also enhances the bone resorptive activity of osteoclasts.

Bone-derived Proteins

Important bone-derived proteins are sclerostin, osteopontin (OPN), osteoprotegerin (OPG), osteocalcin (OCN), prostaglandin E2 (PGE2) and RANKL/RANK [196]. The predominant biological function of bone-derived proteins is the modulation of bone mineralization processes. They also support vascular integrity and remodeling, atherosclerosis and plaque formation, angiogenesis and neovascularization, calcification of additional bone tissue, and bone development and remodeling [197]. Bone-related proteins directly regulate bone formation and resorption through hormones, oxidized lipids, inflammatory cytokines, homocysteine, vitamin D and vitamin K. Numerous cell types such as antigen-presenting cells, fibroblasts, osteoblasts, chondrocytes, osteocytes, endothelial cells, smooth muscle cells, epithelial cells, mammary glands, skeletal muscles and organs, kidneys, including brain, placenta and inner ear, express bone-related proteins [198]. Previous evidence has shown that atherosclerosis, cardiovascular disease, chronic rheumatic diseases, multiple sclerosis, inflammatory bowel disease, autoimmune diseases, cancer

and malignancies can be significantly affected by bone-related proteins [199,200].

Sclerostin (213 amino acids; 40 kDa) is a secretory glycoprotein secreted by osteocytes and is an important regulator of bone formation and homeostasis [201]. It is an antagonist of bone morphogenetic protein and Wnt signaling and controls the growth, differentiation, mineralization and death of preosteoblastic cells and osteoblasts as well as the production of new bone [201]. Humans and experimental animals with sclerostin deficiency have large bones [202]. On the other hand, mice overexpressing sclerostin show a significant decrease in bone volume and mass [203]. Endocrine effects of sclerostin have been reported via its paracrine effects, which can control energy metabolism in the body. The Food and Drug Administration approved romosozumab, a humanized monoclonal sclerostin-neutralizing antibody (Scl-Ab), in 2019 for the treatment of osteoporosis in patients at high risk of fracture [204]. In addition, sclerostin was discovered to contribute to osseointegration of implants, alveolar bone remodeling, pupillary/periodontal inflammation, cementogenesis and dentinogenesis.

Osteocytes and osteoblasts secrete FGF23 and OCN, which are probably new hormones released by the skeleton. FGF23 is a systemic hormone involved in mineral metabolism and a bone-derived factor that controls the mineralization of the extracellular matrix [205]. It has the ability to diffuse into the blood after being released from cells and to reach target cells in various organs. 1,25 Dihydroxyvitamin D is one of the many variables that regulate FGF23 expression. By activating VDR, it can promote the expression of FGF23. At the same time, FGF23 can also prevent the synthesis of 1,25 dihydroxyvitamin D [206]. OCN (49 amino acids; 6 kD) is a non-collagenous acidic glycoprotein and a type of vitamin K-dependent calcium-binding protein that makes up the majority of the bone matrix. 1α,25-dihydroxy-vitamin D3 regulates and controls the synthesis of OCN [207]. There is evidence that leptin can influence OCN carboxylation via the hypothalamus, and OCN in plasma is inversely correlated with fat mass and plasma glucose [208]. It is a useful clinical marker for the diagnosis of metabolic bone diseases such as osteoporosis, Paget's disease and bone tumors [209]. Overactivity of FGF23 and OCN can lead to the development of rare forms of rickets and hypophosphatemic osteomalacia, including tumor-induced osteomalacia and X-chromosome-associated hypophosphatemia. They are primarily involved in the regulation of phosphate metabolism and calcitriol synthesis in the kidneys [210].

OPN is a non-collagenous protein secreted by osteoblasts, osteoclasts and other cells in bone. It is a crucial element in controlling the mineralization of the extracellular matrix. The osteoblast mRNA of bone morphogenetic protein signaling pathways is associated with OPN and can promote osteoblast growth and calcification. It has also been shown to induce cardiac hypertrophy, increase fibrillar collagen content and promote cell signaling, adhesion, survival, proliferation and migration in a variety of cell types [211]. Earlier findings have shown that OPN is a potent biomarker for vascular calcification in patients with chronic kidney disease [212] and asymptomatic coronary artery disease [213]. OPN is closely related to glomerular filtration rate and has renal clearance. There is evidence of a link between OPN and impaired endothelial function, which is considered a sign of poor clinical outcomes in cardiovascular disease, as well as systemic inflammatory activation. The functions of OPN and VEGF in controlling apoptosis, hypoxia response, cell motility and angiogenesis are similar [214]. It is reported that circulating OPN may be a useful indicator of arteriosclerosis and atherosclerosis.

