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Chapter 4

Homocysteine and Leptin in the Pathogenesis of Osteoporosis — Evidences, Conflicts and Expectations

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Homocysteine and leptin in the pathogenesis of osteoporosis: evidences, conflicts and expectations

1.1.1. Osteoporosis

Osteoporosis is a metabolic bone problem, also recognized as "the silent thief" because there is slow bone loss, generally occurs over the years, and without any symptoms until the bone becomes so brittle that suddenly fracture occurs. Osteoporosis is the most common disorder related to age [1]. It is a leading cause of fractures in old age: causing pain, affliction, hospitalization, financial burden, poor life quality leading to early death [2]. Osteoporosis is usually considered a normal part of the ageing process and an unavoidable consequence of growing older. However, osteoporosis is a detectable, preventable, and treatable disease.

1.1.2. Types of osteoporosis

Two types have been identified

- Primary osteoporosis.
  - **Type I** also called postmenopausal osteoporosis, occurs after menopause when the estrogen levels drop in the body. It typically involves the trabecular bone.
  - **Type II** also called senile osteoporosis, takes place after 70 years of age, involving both trabecular and cortical bone.
- Secondary osteoporosis.
  - It is due to the effect of medications like steroids or certain medical conditions.

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1.1.3. Epidemiology

In postmenopausal females, osteoporosis has an enormous social and economic burden. With increasing age, the risk of osteoporotic fractures increases. There are about two million cases of fractures in the USA per year and out of them, there are about three hundred thousand hip fractures. The fractures and resultant health consequences have led to mortality rate up to 24% in women [3].

International osteoporosis foundation has estimated that globally osteoporosis affects one in three women and one in eight men above 50 years of age [4].

1.1.4. Pathogenesis

Osteoporosis develops when there is imbalance between the processes of bone resorption and bone formation. Osteoclasts (bone resorbing cells) eradicate bone by acidification and proteolytic digestion and osteoblasts (bone forming cells) secrete osteoid into the resorption cavity [5]. The normal cycle of bone turnover is needed for bone and maintenance of proper bodily functions. Each year 10 to 30% of the skeleton is remodeled in this way, and many hormones and chemical factors regulate this process and any change in these factors can manipulate the progress of osteoporosis. These influencing factors are estrogen, vitamin D, leptin, homocysteine, parathyroid hormone, testosterone, and blood factors involved in cell growth [6].

The bone turnover is perfectly balanced until the age of forty years. Nevertheless, old age, many diseases and medicines can disturb the balance, ultimately the breakdown process exceeds the bone formation, and as a result, trabecular plates of bone are destroyed causing weakness of the structure of bone with greatly reduced bone mass. Bone strength is a sign of the integration of bone quality (rate of bone remodeling, trabecular connectivity, degree of mineralization, and damage accumulation) and bone mineral density (BMD) [7]. There is doubling in the bone remodeling rate at menopause, becomes triple within 13 years of development of menopause and remains high till the development of osteoporosis. In osteoporosis, the trabecular bone loss is more as compared to cortical bone (50% as compared to 5%) and it occurs more swiftly in first 3-4 years after menopause [6].

1.1.5. Risk factors

It is a multifactorial disease including both modifiable and non-modifiable risk factors. Numerous factors are involved and augment the risk of developing osteoporosis [8-10].

- Non-modifiable risk factors
  - Increasing age
  - Female gender
  - Caucasian and Asian women and men
  - Small, thin-boned women
  - Maternal history of osteoporotic fracture
  - Deficiency of estrogen

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- Modifiable risk factors
  - Smoking
  - Excessive alcohol consumption
  - Sedentary lifestyle over many years
  - Diet deficient in calcium
  - Insufficient exposure to sunlight, resulting in vitamin D deficiency
  - Hyperhomocysteinemia
  - Leptin

1.1.6. Homocysteine

Homocysteine (Hcy) is produced from the methionine metabolism, it is a sulfur-containing, nonproteinogenic amino acid (figure 1) [11]. Methionine, itself is a sulfur containing amino acid obtained from proteins of animal origin. It is metabolized in the body by either remethylation or transsulfuration pathway as shown in the figure 2. Both genetic (methylene tetrahydrofolate reductase or cystathionine β synthase polymorphisms) and environmental (age, renal function, B vitamins status) factors affect the plasma homocysteine concentration [12].

