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The role of leptin in regulating bone metabolism

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Abstract

Leptin was initially best known for its role in energy homeostasis and regulation of energy expenditure. In the past few years we have realized that leptin also plays a major role in neuroendocrine regulation and bone metabolism. Here, we review the literature on indirect and direct pathways through which leptin acts to influence bone metabolism and discuss bone abnormalities related to leptin deficiency in both animal and human studies. The clinical utility of leptin in leptin deficient individuals and its potential to improve metabolic bone disease are also discussed. We are beginning to understand the critical role leptin plays in bone metabolism; future randomized studies are needed to fully assess the potential and risk – benefit of leptin's use in metabolic bone disease particularly in leptin deficient individuals.

Keywords

leptin; bone; osteoporosis

1. Introduction

Leptin is an adipokine composed of 167 amino acids which is secreted in a pulsatile fashion to maintain energy homeostasis [1]. Leptin is primarily secreted from adipocytes at levels determined mainly by the number of adipocytes, and thus amount of body fat, and secondarily by acute changes in food intake [2]. Although circulating leptin levels mainly signify the amount of energy stored in adipose tissue, and thus reflect obesity, insulin levels and alcohol intake have also been associated with increased circulating leptin levels [3]. In epidemiology studies, a wide variability in leptin levels has been reported, even among individuals with the same body mass index (BMI) implying the influence of both genetic and environmental factors. For instance, a comparison of heterozygous relatives of congenitally leptin deficient individuals with control subjects of the same ethnicity and BMI reveals an increased percentage of body fat and reduced leptin levels [4]. In addition to

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genetic determinants, the circulation of leptin also responds to acute caloric changes, decreasing with acute energy deprivation [5]. Sleep and fasting as well as circulating hormone and cytokine levels have been shown to regulate leptin levels in healthy individuals. Finally, circadian sleep/wake cycle is intimately linked in the regulation of leptin levels and disturbance of which could potentially cause an increase in circulating leptin [6].

The primary actions of leptin have been thought to occur in the arcuate nucleus of the hypothalamus, where leptin inhibits the actions of neuropeptide Y (NPY) and agouti-related peptide (AgRP) and enhances the actions of pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) to decrease food intake (Figure 1) [7-9]. Leptin also affects hypothalamic pathways to regulate reproduction and development [10-13] but importantly it also acts in several peripheral metabolically important organs. These actions of leptin are mediated through the leptin receptor (LepRb) which is found throughout the brain and brain stem as well as in peripheral organs [14, 15]. Once leptin binds to LepRb, the receptor dimerizes and initiates a downstream cascade (including janus kinase 2(JAK2)/ signal transducer and activator of transcription 3 (STAT3), src homology-2-containing protein tyrosine phosphatase 2 (SHP2)/mitogen-activated protein kinase (MAPK)/forkhead box protein O1 (FoxO1)/phosphatidylinositol 3 kinase (PI3K)/Protein Kinase B (Akt)/ mammalian target of rapamycin (mTOR)/adenosine monophosphate-activated protein kinase (AMPK), Suppressor of cytokine signaling 3 (SOCS3), Src homology-2 protein tyrosine phosphatase (SHP2), Protein-tyrosine phosphatase 1B (PTP1B), regulating several physiological functions including energy homeostasis, neuroendocrine action and insulin resistance [16]. The range of signaling pathways activated by leptin, as well as the number of peripheral tissues that leptin targets, have recently been expanded. Several of these novel pathways, including inflammatory activation through nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB)/IKK need to be further delineated in the future [17]. Research continues to illuminate and define these pathways, which have widespread impacts throughout the brain as well as in the periphery.

2. Leptin and Neuroendocrine Regulation

In addition to regulating energy homeostasis, leptin also regulates several hypothalamic pituitary peripheral neuroendocrine axes, including the thyroid, gonadal, cortisol and growth hormone axes [10-13]. It is important to understand how all these HPP axes are influenced by leptin and/or leptin deficiency, as they may all mediate the connection between leptin and bone which is further discussed below.

