Artykuł przeglądowy *Review*

Role of leptin as a factor regulating bone metabolism

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Summary

Discovered in 1994, leptin is one of the most important anorexigenic factors in the body. This hormone is synthesized and released mainly by white adipose tissue, but could also be released by other tissues. Its main function is suppressing the feeling of hunger by interacting with LEPRs receptors located in the hypothalamus, which makes it one of the main factors regulating the food intake. Appetite regulation is not the only function of leptin in the organism. By interacting with LEPRs, it can also influence the metabolism of various body tissues and organs, such as gonads, immune system cells, bone marrow, and bones. A very important aspect of leptin activity, though seldom discussed in the literature, is its impact on bone tissue metabolism. Leptin can affect bone cells through two different pathways: a peripheral one and a central one. The peripheral pathway involves a direct interaction of leptin with LEPRs located on the surface of bone cell. The central pathway, on the other hand, involves the interaction of leptin with structures of the central nervous system, which regulates the secretion of many hormones, such as serotonin, growth hormone, and thyroid hormones, directly affecting the metabolic activity of bone cells. Determining the overall effect of leptin on bone metabolism is not an easy task. This is due to significant differences in the way individual leptin activity pathways may affect bone metabolism. Indirect pathways stimulate bone tissue in bone anabolic or bone katabolic processes, leading to an increase or a decrease in bone mass, depending on the hormone through which bone metabolism is regulated. However, most of the literature data suggest that the leptin regulation of bone turnover is determined mainly by the direct pathway, and the overall effect of its activity is an increase in bone tissue mechanical parameters. Nevertheless, a complete understanding of these mechanisms requires further research. It is worth mentioning that this hormone is also involved in the development of several disorders of the skeletal system, such as osteoarthritis, osteoporosis, and rheumatoid arthritis, but the exact impact of leptin on the course of these diseases is still not fully understood.

Keywords: adipokines, leptin, bone, health, animals

Discovered in 1994, leptin is an adipokine hormone synthesized and released primarily by white adipose tissue. However, it can also be derived from other sites in the body, such as the placenta, salivary glands, bone marrow, skeletal and cardiac muscles, lymphatic tissue, and several endocrine glands, such as the pancreas and pituitary gland (9). Another essential source of leptin is gastric mucosa (3, 13). Leptin has a peptide structure, consisting of 167 amino acids, whose total molecular weight is 16 kDa. The Ob genes responsible for encoding leptin in humans are located in the 7th chromosome. This gene is present in all mammals, and its orthologs are widespread in many animal groups, such as fish, amphibians, and reptiles. All peptides encoded by the Ob gene and its orthologs differ in amino acids sequences, but preserve the same function in the organism (3, 8, 13, 29, 35, 61).

The main factors regulating the level of circulatory leptin is the amount of adipose tissue in the body (35). An increase in the level of adipose tissue causes an increase in the serum concentration of leptin. Conversely, starvation causes a significant decrease in its blood concentration. According to some studies, leptin concentration in the blood serum is related to food intake. Researchers have observed that serum leptin levels increase significantly after a meal. This phenomenon has been linked to the activity of the stomach lining cells, which also have the ability to secrete leptin (3, 8, 9, 13). Another important factor that can cause fluctuations in the level of circulating leptin is insulin. Studies conducted on patients with type 1 diabetes showed that serum leptin levels were significantly higher in patients undergoing insulin treatment. On the other hand, in patients suffering from insulinoma, a pancreatic tumor

associated with hyperinsulinemia, a significant decrease in blood insulin and leptin levels was observed, which returned to normal values after surgery. Some researchers, however, indicate that insulin concentration within physiological limits has no effect on serum leptin levels. Cammisotto et al. (7) showed that both glucocorticoids and glucose stimulate leptin synthesis and release, whereas catecholamines, free fatty acids, and thyroid hormones have the opposite effect. The circadian rhythm also plays an important role in the regulation of serum leptin concentration. During the day, the highest level of leptin occurs between midnight and early morning hours, and the lowest in afternoon hours. Interestingly, these fluctuations occur in both thin and obese individuals (22, 33, 35). Leptin concentration depends also on the menstrual cycle in women and achieves the highest values during the luteal phase (22, 26, 29, 31, 32, 35).

Leptin is known as one of the most important anorexigenic factors with neuroendocrine actions. Through the activation of hypothalamic neurons synthesizing proopiomelanocortin and neurons that are part of the cocaine- and amphetamine-regulated transcript, while inhibiting the activity of neurons releasing agouti-related peptide and neuropeptide Y, leptin suppresses the feeling of hunger. It is also one of the main factors responsible for information about the energy reserves stored in the body, the amount of which is directly proportional to its concentration. An often overlooked fact is that, in addition to the actions listed above, leptin can act on many different tissues (11). By influencing the hypothalamus-pituitary axis (HPA), leptin affects the secretion of luteinizing hormone (LH), follicle stimulating hormone (FSH), growth hormone (GH), and prolactin (PRL), which has a profound effect on the activity of the gonads, and therefore the participation of leptin in the regulation of sexual maturation is particularly important (11, 30). The ability to regulate the HPA allows leptin to inhibit the release of cortisol by the adrenal cortex via the ACTH pathway. In the same way, by regulating the activity of the HPA, it can also influence the releasing function of the thyroid gland, stimulating it to secrete triiodothyronine (T3) and thyroxine (T4) hormones. Leptin is also recognized as a key factor stimulating the proliferation and antimicrobial effect of immune cells. Moreover, some researches believe that leptin may act as a proinflammatory cytokine released from tissues under the influence of damaging stimuli (19, 21, 26, 36, 37, 42, 51, 62).