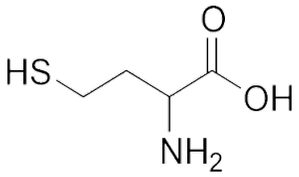
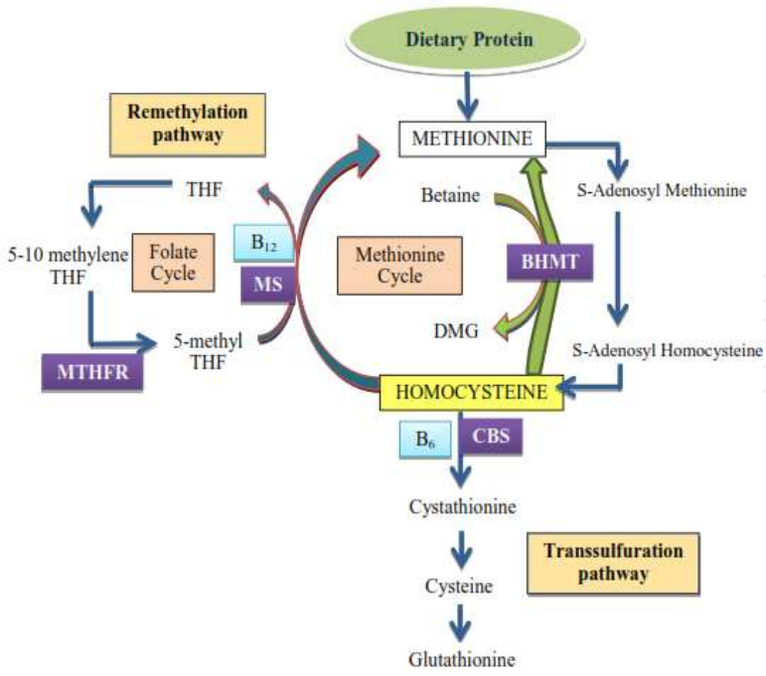


Figure 1. Structure of Homocysteine

2. Hcy and bone metabolism

Hyperhomocysteinemia (HHcy) is the elevated levels of total plasma Hcy. Generally, the Hcy level <15 μmol/L is considered normal but an increased plasma Hcy level (>15 μmol/L) is common in about 30–50% of elderly people (>60 years)[13]. There are multifactorial contributing factors like, a combination of genetic and environmental factors, lifestyle, diet, and hormonal factors might play a key role [14]. In addition, of being a known potent thrombogenic compound, [15] it has been proposed as a new risk factor for primary osteoporosis [16-18]. Like osteoporosis, HHcy is a frequent age related issue in aged people [19-20]. In old age, deficiency of vitamin B-12 and folate is common, and the prevalence of both vitamin deficiencies increases with age. Deficiency of either folate or vitamin B-12 results in increased tHcy levels because vit B12 acts as a cofactor for methionine synthase, the enzyme that remethylates homocysteine to methionine by using 5methyltetrahydrofolate as a methyl donor [20].



BHMT: betaine-homocysteine methyltransferase **DMG:** dimethylglycine **vitamin B6:** pyridoxyl phosphate **CBS:** cystathionine beta-synthase **vitamin B12:** cobalamine **MS:** methionine synthase **THF:** tetrahydrofolate **MTHFR:** 5,10-methylenetetrahydrofolate-reductase