Farooqi et al. [4, 11, 18] and Ozata et al. [19] identified leptin deficient homozygous individuals and described neuroendocrine responses in this phenotype. A missense leptin gene mutation was identified in his family and homozygous individuals were found to have extreme obesity [10]. Thus, congenital, complete leptin deficiency is associated with extreme obesity, and leptin replacement in such individuals has led to improvement in obese state by increasing energy expenditure and reducing caloric intake [11]. Additionally, leptin therapy for patients who have disturbed neuroendocrine axes has been shown to restore

functioning of other hypothalamic axes, including the thyroid, gonadal, cortisol, and growth hormone [11, 20-23], which are all linked to bone metabolism.

All heterozygous members of the extended family with leptin deficiency studied by Ozata et al. [19] had normal weight while homozygous members had morbid obesity. Out of the four heterozygous individuals, the adult patients (2 females and 1 male) had normal thyroid function while the child had elevated thyroid-stimulating hormone (TSH), negative antibodies and exaggerated response to TSH stimulation [19]. Significant elevations of TSH levels have been seen in patients with leptin deficiency which has normalized on leptin replacement therapy and has subsequently led to treatment discontinuation of levothyroxine [24]. Studies in healthy, lean men were done to see the changes in neuroendocrine hormones in well fed state as compared to a 72 hour fasting state with placebo or replacement doses of metreleptin [5]. Changes in hypothalamic-pituitary-gonadal axis, in part changes of hypothalamic-pituitary-thyroid axis and binding capacity of insulin-like growth factor 1 (IGF1) in serum were rescued in patients who were starving but received replacement doses of r-met Huleptin as opposed to the patients who received placebo [5].

Leptin also plays a significant role in the maintenance of hypothalamic-gonadal-pituitary axis. Delayed puberty is often seen in leptin deficient states. Indeed, both congenital and acquired leptin deficiencies have been associated with hypothalamic amenorrhea or the cessation of the menstrual cycle and infertility [25]. Decrease leptin levels and increase soluble leptin receptor protein (sLep-R) were also seen in healthy volunteers after a four-week reduced calorie diet of 1000-1200 kcal/day intake [26]. Ozata et al. [19] described hypogonadism in all three adult homozygous patients in his study. Normal gonadotropin responses were demonstrated in all these patients in response to gonadotropin releasing hormone (GnRH) stimulation indicating a hypothalamic defect in these individuals. A leptin rise of approximately 50% was described just before the onset of puberty in prepubertal boys, which decreased to baseline levels after the initiation of puberty [27]. Normal pituitary gonadal axis was noted in healthy men after 72 hour fast with replacement of recombinant leptin as opposed to placebo, indicating important physiological role of leptin in regulation of neuroendocrine axes in healthy individuals [5]. Leptin replacement for 2-3 months was also shown to result in resumption in ovulation, increase in LH and estradiol levels in blood and increase in follicular diameter and number in women with hypothalamic amenorrhea as compared to control subjects [28]. Moreover, replacement of leptin in deficient individuals has led to the successful treatment of hypogonadism by gonadotropin secretion and the restoration of puberty and fertility [29].

An inverse relationship has been described between leptin levels and serum cortisol and adrenocorticotropic hormone (ACTH) levels [30]. The homozygous leptin deficient patients were also found to have high cortisol, high ACTH levels, a disturbed diurnal variation, but a normal dexamethasone suppression response [19]. Higher body fat has been shown to be associated with decreased cortisol inhibitory feedback signaling [31]. In a study of leptin therapy in lean humans, no significant change was noted in cortisol or corticotropin levels from their baseline during leptin treatment [28]. Also, no significant change in corticotropin pulsatility was noted after two week treatment with metreleptin [28]. Similarly no significant change was noted in the baseline cortisol or 24-hour urine free cortisol with fasting and/or

metreleptin replacement healthy volunteers after a 72 hour fast [5]. Longer, randomized controlled trials of leptin administration demonstrated an effect of leptin to normalize the ACTH-cortisol axis in women with exercise induced hypothalamic amenorrhea [5].