Leptin receptor

Leptin influences cell metabolism by interacting with specific membrane receptors LEPRs, (some authors use the abbreviation ObR). These receptors belong to class 1 cytokine receptors with a protein structure. To date, six LEPRs isoforms have been recognized, A to F, all of which are encoded by a gene located on the first human chromosome. The highest concentration of LEPRs is found in hypothalamic neurons, but many other cell types also contain these receptors in their membrane and cytoplasmic structures. These include cells located in the gonads, bone tissue, bone marrow, and cells of the immune system (1, 47, 48, 61, 62). LEPRs consist of several domains with different functions. A key role in receptor activity is played by two homologous domains of cytokine receptors (CRH1, CRH2), immunoglobulin-like domain (IGD), and two domains of membrane fibronectin type III (FN III). The crucial function of the CRH2 domain is to bind a molecule of leptin with a receptor. The domains IGD and FN III are essential for LEPRs activation and transmission of the signal to the cell although they cannot interact directly with leptin molecules. The function of CRH1 is still a subject of research (1, 49, 62, 63).

The association of LEPRs with leptin initiates a signaling pathway leading to changes in cell metabolism. There are a few different types of signaling pathways connected with an active leptin receptor, namely the JAK/STAT pathway, the SHP2/MAPK, PI3K pathway, the AMPK pathway, and the TOR pathway. The best studied way of transmitting signals from LEPRs is the JAK/STAT pathway. It is related to the activation of the Janus kinase, which leads to the phosphorylation of the STAT3 factor. The active form of STAT3 is transported to the cell nucleus, where it plays an important role in regulating the processes of transcription and translation (62, 63). Some mutations in the genes encoding LEPR can lead to abnormalities in leptin binding to CRH2 and disruptions in signaling from the receptor to the cell nucleus, so that the brain does not respond appropriately to signals from leptin in the body. As a result, the brain continues to feel hungry and does not signal that the body has enough fat. This often leads to morbid obesity in people with this disorder (23, 27).

An often overlooked aspect of leptin's action is its influence on bone metabolism. It has been proven that leptin can have a significant influence on the mechanical properties of bone tissue in both humans and animals. This interaction can be an important factor contributing to the development of many skeletal disorders. The aim of this review is to present the influence of leptin on bone metabolism, characterized by an intimate cooperation of bone cells, including osteoblasts, osteoclasts, and osteocytes, to maintain the quantity of bone tissue and the integrity of bone structure. A better understanding of changes occurring in bone tissue under the influence of regulation via leptin-linked metabolic pathways may help improve our knowledge about possible causes of skeletal impairments.

The ways of leptin's action

It is known that leptin can affect bone metabolism in two different ways. The first is a direct mechanism in which it regulates the activity of bone cells through

direct interaction with LEPRs located in their cell membrane. The second way can be described as an indirect mechanism, in which leptin interacts with receptors located in the central nervous system (CNS), which regulates the release of hormones responsible for the modulation of bone turnover (41, 59).

Direct mechanism

Leptin is delivered to the bone mainly through the bloodstream, but it has been shown that it can also be synthesized by bone marrow adipocytes (2). LEPRs have been confirmed to be located on the surface of bone tissue cells and bone marrow mesenchymal stem cells. Mesenchymal stem cells are found in the bone marrow and have the ability to transform into other cell types, namely osteocytes, chondrocytes, osteoblasts, and adipocytes (2). By interacting with receptors on these cells, leptin stimulates them to transform into osteoblasts and inhibits their transformation into adipocytes. Osteoblasts are responsible for the synthesis of the organic component of the bone matrix and participate in the process of bone tissue mineralization (2, 31). Through interaction with osteoblast LEPRs receptors, leptin increases their activity, which results in increased bone mass and density. On the other hand, by stimulating bone marrow stromal cells to release osteoprotegrin and inhibiting the activity of the leptin ligand activator receptor of nuclear factor-κB (RANK-L), it reduces the activity of osteoclasts, that is, cells responsible for the degeneration of the bone matrix. These processes are responsible for maintaining bone mineral density (BMD) and bone mass at the correct level (2, 31, 46). Turner et al. (58) showed in their study that mice with a mutation in the LEPRs gene leading to receptor deficiency, had significantly lower bone mass and bone density compared to mice with properly functioning receptors. Studies conducted by Steppan et al. (55) confirm that leptin, acting directly on bone structures, plays a key role in stimulating the growth of long bones. In addition to the above-mentioned positive aspects of leptin activity on bone parameters, high serum leptin levels, which may occur in morbidly obese individuals, may be a factor initiating inflammatory processes in bone tissue. This results from one of the aspects of leptin's function, namely, at high concentrations, it acts as a proinflammatory cytokine and, through interaction with specific receptors, increases the inflammatory process in different tissues and organs.