Figure 2. Homocysteine metabolism

Ozdem et al., (2007) reported that experimental hyperhomocysteinemia disturbs bone metabolism in rats. They found that rats fed with a methionine-enriched diet had increased bone resorption markers (hydroxyproline & N-terminal collagen I telopeptides) and decreased bone formation marker (osteocalcin) [21]. Additionally, chronic HHcy may take part an imperative role in the development of arterial and venous thrombosis, senile osteoporosis, presbyopia and cognitive decline. These diseases are usually common in elderly [22]. An inverse correlation of total homocysteine (tHcy) concentrations with BMD has been documented by several reports, especially in postmenopausal women, and HHcy has been labeled as a modifiable risk factor for osteoporotic hip fracture [16-17, 23-26], while several other studies could not establish any correlation [27-29]. Similarly, an Italian study showed an inverse association of plasma concentration of tHcy with BMD of the total femur in post-menopausal women and the study concluded that it is independent of other recognized reasons of bone mineral loss, such as reduced BMI and old age [30]. Recently, in Pakistan, we investigated correlation of serum Hcy with BMD in postmenopausal osteoporotic females but could not find any correlation [31]. It has been reported that increased Hcy levels, decreased vitamin B12, and folate status have been related with reduced BMD and increased fracture risk and thus serum Hcy level can be used as an indicator of such micronutrient insufficiencies [16-17, 25, 27].

Herrmann et al., (2007) provided the first evidence regarding effects of chronic HHcy on bone quality in rats. In this study, healthy adult rats displayed reduction in bone strength in

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cancellous bone as reflected by biomechanical testing and histomorphometry, after 3 months of HHcy. The study did not explain the main mechanism behind this result [32]. Few mechanistic studies recommended that Hcy excites osteoclasts and causes disproportion between osteoclasts and osteoblasts in support of the osteoclasts, which are the main bone resorbing cells [33-36]. Furthermore, it appears that a number of extracellular mechanisms are also implicated. A study exhibited a reduced level of enzymatic cross-links in the bones of hyperhomocysteinemic female fracture patients that indicates impaired collagen cross-linking [37]. A study reported that in hyperhomocysteinemic animals, Hcy is deposited in bone tissue that causes considerable bone loss and consequently decreased bone strength [38].

3. Hcy and bone interaction: conflicts and evidences

During last few years, abundant literature has been published about the interaction of HHcy and bone. Up till now, several mechanisms have been proposed about the involvement of Hcy in bone pathology. HHcy is an emerging, but still non established, modifiable risk factor for osteoporotic fractures [39].

An elevated level of Hcy has been proposed as a new threat for primary osteoporosis [16-17]. Tyagi et al., 2011 in their study concluded that Hcy may cause reduced blood flow in bone as it stimulates the atherogenic process, promotes platelet adhesion and has also been recognized as a potent thrombogenic compound that might contribute to compromised bone biomechanical properties [40].

A prospective population-based study, reported that the highest quartile of tHcy was related with a two-fold augmented risk of fracture, and the relationship was continuous and there was 30% increased fracture risk with each standard deviation raise in tHcy [17]. Recently, a study by Enneman (2014) reported inverse correlation of plasma homocysteine levels with BMD [41].

In the early years of Hcy and bone research, it seemed that Hcy directly affects biomechanical properties because deposition of Hcy in bone coupled with a decrease in cancellous bone. A study suggested that deficiency of B12, folate and vitamin B6 elevates the plasma level of tHcy [35]. Another study found that the interaction of tHcy molecule with protein (collagen) in bone matrix takes place through thiol group and an amino group. This study also demonstrated that bone strength is reduced because most of the tHcy (65%) attaches with collagen [38].

A study proposed four mechanisms by which modification in bone remodeling takes place by tHcy: (i) enhancement in osteoclastic activity, (ii) reduction in osteoblastic activity, (iii) reduction in blood flow in bone, (iv) direct interaction of Hcy and bone matrix [42].

A study illustrated that tHcy inhibits lysyl oxidase, thus interferes with post-translational changes of collagen and this leads to decrease in bone quality [43]. The tHcy stimulated interleukin-6 (IL-6) production in osteoblasts, affects metabolism of bone by osteoclast. Janus kinase 2 (JAK2), DNA (cytosine-5) – methyltransferase 1 (DNMT1) stimulate IL-6, which affects bone matrix formation [44]. A study documented that the skeleton and muscles movements reduce tHcy level and this link was not dependent on vitamin supplements, vegetables and

fruits intake. Thus, it was suggested that levels of tHcy are also mainly affected by physical activity, though, nutritional condition also contribute significantly [16]. Thus, it seems that, regular exercise may decrease the Hcy level in HHcy individuals while it may help in maintaining Hcy level in normal subjects.