Studies on growth hormone deficient individuals as compared to healthy adults showed a negative correlation of leptin to IGF1 [32]. Blunt growth hormone response is seen in obese individuals in response to insulin induced hypoglycemia as compared to healthy people [33]. In normal healthy men, after a 72-hour fasting, a rise in serum growth hormone (GH) levels, pulsatile frequency of GH and 24-hour integrated GH concentrations, but a decrease in IGF1, were noted, which was not reversed with leptin recombinant therapy [5]. Although no change was noticed in free IGF-1 with leptin replacement, total IGF-1 levels were increased, reflecting increase in binding capacity in the serum [5]. In women with hypothalamic amenorrhea increase in IGF1 was seen in month 1 and an increase in IGF binding protein 3 (IGF-BP3) was seen in months 2 and 3. IGF1 levels declined to baseline on follow-up at 2 and 3 months [28].

Several animal studies have been done to establish relationship between leptin and its effect on sympathetic system, but similar studies have failed to demonstrate a similar role in response to at least short term leptin changes in humans [34]. Since the main role of leptin as an adipokine is to maintain energy homeostasis, it can be considered a messenger that relays information about energy stores in the body to the brain. Its role in bone formation was thought to be regulated by sympathetic nervous system. Offspring whose mothers were on a high fat diet have altered sensitivity to leptin and ghrelin in the hypothalamus that results in adverse cardiovascular outcomes [35]. Central leptin infusion increased insulin sensitivity via sympathetic regulation of insulin-like growth factor binding protein 2 (IGFBP-2) levels in animal models. An intracerberoventricular leptin infusion in sheep was shown to increase skeletal muscle IGFBP-2 resulting in improved glucose tolerance and increased insulin levels in response to a glucose challenge, which was blocked by a beta-adrenergic blocker, indicating sympathetic regulation of leptin [36]. High bone mass is shown to result after ablation of adrenergic signaling, which is even resistant to correction by intracerebroventricular leptin [37]. Decreased leptin states show a decline in sympathetic nervous system tone [38]. This may only be the case in animals, as these findings have not been reliably replicated in humans. For instance, it was found that changes in heart rate, catecholamines, and other sympathetic nervous system parameters during fasting were independent of leptin levels in healthy humans [34].

3. Leptin's Impacts on Bone Metabolism

3.1. Direct Mechanisms

The leptin receptor can be found in adult primary osteoblasts and chondrocytes, suggesting that the effects of leptin on bone growth and metabolism may be direct [39]. Other studies have shown that leptin may impact bone growth through the activation of fibroblast growth factor 23 (FGF-23) [40]. Leptin also impacts and regulates osteocalcin, which in turn regulates not only bone metabolism, but also insulin sensitivity and energy expenditure [41]. Locally, bone marrow adipocytes have been found to secrete leptin, and this may mediate leptin's local effects on bone [42]. Indeed, replacement of bone tissue in mice that lack a

functional leptin receptor (*db/db*) increases bone mass without affecting energy homeostasis, suggesting that some of the effects of leptin on bone metabolism may be peripheral rather than central [43].

3.2. Indirect Mechanisms

Although leptin may act peripherally on bone, central leptin administration in *ob/ob* mice has been found to restore bone mass to control levels, suggesting that leptin may indirectly impact bone mass [44]. The ventromedial hypothalamus (VMH) may activate local noradrenergic signaling at the osteoblasts in response to leptin, mediating this effect [37]. Indeed, lesions of the VMH have been found to prevent the restoration of bone mass with leptin administration for *ob/ob* mice, suggesting that the VMH is key to leptin's control of bone mass [37].

Leptin may also act indirectly through the brainstem and serotonergic signaling, though these effects shown in animal models have not been shown in humans yet. Leptin and serotonin have opposite effects on bone mass [45]. Leptin appears to decrease serotonin synthesis and inhibit serotonergic receptors [45]. Serotonin appears to bind to the serotonin 2c receptors in the VMH and serotonin 1b receptor on osteoblasts to inhibit bone growth [45, 46]. In cases of leptin inhibiting serotonin, these effects would be reversed, inducing bone growth.