Indirect mechanism

Although the central pathway of leptin's action mentioned above is not fully understood, there are some studies suggesting that there are several different pathways regulating bone metabolism through its indirect activity. These pathways are related mainly to interaction between leptin and LEPRs located in the hypothalamus, particularly in the ventromedial hypothalamus (VMH), which modulate the release of a number of hormones that can directly affect the activity of bone tissue cells. This makes leptin one of the most important hormones influencing the central regulation of bone turnover (16, 31, 46).

The most important of all indirect pathways is the interdependence between leptin-serotonin and the activity of the sympathetic nervous system (SNS). Catecholamines released from SNS neurons through interactions with beta2-adrenergic receptors located on the surface of osteoblasts inhibit their osteogenic activity while stimulating bone resorption processes. This dependence remains under regulatory impact of the brain-derived serotonin (BDS). Through the interaction of BDS with Htr2c receptors located in VMH neurons, SNS activity is inhibited, which leads to increased osteoblast activity, as well as increased BMD, bone mineral content (BMC) and total bone mass. Leptin activity in the CNS reduces BDS release, which results in increased SNS activity leading to increased bone resorption (40). The interrelation between the leptin, SNS, and bone cell activity was proven by Takeda et al. (56), who showed that the use of beta-adrenergic receptor agonists in leptin-deficient Ob/Ob mice subjected to leptin infusion into the third ventricle of the brain caused a decrease in BMD, BMC, and total bone mass compared to mice treated with beta-adrenergic receptor antagonists. In addition, studies conducted by Yadav et al. (65) showed that high leptin activity in the CNS causes a decrease in serotonin secretion, which in turn leads to changes in bone turnover towards bone resorption.

A factor whose secretion is also strongly dependent on the level of leptin is neuropeptide Y (NPY). In addition to the influence on the regulation of food intake, a correlation has been proven between the concentration of NPY and bone tissue parameters. Wong et al. (64) showed that high concentrations of NPY caused a decrease in bone tissue parameters, such as BMD and BMC in both, cortical and trabecular bone. Similar results showing an increase in bone parameters in mice with leptin and NPY deficiency were obtained by Baldock and colleagues (4). The direct mechanism of these actions is not yet fully understood, but there are studies suggesting that high concentrations of NPY may activate the SNS, which stimulates the bone resorption process thorough the release of catecholamines (46).

Leptin's ability to regulate blood cortisol levels also significantly affects bone metabolism. Guo et al. (24) showed that individuals with high plasma cortisol levels have a significantly lower BMD and, concomitantly, high serum levels of bone resorption markers. This indicates a strong negative effect of cortisol on bone quality parameters. The decrease in blood cortisol levels under the influence of leptin, which affects ACTH secretion in the pituitary gland, can significantly increase bone density, which in turn minimizes the risk of fractures (24, 45, 51).

Another leptin signaling pathway through which it is involved in bone metabolism is the way via T3 and T4 hormones. Leptin is known to influence the release of both T3 and T4, and high levels of these hormones in blood alter bone turnover, leading to reduced BMD, which significantly increases the risk of fracture (5). A study by Foo et al. (20) clearly confirms the negative correlation between the concentration of leptin and circulating parathormone (PTH), indicating that PTH is one of the most important factors responsible for bone resorption, which is related to a reduction in BMD and BMC values. That study showed that the administration of metraleptin to women with hypoleptinemia caused a significant decrease in PTH blood concentration, which was closely related to a decrease in RANKL expression, one of the critical mediators of bone resorption and overall bone activity. Among the above-mentioned indirect ways of leptin's influence on bone metabolism, mechanisms dependent on growth hormone (GH) and IGF-1, as well as those related to the release of sex hormones, especially estrogen, also play an important role. For example, Chan et al. (10) indicated that GH levels in Ob/Ob mice were significantly lower than in the control group. These results may suggest that leptin stimulates the release of GH from the hypothalamus, which increases IGF-1 synthesis by hepatic cells. Through direct interactions with specific receptors located on the surface of osteoblasts and osteoclasts, both these factors stimulate the bone formation process (6, 10, 15).

It has also been confirmed that there is a positive correlation between leptin levels and estrogen levels. Estrogen is one of the factors stimulating bone-forming activity. Some clinical studies clearly indicate that women characterized by an estrogen level within the physiological limit are characterized by a significantly higher bone density and a lower incidence of osteoporosis in elderly age. Chou et al. (12) used leptin in the treatment of hypothalamic amenorrhea in women, which is associated with a decrease in the serum estrogen level and a related decrease in BMD and BMC values. Their study showed that an increase in serum leptin levels in women was directly related to an increase in serum estrogen concentration. Restoration of normal estrogen levels improved the activity of bone formation markers and overall fertility (11, 12).