A study observed that the maximum tertile of tHcy was related with a higher hip BMD loss over 4 years (-2.8%) compared to middle (-1.6%) and lowest tertiles (-1.2%) in elderly women (age ranges from 70 to 85 years). It was stated that the incidence and prevalence of fractures were not affected by elevated tHcy levels, but the augmented tHcy level is related with considerable hipbone loss in aged subject [45].

No association of fracture risk with tHcy in the highest quartile was shown in a study after adjustment for age but without adjustment of age risk was higher. They described that tHcy level could be modulated by nutritional conditions, renal failure and physical activity [46]. An animal study demonstrated that HHcy causes impairment in fracture repair. In their study, a closed femoral fracture was induced in mice after feeding them Hcy for 3 weeks, and biomechanical parameters were monitored after 4 weeks of healing. They found that hyperhomocysteinemic rats with fracture have reduced bending rigidity of femora and smaller callus diameter with no change in tissue composition and consequently it impaired fracture repair and reduced bone quality [47].

First clinical evidence about the relationship of HHcy and fracture risk came from the longitudinal study in healthy participants of different age groups of both genders [48]. The results showed that HHcy levels are the independent risk factor for the future worsening of bone mass in premenopausal women and men. Conversely, they could not find same results in postmenopausal women (PMW). It was suggested that, even if a high serum tHcy level in postmenopausal women is not a factor related to the reduction in BMD, so it is likely that HHcy may be implicated in the fractures risk in PMW via some other method not involving BMD.

It is known that in the regulation of osteoblasts function, estrogen receptors play important role and this phenomenon is particularly important after menopause in women [49]. Aaron et al., (2009) probed the link of tHcy levels and methylation of estrogen receptor α. Their data pointed out that tHcy can support hypermethylation of promoter A region, by this means decreases transcription of estrogen receptor α mRNA. It was anticipated that in the pathogenesis of postmenopausal osteoporosis it could be a probable mechanism. Therefore, an estrogen receptor mediated role of tHcy may cause worsening in biomechanical bone characteristics. Additionally, higher levels of Hcy lead to down regulation of estrogen receptor transcription in bone and other useful osteogenic effects turn out to be down regulated [50].

A study tried to devise some likely therapeutic options for reducing increased plasma levels of tHcy that may cause damaging effect on bone. They used strontium ranelate 2 g/day to lessen increased plasma levels of tHcy because such material found to extensively reduce tHcy concentrations in osteoporotic women and was suggested to be employed as a mean to lessen fracture risk by reducing tHcy levels [51]. Strontium ranelate was selected because of its recognized positive outcome of lessening resorption of bone and supporting bone construction. It is not unlikely that decrease in levels of tHcy is accountable for permitting the recognized effects of strontium ranelate to happen [52].

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It is suggested that if changed bone biomechanical characteristics are result of increased Hcy and hormone replacement therapy (HRT) is recognized to ameliorate quality of bone, it was assumed that HRT would ameliorate quality of bone by reducing tHcy concentration. But the researcher could not confirm this effect of HRT on Hcy in postmenopausal osteoporotic women [53].

A study in hip arthroplasty patients because of osteoarthritis, tried to investigate the link of serum tHcy levels with osteoarthritis. But this study could not establish any noteworthy association of tHcy levels with biomechanical or morphological bone characteristics as evaluated by histomorphometry and DEXA [54]. Bayhan et al., (2009) demonstrated that elevated tHcy levels appear to influence bone quality and fracture risk, but there have been no distinguishing alterations in bone density [51].