In the most human studies, it is difficult to parcel apart the effects of leptin per se vs. its hypothalamic effectors, such as estrogen, cortisol, IGF-1and parathyroid hormone on bone mass [47]. Leptin therapy increases all of these hormones along with improving bone mass, and thus whether the effects on bone mass occur directly or indirectly through other hormones remains to be fully clarified [12, 48]. Estrogen, activated through the hypothalamic-pituitary-gonadal axis by leptin [49], itself induces growth of human osteoblasts [50, 51]. The effect of hormonal replacement therapy in women with postmenopausal osteoporosis on the increase in bone density and reduction of osteoporotic fracture is established [52, 53] although a few studies have not linked improvement in estrogen levels with improvements in bone density [54-56]. Although the potential role of estrogen indirectly modulating this connection cannot be discounted, the combination of low bone density or mass with low estrogen levels may be more of an impact of leptin on both estrogen and bone mass than of estrogen on bone mass.

Cortisol is another potential indirect pathway for leptin to act on bone, as it is inhibited through the hypothalamic-pituitary-adrenal axis by leptin [57]. Cortisol has been found to inhibit the growth of osteoblasts and osteoclasts, as well as inhibiting growth hormone, which also have an anabolic effect on bone [58-60]. Indeed, strong correlations have been seen between cortisol and markers of bone growth, where higher cortisol levels correlate with decreased bone mass and growth markers like osteocalcin [58, 61]. The effect of cortisol and other glucocorticoids on bone may be mediated through pathways such as the hepatocyte growth factor signaling pathways (e.g. IGF-1) [59]. In the case of high adiposity, which can increase leptin and cortisol, central leptin resistance may mediate the unexpected negative effects of obesity on bone metabolism [62, 63]. Thus, leptin's inhibition of cortisol and glucocorticoids may help to improve bone growth.

Thyroid and parathyroid hormones may also mediate relationships between leptin and bone metabolism. Leptin activates thyroid hormones through the hypothalamic-pituitary-thyroid axis [64]. Leptin is known to regulate thyroid-stimulating hormone (TSH) levels and thus influence this axis [65]. Parathyroid hormone activates osteoblasts and bone growth when administered intermittently, whereas it has catabolic action in bone when it is stably increased (e.g., in hyperparathyroidism or hypothalamic amenorrhea) [66]. Parathyroid hormone also increases calcium absorption in the intestines and reabsorption in the kidneys [67]. Metreleptin decreased parathyroid hormone and RANKL and increased osteoprotegerin (OPG) in women with hypothalamic amenorrhea together with an increase in bone mass [68].

Growth hormone and IGF-1 are other potential mediators, activated through the hypothalamic-pituitary-growth hormone axis by leptin [69]. Growth hormone causes IGF-1 secretion from the liver and bone [70]. Importantly, growth hormone is not the only activator of IGF-1, but parathyroid hormone, estrogen and cortisol have also been shown to affect IGF-1 levels at bone [71-76]. Given these complex relationships, it is not hard to believe that leptin may act indirectly to affect bone metabolism.