General effect of leptin on bone metabolism

The existence of so many pathways through which leptin may affect bone metabolism makes it difficult to determine the overall effect of this hormone on bone parameters. The main challenge that researchers are still facing is to determine which of the two main pathways, the direct one or the indirect one, is more important, since these pathways often have completely opposite effects on bone metabolism. Leptin, acting directly on bone tissue, has a strong osteoblast-activating effect and leads to increased bone mass and strength. On the other hand, most of the peripheral pathways engaging mainly CNS are characterized by a catabolic effect on bones. The activation of these pathways decreases the intensity of bone formation by stimulating osteoclast cell activity, which causes a decrease in BMD and overall bone parameters (59). Results of research conducted by Steppan et al. (55) on mice with congenital leptin deficiency (Ob/Ob) clearly indicate that bone parameters, including femur length and the thickness of cortical and trabecular bones, were significantly higher in Ob/Ob mice with an exogenous supply of leptin than in controls. Hamrick et al. (25) made an experiment to estimate the effect of caloric restrictions on bone tissue parameters. Caloric regime periods reduced the body fat level, which was strongly correlated with serum leptin. Results of that study indicated that the cortical bone parameters of the peripheral skeleton decreased in calorically restricted mice with a low leptin concentration, but their trabecular bone parameters did not change compared to those in control animals. Assessment of the axial skeleton showed a decrease in cortical bone thickness, whereas trabecular bone parameters, such as BMD and BMC, increased in the experimental group. It is also worth noting that there was no decrease in overall BMC and BMD in calorie-restricted mice. Studies by Philbrick et al. (43) confirmed the above conclusions and also revealed that the increase in parameters related to bone tissue formation processes occurred in the experimental groups at lower leptin concentrations than those needed to induce general energy metabolic changes. This means that bone tissue cells are more sensitive to leptin than the structures of the central nervous system regulating the metabolism of the whole organism.

Although data obtained from animal studies clearly indicate an anabolic effect of leptin on bone metabolism, the results of similar studies conducted in humans are ambiguous. Some researchers claim that there is no correlation between bone metabolism and serum leptin levels in adults (14, 33, 52). However, there are studies indicating a positive correlation between leptin levels and bone formation. For instance, Sienkiewicz et al. (50) showed that leptin therapy in individuals with congenital leptin deficiency resulted in reduced BMD and BMC in the lumbar spine. Moreover, the results of some studies conducted in women with a low bone mineral density indicate an anabolic effect of leptin on bone turnover, and its introduction to the treatment protocol improved bone tissue parameters, reducing the incidence of bone fractures (6, 57).

Leptin and bone health

Given the numerous mechanisms of leptin's action on bones, this adipokine may be responsible for many disorders of the skeletal system. The main one is undoubtedly osteoporosis occurring primarily in postmenopausal women. Osteoporosis is manifested by low

bone mass, bone tissue deterioration, and disruption of bone microarchitecture. In such conditions, there is a gradual deterioration of bone parameters, mainly BMD and BMC, which is one of the most important factors contributing to the development of bone fragility and ultimately to pathological fractures. Numerous studies have shown that there is a positive correlation between BMC and BMD and the high serum leptin concentrations in postmenopausal women, but no similar relationship has been observed in men (54, 57, 66). Interestingly, there are also reports indicating a complete lack of association between high leptin levels and improvement in bone tissue parameters in women at risk of osteoporosis (38). Due to the aforementioned discrepancies in the results of studies on the role of leptin in the development of osteoporosis, it is impossible to draw clear conclusions as to its role in this process. Therefore, such studies should be continued.

Another skeletal disorder in which leptin may be involved is osteoarthritis (OA), a polyetiological disease widespread in elderly population and caused by a gradual destruction of the articular cartilage. This chronic process leads to the development of progressive lesions in subarticular bone tissue. As the disease progresses, the patient experiences severe pain, develops inflammation, and gradually loses the mobility of the degenerated joints (17). One of the most important risk factors for osteoarthritis appears to be obesity, which is associated with high levels of leptin in the blood. Dumond et al. (18) have shown that the concentration of leptin in synovial fluid and articular cartilage is strongly correlated with the concentration of leptin in serum, which depends on the content of body fat. The concentration of leptin in synovial fluid was also positively correlated with the degree of advancement of OA. Furthermore, they showed that an intra-articular injection of leptin solution strongly stimulates the activity of articular cartilage chondrocytes. Increased circulatory leptin levels in OA are also associated with increased synthesis of IGF-1 and transforming growth factor beta (TGF-beta). Both of these factors have a stimulating impact on chondrocyte's activity. Similar results, confirming a high concentration of leptin in structures of degenerated joints, was obtained by others, namely Simopoulou et al. and Mutabaruka et al. (34, 53). There are also studies suggesting that leptin could be involved in the development of OA as a proinflammatory cytokine which stimulates the synthesis of factors such as NO, PGE2, IL-6, and IL-8, which intensify the progression of degenerative processes in joints (28, 60, 67). The abovementioned data demonstrate that leptin is a hormone actively involved in the development of OA, but its direct role in this process requires more detailed research.