PGE2 is one of the many prostaglandins and consists of 378 amino acids. PGE2 has a relative molecular mass of about 43 and belongs to the metabolites of arachidonic acid. PGE2 is secreted by osteoblastic cells, resembles a hormone and is rapidly oxidized by the body [215]. It fulfills biological functions by binding to its receptors, which then activate and transmit the associated signaling pathways in the cells. TGF-β is a polypeptide signaling molecule that regulates a variety of cellular processes, such as growth regulation and maintenance of internal environmental balance. To coordinate bone remodeling, TGF-β influences osteoblasts, osteoclasts and their precursor cells [216]. It controls the development and activity of osteoblasts and osteoclasts and promotes the formation of matrix proteins. Due to its potent chemotactic impact on fibroblasts and inflammatory cells, it can exacerbate local inflammation. OPG is a soluble protein that belongs to the tumor necrosis factor receptor superfamily and is produced by osteoblasts, osteoblastic stromal cells and activated mononuclear cells. The OPG/RANKL/RANK system has been shown to contribute to cardiac remodeling and left ventricular dilatation in both the acute and chronic phases of heart failure development [217]. Reports suggest that RANKL and OPG are associated with vascular calcification, osteoporosis, bone remodeling, inflammation and cardiovascular disease [218]. Recent clinical studies show that coronary atherosclerosis is associated with a marked increase in OPG as well as a tendency towards soluble RANKL and the RANKL/OPG ratio [219]. The overproduction of bone-related proteins is caused by RANKL-stimulated expression of a wide range of transcription factors such as TRAF6, p38 MAPKs, JNK IκB-α and NF-κB p65 DNA [220]. Overall, the production of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10, IL-21 and IL-23) tightly regulates the RANKL/RANK/OPG system and its downstream signaling pathway [221].

Conclusion

In this minireview, we have discussed the basic structure of bone and the regulation of bone homeostasis by endocrine, immune and nervous systems. Bone is composed of cellular components such as osteoclasts, osteoblasts, os-

teocytes and bone lining cells and is continuously remodelled through formation and resorption. In addition to biological components such as type I collagen and non-collagenous proteins, water and hydroxyapatite, trace elements such as calcium, phosphorus, iron, zinc, copper and magnesium are crucial for the homeostasis of bone. Hormones such as GnRH, FSH, LH, prolactin, oxytocin, estrogens, testosterone, parathyroid hormones, vitamin D, thyroid hormones, ACTH and glucocorticoids work together to regulate bone formation and resorption. Nerve damage occurs along with bone injury, and bone regeneration requires reinnervation. Neurotransmitters such as serotonin, nerve growth factor, neuropeptide Y, substance P, noradrenaline and acetylcholine interact with various bone cells and prevent bone resorption and promote bone growth. The connection between the immune system and the skeletal system is complicated under both pathogenic and normal circumstances. Immune cells such as CD4+ Treg cells, CD8+ Treg cells, TH17 cells, natural killer T cells, B cells, neutrophils, etc., regulate the function of osteoblasts and osteoclasts. Cytokines such as TNF-α, TGF-β, GM-CSF, IL-1, IL-3, IL-4, IL-6, IL-10, IL-17, IL-18, IL-23, IL-27 are involved in bone formation and resorption. Bone-derived proteins such as sclerostin, FGF23, osteocalcin, osteopontin, prostaglandin E2, TGF-β, etc., regulate the development and activity of osteoblasts and osteoclasts and also influence the function of other organs and systems. Further research is required to expand our knowledge of the complex relationships between bone homeostasis and nervous, immune and endocrine systems.

Availability of Data and Materials

Not applicable.

Author Contributions

GKB, VKS and RKK-conceptualization, writing of the initial draft and monitoring. RM, VKS and RKK - design of the review article, collection of published articles, writing of the draft, help and advice on topical references and editorial changes. All authors were involved in the critical revision of the manuscript for important intellectual content. All authors give their final approval of the version to be published. All authors have participated sufficiently in the work and have agreed to be responsible for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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