4. Impacts of leptin deficiency on bone mass: Evidence from animal studies

Leptin has been linked to decreased bone mass in both cases of obesity with hyperleptinemia but leptin resistance, and in cases of extreme leanness with hypoleptinemia. Mice who cannot produce leptin (*ob/ob*) are obese and have reduced bone mass [77]. Hamrick et al. [78] first studied the bone microarchitecture in leptin deficient obese mice as compared to lean controls. They had reported a differential leptin action on bone density and mineralization in axial and appendicular skeleton. In the peripheral skeleton, namely femur, leptin-deficient mice had shorter length, decreased mineralization and low bone mineral density. Cortical thickness, and trabecular bone volume of femur was also low as compared to the controls. On the other hand, in the axial skeleton (lumbar vertebrae) of leptin deficient mouse increase in trabecular volume, cortical thickness, mineralization and density were observed. Increased number of adipocytes were noted in femoral bone marrow and decreased in vertebrae bone marrow. Muscle mass likely may contribute to this difference, as low muscle mass (sarcopenia) in obese mice were associated with low mineral density [78]. Intracerebrovesicular infusion of leptin in leptin deficient mice was initially shown to result in bone loss indicating that leptin, through central nervous system, inhibits bone formation [44]. However, more recently, intracerebroventricular injection of leptin was shown to promote the expression of pro-osteogenic factors in bone marrow, leading to enhanced bone formation in ob/ob mice [79]. Similarly, peripheral effect of leptin on bone was found to be anabolic. Leptin increased proliferation of isolated fetal rat osteoblasts in bone and inhibited osteoclastogenesis in bone marrow, leading to new bone formation, higher bone density and reduction in fracture risk [80]. Similarly, other authors recently observed decreases in bone growth, osteoblast-lined bone perimeter and bone formation rate were observed in *ob/ob* mice, which was greatly increased following subcutaneous administration of leptin [81]. Similarly, hypothalamic leptin gene therapy increased osteoblast-lined bone perimeter in *ob/ob* mice. In spite of normal osteoclast-lined bone perimeter, *db/db* mice exhibited a mild but generalized osteopetrotic-like (calcified cartilage

encased by bone) skeletal phenotype and greatly reduced serum markers of bone turnover [81]. The authors of this study supported that leptin, acting primarily through peripheral pathways, increases osteoblast number and activity [81]. Therefore, it seems that, regardless of intracerebroventricular or subcutaneous leptin administration, leptin increased muscle mass, bone mineral density, bone mineral content, bone area, marrow adipocyte number and mineral apposition rate in both the appendicular and axial skeleton [43, 79].

Furthermore, it was reported that leptin is expressed in a unique time course during fracture healing. Delay in callus maturation was demonstrated radiographically and histologically in the *ob/ob* mice, which was reversed by local leptin administration, thereby indicating that leptin deficiency (*ob/ob* mice) leads to impaired fracture healing, which is reversed by its administration [82].

5. Bone abnormalities in hypoleptinemia and leptin resistance: Evidence from human studies

Individuals with anorexia nervosa have low leptin levels that correlate directly to low BMI and percent body fat [83]. Additionally, low BMI in constitutionally thin women is also associated with lower bone mass and poor bone mineralization [84]. Higher bone mass density (BMD) in obese patients was believed to be protective effect of obesity on bone health and mineralization [85], which may be partially true, since obese patients with sarcopenia may have low bone density and increased fragility [86]. Poor bone quality and increased fracture risk is found in patients with anorexia nervosa and hypoleptinemia. Low bone mineral density was seen in women with anorexia nervosa at lateral spine, AP spine and total hip [87]. Although bony abnormalities are multifactorial in anorexia nervosa, leptin has been shown to play a major role in bone health. Leptin levels are positive associated with bone microarchitecture and structural integrity [88]. Abnormal microarchitecture, even in the presence of normal BMD, results in increased fracture risk, thus placing low leptin state conditions with abnormal microarchitecture at a higher fracture risk category.

In cases of obesity, a state of leptin resistance, there have also been observed abnormalities. Obesity caused decreased bone mass density in a controlled study of rats [62]. Obesity may also cause increased fracture risk in humans [63]. Although in the past, it was thought that obesity was protective against osteoporosis and bone fracture risk, new evidence may suggest that obesity, implicated with low-grade inflammation and sarcopenia, may not confer benefits on bone mass [63, 89]. This relationship may be altered through the states of leptin or insulin resistance found in obesity and which in turn seem to relate to poorer bone health outcomes [90, 91]. In a large study of lean, healthy adolescents, bone mass was found to be inversely related with percent fat mass, when body weight was controlled [92]. Several other studies have found similar results of increasing adiposity leading to decreased bone mass with obese and/or lean participants, an effect that is most pronounced in obesity [93-96]. Certain bone regions may be more sensitive to these effects. For instance, cortical bone may be more sensitive to adiposity than trabecular bone [92, 94]. At higher levels, leptin, acting as a proinflammatory adipokine, may activate inflammatory pathways in osteoblasts that may cause poorer bone and cartilage health [97].