Some data indicate that leptin may also play an important role in rheumatoid arthritis (RA), a severe inflammation of joints leading to irreversible changes in their structure, the etiology of which has not yet been fully explained. Researches have shown that there is a positive correlation between the level of leptin in blood and joint elements in patients suffering from RA. It is hypothesized that leptin may play the role of a proinflammatory cytokine and a factor stimulating cartilage cells to synthesize extracellular matrix components (6, 39). However, literature data indicate no correlations between the levels of leptin in patients showing symptoms of RA and healthy people constituting the control group (44).

The effect of leptin on the bone turnover process is, as can be seen from the above analysis, very diverse and dependent on the pathways of its action. Different pathways can produce different and often opposite effects on bone metabolism. For this reason, determining the general effect of leptin on bone metabolism is very problematic. Furthermore, there are not many sources that could serve as a basis for determining the general effect of leptin's functioning in the body, the results obtained during those experiments are ambiguous, and some of the experiments were performed as much as 20 years ago. In addition, there are also many differences between data obtained from experiments conducted on animal and human models. This may be due to differences in leptin activity across species as well as cell and/or tissue leptin sensitivity. Studies also confirm that interspecies differences are of considerable importance and are the main cause of differences observed in the activity of not only leptin, but also other hormones, in bone metabolism. It is still not entirely clear which leptin pathway, the direct one or the indirect one, plays a more important role in regulating bone turnover. The most probable hypothesis, however, seems to be the dominance of the direct effect of leptin on the regulation of bone turnover. This is due to the significantly higher concentration of leptin in bone tissue than in the central nervous system, where the indirect hormonal pathways regulating bone metabolism via leptin is initiated. This is a result of the sources from which leptin can reach the effector cells in bones, namely blood and bone marrow adipocytes. Otherwise, there are no local sources of leptin in the central nervous system, and therefore it must be supplied in its entirety by blood. Studies on direct metabolic pathways, conducted mainly *in vitro*, indicate that the presence of leptin in the environment of bone tissue cells shifts their metabolism towards osteogenic processes. Also some indirect pathways, such as the mechanism dependent on cortisol, GH, and sex hormones, induce an increase in bone tissue parameters. In light of the above data, it seems most likely that high leptin concentrations in both bone tissue and serum have a positive effect on BMD, BMC, and other parameters of bone quality. However, despite these relationships, the overall effect of leptin on bone metabolism in various species is still not fully understood and requires more detailed studies.