6. Interventional studies in humans

Several interventional studies have been done with leptin to look at its effect on body mass, body fat content, bone composition and bone mass, particularly in individuals with hypothalamic amenorrhea and lipodystrophy. Much of the evidence comes from women with hypothalamic amenorrhea, a state of infertility which can be caused by energy deficiency-through excess exercise and/or inadequate food intake [25]. Women with hypothalamic amenorrhea have markedly low leptin levels in addition to decreased estrogen and other hypothalamic output hormones, including thyroid hormones and growth hormones [12, 25]. They also have poor bone mass density, which can lead to low-energy bone fractures despite young age [25]. Remarkably, all hormonal abnormalities and inappropriate bone density can be reversed by metreleptin therapy [12, 25, 28, 98]. Welt et al. [28] examined eight women with more than six month long hypothalamic amenorrhea due to strenuous exercise, i.e. by definition women with decreased bone mass. All the study patients were treated with metreleptin subcutaneously for two to three months, with forty percent of the daily dose of leptin given in the morning and the remaining sixty percent at night to mimic natural diurnal variation [28]. Women were studied on and off treatment, serving as their own controls, in addition to a separate untreated control group [28]. Leptin treatment resulted in increased mean luteinizing hormone (LH) levels and LH pulse frequency, as well as in increased levels of estrogen, IGF1, IGF-BP3, and thyroxine, all of which have positive impacts on bone health [28]. It also increased levels of bone turn over markers, including bone alkaline phosphatase and osteocalcin (markers of bone formation), thereby indicating an osteoanabolic action [28]. Bone mineral density remained stable at a 3 months follow-up visit of the study [28], but the duration of this pilot study may not be long enough to detect changes in bone density. A longer study in young women with hypothalamic amenorrhea who underwent metreleptin treatment for two years showed significant improvements in bone mineral density and content at the lumbar spine [98]. The bone mineral density of hip and radius showed a trend towards improvement as well [98]. This may be related to the influences of estrogen, a hormone which also improves with leptin therapy in hypothalamic amenorrhea [98] in addition to other hormonal axes that were improved in response to exogenously administered leptin. Indeed, leptin's effect on bone is very similar to that of estrogen. Like estrogen, it also increases osteoprotegerin (OPG) levels, which leads to binding receptor activator of nuclear factor kappa-b ligand (RANKL), and in turn, results in reducing osteoclast activity [99]. Therefore, in clinical trials, it is difficult to parcel apart which hormone may causing the end effects of improving bone density and further studies may need to determine whether this is a direct or indirect effect of leptin. Regardless, these findings do show that leptin does, whether directly or indirectly, restore normal hypothalamic and bone metabolism/functioning. While leptin levels have shown strong positive correlation with BMD in women, it seems to have a weaker effect in men [100]. It seems to be rational, since testosterone, rather than estrogen, is a stronger determinant of bone mass in men; in this regard, it would be of interest to investigate the effect of metreleptin treatment in men with hypogonadotrophic hypogonadism and hypoleptinemia.

Leptin therapies, in the context of non randomized uncontrolled studies, have also be proven useful for lipodystrophic patients [101]. Lipodystrophy is characterized by a complete or partial loss of adipose tissue [101]. Moran et al. [102] studied 14 patients (3 men and 11 women) with congenital hypoleptinemia due to congenital or acquired lipodystrophy. At baseline, they had decreased fat mass, BMI and very low leptin levels, whereas their baseline BMD was normal. By four months of therapy, leptin levels were restored [102]. Leptin administration decreased lean body mass and fat content, decreased energy expenditure and caloric intake, but had no impact on bone mineralization/BMD, bone resorption, or bone metabolism biomarkers in these patients with lipodystrophy [102]. However, high baseline BMD may partly account for this paradox. Unlike patients with hypothalamic amenorrhea, patients with lipodystrophy often have comorbid insulin resistance which may increase their bone density due to the high insulin and IGF1 levels present [103].

Summarizing the aforementioned data, leptin may normalize bone density in hypoleptinemic individuals, when it is impaired, whereas it may have no or minimal action when it is not. However, further larger studies are needed to elucidate the effect of metreleptin treatment on bone metabolism.

7. Clinical Utility of Leptin

Leptin plays a crucial role in regulation of neuroendocrine axes, fat and glucose metabolism and hence has been studied in detail in several “proof of concept” clinical trials as a potential therapeutic agent in leptin deficient states. Treatment with leptin in deficient individuals not only decreases appetite and weight but also has significant effect on neuroendocrine axes leading to normalization of several hormone levels [103, 104]. In addition to congential lipodystrophy mentioned above, metreleptin replacement in leptin deficient HIV patients with highly active antiretroviral therapy (HAART)- induced lipoatrophy has shown improvement in fasting insulin levels, insulin resistance, body fat-mass (especially truncal) and high-density lipoprotein levels [105]. Leptin replacement has also shown benefit in balancing immune function in deficient individuals. Interventional studies have shown improvement in circulating cytokines and CD4 (+) T cells with leptin replacement in congenitally deficient individuals [18]. In lean women with chronic energy deprivation and relative leptin deficiency, replacement with recombinant leptin for 8 weeks showed increase in TNFα receptor levels, indicating correction of immunological function [106]. Myalept (metreleptin) is now approved for use in individuals with lipodystrophy but not those with HIV lipodystrophy. The potential side effects and contraindications include headache, weight loss, abdominal pain, arthralgia, dizziness, ear infection, fatigue, nausea, anemia, back pain, and diarrhea. It also bears the risks of neutralizing antibodies, lymphoma, hypoglycemia (when used with insulin), autoimmune disease, and allergic reactions to the compound.

Leptin replacement has shown significant improvement in bone mineral density of lumbar spine giving hope of leptin use in metabolic bone disease, including osteoporosis, particularly in leptin deficient individuals [98]. Osteoporosis is characterized by low bone mass and density that makes bone fragile and increases fracture risk. Over 10 million people

worldwide have proven to have osteoporosis and 34 million have osteopenia. The disease carries a huge burden and osteoporosis related fractures cost the U.S. healthcare system nearly $17 billion annually with an increasing curve every year [107]. Several pharmacological drugs have been FDA approved for treatment of osteoporosis. Most of them are antiresorptive agents that directly or indirectly inhibit osteoclasts (e.g. bisphosphonates and calcitonin).

Given the heavy socio-economic burden of osteoporosis, newer molecules, ideally in the context of a more personalized treatment, are needed. Leptin provides a potentially promising future anabolic therapy for leptin deficient individuals, due to its effect on bone formation markers. Osteocalcin and bone alkaline phosphatase have shown significant increases after treatment with leptin in hypothalamic amenorrheic women. Long-term metreleptin treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women [12, 98]. There is currently no approved therapy for women with hypothalamic amenorrhea, and this unmet clinical need should be addressed; in this regard, current data warrant the design of larger controlled phase III clinical trials involving metreleptin administration [12].

Long-term trials with recombinant leptin therapy and its effect on bone mineral density and turnover markers in leptin deficient osteoporotic women should also be studied. Studies have definitively shown positive correlations of leptin with BMD, especially in postmenopausal women. The effect of leptin treatment on bone density, bone turnover markers, and mainly on low-energy fracture of hypoleptinemic postmenopausal women needs further clarification. Although the association between leptin treatment and lymphoma remains to be elucidated, leptin treatment seems to be safe and well tolerated [108]. However, it remains unknown whether the side effects and potential complications mentioned in trials on lipodystrophic individuals would also be seen in the context of randomized, placebo controlled studies in women with osteoporosis or osteopenia.

This adipokine can possibly provide therapeutic option in osteoporosis and other metabolic bone diseases in leptin deficient individuals, and future research should test and expand on this possibility.