References

1. *Amrita B., Singh R., Rai U.*: Trajectory of leptin and leptin receptor in vertebrates: Structure, function and their regulation. Comp. Biochem. Physiol. B. Biochem. Mol. Biol. 2022, 257, 110652.
2. *Astudillo P., Ríos S., Pastenes L., Pino A. M., Rodríguez J. P.*: Increased adipogenesis of osteoporotic human-mesenchymal stem cells (MSCs) characterizes by impaired leptin action. J. Cell. Biochem. 2008, 03, 1054-1065.
3. *Bado A., Levasseur S., Attoub S., Kermorgant S., Laigneau J. P., Bortoluzzi M. N., Moizo L., Lehy T., Guerre-Millo M., Le Marchand- Brustel Y., Lewin M. J.*: The stomach is a source of leptin. 1998, 394, 790-793.
4. *Baldock P. A., Lee N. J., Driessler F., Lin S., Allison S., Stehrer B., Lin E. J. D., Zhang L., Enriquez R. F., Wong I. P. L., McDonald M. M., During M., Pierroz D. D., Slack K., Shi Y. C., Ylyaningih E., Aljanova A., Little D. G., Ferrari S. L., Sainsbyry A., Eisman J. A., Herzog H.*: Neuropeptide Y knockout mice reveal a central role of NPY in the coordination of bone mass to body weight. PloS one 2009, 4, e8415.
5. *Bassett J. H. D., Graham R. W.*: Role of thyroid hormones in skeletal development and bone maintenance. Endocr. Rev. 2016, 37, 135-187.
6. *Bokarewa M., Bokarew D., Hultgren O., Tarkowski A.*: Leptin consumption in the inflamed joints of patients with rheumatoid arthritis. Ann. Rheum. Dis. 2003, 62, 952-956.
7. *Cammisotto P. G., Gélinas Y., Deshaies Y., Bukowiecki L. J.*: Regulation of leptin secretion from white adipocytes by insulin, glycolytic substrates, and amino acids. Am. J. Physiol. Endocrinol. Metab. 2005, 289, 166-171.
8. *Cammisotto P. G., Levy E., Bukowiecki L. J., Bendayan M.*: Crosstalk between adipose and gastric leptins for control of food intake and energy metabolism. Prog. Histochem. Cytochem. 2010, 45, 143-200.
9. *Cammisotto P. G., Renaud C., Gingras D., Delvin E., Levy E., Bendayan M.*: Endocrine and exocrine secretion of leptin by the gastric mucosa. J. Histochem. Cytochem. 2005, 53, 851-860.
10. *Chan J. L., Williams C. J., Raciti P., Blakeman J., Kelesidis T., Kelesidis I., Johnson M. L., Thorner M. O., Mantzoros C. S.*: Leptin does not mediate short-term fasting-induced changes in growth hormone pulsatility but increases IGF-I in leptin deficiency states. J. Clin. Endocrinol. Metab. 2008, 93, 2819-2827.
11. *Childs G. V., Odle A. K., MacNicol M. C., MacNicol A. M.*: The importance of leptin to reproduction. Endocrinology 2021, 162, bqaa204.
12. *Chou S. H., Chamberland J. P., Liu X., Matarese G., Gao C., Stefanakis R., Brinkoetter M. T., Gong H., Arampatzi K., Mantzoros C. S.*: Leptin is an effective treatment for hypothalamic amenorrhea. Proc. Natl. Acad. Sci. USA 2011, 108, 6585-6590.
13. *Cinti S., Matteis R. D., Pico C., Ceresi F., Obrador A., Maffeis C., Olivier J., Palou A.*: Secretory granules of endocrine and chief cells of human stomach mucosa contain leptin. Int. J. Obes. Relat. Metab. Disord. 2000, 24, 789-793.
14. *Conroy R., Girotra M., Shane E., McMahon D. J., Pavlovich K. H., Leibel R. L., Rosenbaum M., Korner J.*: Leptin administration does not prevent the bone mineral metabolism changes induced by weight loss. Metabolism 2011, 60, 1222-1226.
15. *Devesa J., Almengló C., Devesa P.*: Multiple effects of growth hormone in the body: Is it really the hormone for growth? Clin. med. insights, Endocrinol. 2016, 9, CMED-S38201.
16. *Dimitri P., Rosen C.*: The central nervous system and bone metabolism: An evolving story. Calcif. Tissue. Int. 2017, 100, 476-485.
17. *Dobson G. P., Letson H. L., Grant A., McEwen P., Hazratwala K., Wilkinson M., Morris J. L.*: Defining the osteoarthritis patient: back to the future. Osteoarthritis and Cartilage 2018, 26, 1003-1007.
18. *Dumond H., Presle N., Terlain B., Mainard D., Loeuille D., Netter P., Pottie P.*: Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum. 2003, 48, 3118-3129.
19. *Duncan B. J. H., Williams G. R.*: Role of thyroid hormones in skeletal development and bone maintenance. Endocr. Rev. 2016, 37, 135-187.
20. *Foo J. P., Polyzos S. A., Anastasilakis A. D., Chou S., Mantzoros C. S.*: The effect of leptin replacement on parathyroid hormone, RANKL-osteoprotegerin axis, and Wnt inhibitors in young women. With hypothalamic amenorrhea. J. Clin. Endocrinol. Metab. 2014, 99, 2252-2258.
21. *Francisco V., Pino J., Campos-Cabaleiro V., Ruiz-Fernández C., Mera A., Gonzalez-Gay M. A., Gualillo O.*: Obesity, fat mass and immune system: role for leptin. Front. Physiol. 2018, 9, 640.
22. *Friedman J. M., Mantzoros C. S.*: 20 years of leptin: From the discovery of the leptin gene to leptin in our therapeutic armamentarium. Metabolism 2015, 64, 1-4.
23. *Gruzdeva O., Borodkina D., Uchasova E., Dyleva Y., Barbarash O.*: Leptin resistance: Underlying mechanisms and diagnosis. Diabetes Metab. Syndr. Obes. Targets Ther. 2019, 12, 191-198.
24. *Guo W., Li F., Zhu C., Wang B., Wang K., Dai C., Jia H., Wei H., He Q., Cui J., Yuan M., Teng S., Liu W., Zhu T., Gao Z., Zheng F., Ma Z., Zhu M.*: Effect of hypercortisolism on bone mineral density and bone metabolism: A potential protective effect of adrenocorticotropic hormone in patients with Cushing's disease. Int. J. Med. Res. 2018, 46, 492-503.
25. *Hamrick M. W., Ding K. H., Ponnala S., Ferrari S. L., Isales C. M.*: Caloric restriction decreases cortical bone mass but spares trabecular bone in the mouse skeleton: implications for the regulation of bone mass by body weight. J. Bone. Miner. Res. 2008, 23, 870-878.
26. *Hyeong-Kyu P., Ahima R. S.*: Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Endocrionology 2015, 64, 24-34.
27. *Izquierdo A. G., Crujeiras A. B., Casanueva F. F., Carreira M. C.*: Leptin, obesity, and leptin resistance: where are we 25 years later? Nutrients 2019, 11, 2704.
28. *Lajeunesse D., Pelletier J. P., Martel-Pelletier J.*: Osteoarthritis: a metabolic disease induced by local abnormal leptin activity? Curr. Rheumatol. Rep. 2005, 7, 1-3.
29. *Li S., Li X.*: Leptin in normal physiology and leptin resistance. Sci. bull. 2016, 61, 1480-1488.
30. *Malik I. A., Durairajanayagam D., Singh H. J.*: Leptin and its actions on reproduction in males. Asian J. Androl. 2019, 21, 296-299.
31. *Mantzoros C. S., Magkos F., Brinkoetter M., Sienkiewicz E., Dardeno T. A., Kim S. Y., Hamnvik O. P. E., Koniaris A.*: Leptin in human physiology and pathophysiology. American Journal of Physiology-Endocrinology and Metabolism 2011, 301, 567-584.
32. *Marques-Oliveira G. H., Silva T. M., Lima W. G., Valadares H. M. S., Chaves V. E.*: Insulin as a hormone regulator of the synthesis and release of leptin by white adipose tissue. Peptides 2018, 106, 49-58.
33. *Moran S. A., Patten N., Young J. R., Cochran E., Sebring N., Reynolds J., Premkumar A., Depaoli A. M., Skarulis M. C., Oral E. A., Gorden P.*: Changes in body composition in patients with severe lipodystrophy after leptin replacement therapy. Metabolism 2004, 53, 513-519.
34. *Münzberg H., Morrison C. D.*: Structure, production and signaling of leptin. Metabolism 2015, 64, 13-23.
35. *Mutabaruka M. S., Aoulad Aissa M., Delalandre A., Lavigne M., Lajeunesse D.*: Local leptin production in osteoarthritis subchondral osteoblasts may be responsible for their abnormal phenotypic expression. Arthritis Res. Ther. 2010, 12, 1-13.
36. *Naylor C., William A. P.*: Leptin regulation of immune responses. Trends. Mol. Med. 2016, 22, 88-98.
37. *Obradovic M., Sudar-Milovanovic E., Soskic S., Essack M., Arya S., Stewart A. J., Gojobori T., Isenovic E. R.*: Leptin and obesity: Role and clinical implication. Frontiers in Endocrinology 2021, 12, 585887.
38. *Odabasi E., Ozata M., Turan M., Bingol N., Yonem A., Cakir B., Ozdemir I.C.*: Plasma leptin concentrations in postmenopausal women with osteoporosis. Eur. J. Endocrinol 2000, 142, 170-173.
39. *Olama M. S., Senna M. K., Elarman M.*: Synovial/serum leptin ratio in rheumatoid arthritis: The association with activity and erosion. Rheumatol. Int. 2012, 32, 683-690.
40. *Oury F., Yadav V. K., Wan Y., Zhou B., Liu X. S., Guo X. E., Tecott L. H., Schutz G., Means A. R., Karsenty G.*: CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. Genes Dev. 2010, 24, 2330-2342.
41. *Pawlak D., Domaniewski T., Znorko B., Oksztulska-Kolanek E., Lipowicz P., Doroszko M., Karbowska M., Pawlak K.*: The impact of peripheral serotonin on leptin-brain serotonin axis, bone metabolism and strength in growing rats with experimental chronic kidney disease. Bone 2017, 105, 1-10.
42. *Pérez-Pérez A., Sánchez-Jiménez F., Vîlariño-García T., Sánchez-Margalet V.*: Role of leptin in inflammation and vice versa. Int. J. Mol. Sci. 2020, 21, 5887.
43. *Philbrick K. A., Wong C. P., Branscum A. J., Turner R. T., Iwaniec U. T.*: Leptin stimulates bone formation in ob/ob mice at doses having minimal impact on energy metabolism. J. Endocrinol. 2017, 232, 461.
44. *Popa C., Netea M. G., Graaf de J., Hoogen van den F. H., Radstake T. R., Toenhake-Dijkstr H., Riel van P. L. C. M., Meer van der J. W., Stalenhoef A. F. H., Barrera P.*: Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. J. Rheumatol. 2009, 36, 724-730.
45. *Pralong F. P., Roduit R., Waeber G., Castillo E., Mosimann F., Thorens B., Gaillard R. C.*: Leptin inhibits directly glucocorticoid secretion by normal human and rat adrenal gland. Endocrinology 1998, 139, 4264-4268.
46. *Reid I. R., Baldock P. A., Cornish J.*: Effects of Leptin on the Skeleton. Endocr. Rev. 2018, 39, 938-959.
47. *Reis B. S., Lee K., Fanok M. H., Mascaraque C., Amoury M., Cohn L. B., Rogoz A., Dallner O. S., Moraes-Vierira P. M., Domingos A. I., Mucida D.*: Leptin receptor signaling in T cells is required for Th17 differentiation. J. Immun. 2015, 194, 5253-5260.