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Abbreviations

BMI	body mass index
ARC	arcuate nucleus of hypothalamus
NPY	neuropeptide Y
AgRP	agouti-related peptide
POMC	pro-opiomelanocortin
CART	cocaine-and amphetamine-related transcript
LepRb	leptin receptor
JAK2	janus kinase 2
STAT3	signal transducer and activator of transcription 3
SHP2	src homology-2-containing protein tyrosine phosphatase 2
MAPK	mitogen-activated protein kinase
PI3K	phosphatidylinositol 3 kinase
AMPK	adenosine monophosphate-activated protein kinase
Mtor	mammalian target of rapamycin
FoxO1	forkhead box protein O1
TSH	thyroid-stimulating hormone
FGF23	fibroblast growth factor 23
VMH	ventromedial hypothalamus
IGF1	insulin-like growth factor 1
IGF-BP2/3	insulin-like growth factor binding protein 2/3
GH	growth hormone
ACTH	adrenocorticotropic hormone
HAART	highly active antiretroviral therapy
Akt	Protein Kinase B
SOCS-3	Suppressor of cytokine signaling 3

Highlights

- Leptin has both direct and indirect effects on bone metabolism.
- Leptin therapy has a normalizing effect on bone density of hypoleptinemic subjects.
- Future studies need to assess benefits and risk of leptin's usefulness in bone disease.

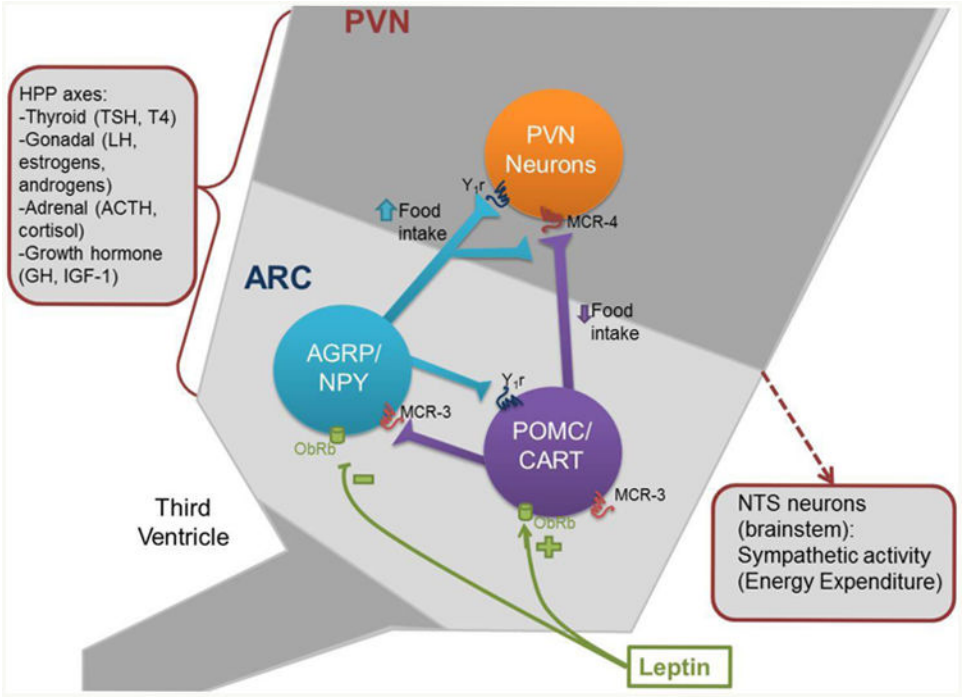

Figure 1.

Actions of leptin to alter food intake and energy expenditure. Leptin inhibits AGRP/NPY and activates POMC/CART neurons in the arcuate nucleus of the hypothalamus. These neurons in turn act on paraventricular (PVN) neurons to increase or decrease food intake as well as to modulate sympathetic activity and energy expenditure through the Nucleus of the Solitary Tract. Leptin signaling in the hypothalamus also activates other hypothalamic-pituitary-peripheral (HPP) axes, which also have consequences for bone metabolism.