48. *Saxton R. A., Caveney N. A., Moya-Garzon M. D., Householder K. D., Rodriguez G. E., Burdsall K. A., Long J. Z., Garcia K. C.*: Structural insights into the mechanism of leptin receptor activation. Nat. Commun. 2023, 14, 1797.
49. *Schaab M., Kratzsch J.*: The soluble leptin receptor. Best. Pract. Res. Clin. Endocrinol. Metab. 2015, 29, 661-670.
50. *Sienkiewicz E., Magkos F., Aronis K. N., Brinkoetter M., Chamberland J. P., Chou S., Arampatzi K. M., Gao C., Koniaris A., Mantzoros C. S.*: Long-term metreleptin treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women. Metabolism 2011, 60, 1211-1221.
51. *Silva Gomes da A., Toffolo M. C. F., van Keulen H. V., e Silva F. M. C., Ferreira A. P., Luquetti S. C. P. D., Mendes L. L., Volp A. C. P., de Aguiar A. S.*: Influence of the leptin and cortisol levels on craving and smoking cessation. Psychiatry Res. 2015, 229, 126-132.
52. *Simha V., Zerwekh J. E., Sakhaee K., Garg A.*: Effect of subcutaneous leptin replacement therapy on bone metabolism in patients with generalized lipodystrophy. J. Clin. Endocrinol. Metab. 2002, 87, 4942-4945.
53. *Simopoulou T., Malizos K. N., Iliopoulos D., Stefanou N., Papatheodorou L., Ioannou M., Tsezou A.*: Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. Osteoarthr. Cartil. 2007, 15, 872-883.
54. *Sözen T., Özışık L., Başaran N. Ç.*: An overview and management of osteoporosis. Eur. J. Rheumatol. 2017, 4, 46-56.
55. *Steppan C. M., Crawford D. T., Chidsey-Frink K. L., Ke H., Swick A. G.*: Leptin is a potent stimulator of bone growth in ob/ob mice. Regul. Pept. 2000, 92, 73-78.
56. *Takeda S., Elefteriou F., Levasseur R., Liu X., Zhao L., Parker K. L., Armstrong D., Ducy P., Karsenty G.*: Leptin regulates bone formation via the sympathetic nervous system. Cell 2002, 111, 305-317.
57. *Thomas T., Burguera B., Melton Iii L. J., Atkinson E. J., O'Fallon W. M., Riggs B. L., Khosla S.*: Role of serum leptin, insulin, and estrogen levels as potential mediators of the relationship between fat mass and bone mineral density in men versus women. Bone 2001, 29, 114-120.
58. *Turner R. T., Kalra S. P., Wong C. P., Philbrick K. A, Lindenmaier L. B., Boghossian S., Iwaniec U. T.*: Peripheral leptin regulates bone formation. J. Bone. Miner. Res. 2013, 28, 22-34.
59. *Upadhyay J., Farr O. M., Mantzoros C. S.*: The role of leptin in regulating bone metabolism. Metabolism 2015, 64, 105-113.
60. *Vuolteenaho K., Koskinen A., Kukkonen M., Nieminen R., Päivärinta U., Moilanen T., Moilanen E.*: Leptin enhances synthesis of proinflammatory mediators in human osteoarthritic cartilage – mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production. Mediators of inflammation 2009, 345838.
61. *Wasim M., Awan F. R., Najam S. S., Khan A. R., Khan H. N.*: Role of leptin deficiency, inefficiency, and leptin receptors in obesity. Biochem. Genet. 2016, 54, 565-572.
62. *Wauman J., Lennart Z., Jan T.*: The leptin receptor complex: Heavier than expected? Front. Endocrinol. 2017, 8, 30.
63. *Wauman J., Tavernier J.*: Leptin receptor signaling: pathways to leptin resistance. Front. Biosci. 2011, 16, 2771-2793.
64. *Wong I. P., Nguyen A. D., Khor E. C., Enriquez R. F., Eisman J. A., Sainsbury A., Herzog H., Baldock P. A.*: Neuropeptide Y is a critical modulator of leptin's regulation of cortical bone. J. Bone. Miner. Res. 2013, 28, 886-898.
65. *Yadav V. K., Oury F., Suda N., Liu Z. W., Gao X. B., Confavreux C., Kelemnhegen K. C., Tanaka K. F., Grinch J. A., Guo E. X., Tecott L. H., Mann J. J., Hen R., Horvath T. L., Karsenty G.*: A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. Cell 2009, 138, 976-989.
66. *Yamauchi M., Sugimoto T., Yamaguchi T., Nakaoka D., Kanzawa M., Yano S., Ozuru R., Sugishita T., Chihara K.*: Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women. Clin. Endocrinol. 2001, 55, 341-347.
67. *Yang W. H., Tsai C. H., Fong Y. C., Huang Y. L., Wang S. J., Chang Y. S., Tang C. H.*: Leptin induces oncostatin M production in osteoblasts by downregulating miR-93 through the akt signaling pathway. Int. J. Mol. Sci. 2014, 15, 15778-15790.

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