The Hcy impairs the cross-linking of collagen and for the solidity and potency of the collagen network, these cross-links are essential. Any meddling in cross-link formation would therefore, affect the quality of bone matrix, which in turn causes the fragility of bones due to defective collagen formation but would not affect BMD, which is the representative of bone mineralization only [37]. It was found in an animal study that elevated levels of Hcy for three months increase femoral neck fragility by 18% in methionine-fed rats, and two-fold in Hcy-fed rats. Lumbar spine and femoral neck also demonstrated reduce biomechanical characteristics, however, more in methionine- versus Hcy-fed rats [32].

Recently, a meta-analysis by Zhong et al., (2014) suggested that vitamin B12 and Hcy levels were considerably elevated in postmenopausal osteoporotic (PMOP) group compared to controls and these were linked with BMD in PMOP [55].

Bone component	Effect	Mechanism
Osteoblast	Decrease activity	Reducing OPG and elevating RANKL production in osteoblast [58]
	Increase activity	Moderate stimulation of osteoblast activity but predominant effect on osteoclast [35]
Osteoclast	Increase activity	Shift the OPG:RANKL ratio in favour of elevated osteoclast activity and reduced bone quality by altering the redox regulatory system in the osteoblast [40, 58]
Bone matrix	Degradation	Reduction in bone blood flow [40] Activation and amplification in matrix metallo-proteinases through generation of ROS [59]. By inhibiting enzyme of collagen cross-linking (lysyl hydroxylase and lysyl oxidase) thus directly manipulate the stable bone matrix formation [44, 60].
Osteocalcin	Inhibit secretion	Suppress the expression of OC mRNA [61]
Osteopontin	Activated	By enhancing the expression of osteopontin mRNA (6).

OPG osteoprotegrin, **RANKL** receptor activator of nuclear factor-κB ligand, **Hcy** Homocysteine, **ROS** reactive oxygen species, **MAPK** Mitogen-activated protein kinases, **OC** osteocalcin **mRNA** messenger ribonucleic acid.

Table 1. Effect of Homocysteine on different Bone components

A meta-analysis provided a proof on homocysteine and fracture risk, displaying that HHcy augments the fracture risk [56]. A very important evidence of effect of HHcy on fracture risk was provided by another meta-analysis including more than ten thousand subjects, demonstrated 4% augmented risk of fracture by per μmol/L raise in Hcy level [57].

3.1. Expectations

In spite of substantial evidence that indicating the direct damaging role of HHcy on bone metabolism, the role of serum tHcy in bone loss is still unclear. HHcy can be reduced by vit B12, and folate therapy, so by designing randomized controlled trials (RCTs) of B-vitamins vs. placebo, it is quite likely to establish whether tHcy is a contributory risk factor for bone fracture or not [62].There are few RCTs available in literature but because of various reasons these are not up to the mark.

Based on evidences, provided in the literature, it seems that HHcy may have negative role in bone metabolism generally and in the process of osteoporosis particularly. However, more interventional studies are required to confirm the unfavorable role of HHcy, particularly in subjects who are at the risk of developing low bone mass. It is suggested that there is a need to develop several multicenter, well-designed trials on determining the effects of Hcy-lowering treatment on the prevention and/or management of osteoporosis. These longitudinal trials would determine the accurate nature of Hcy and bone interaction and that will establish the outcome of different bisphosphonate therapies on Hcy levels in treating osteoporosis.

4. Leptin

Adipose tissue is the largest endocrine organ in the human body; it serves considerable role in the energy homeostasis and several metabolic processes. It also has a multifaceted association with the bone. It is a general phenomenon that with increasing age the fat tissue in the bone marrow increased while the bone mass decreased. It is because both the osteoblast and adipocyte are developed from the same cell lineage the mesenchymal stromal cells (MSCs). The segregation tendency to preadipocytes or preosteoblasts is competitive and being inhibited by each other. Nevertheless, published literature advocates that through adipokines, adipose tissue have intricate effects on bone metabolism [63]. The family of adipokines, including leptin, adiponectin, chemerin, resistin, omentin, visfatin and vaspin, take part in several physiological, biochemical and pathological processes, including, the glucose and lipid oxidation, energy expenditure, immunity, reproduction, inflammation, and others. Because of growing evidences regarding interaction of adipokines and bone metabolism, the researchers are paying special attention to their relationship.

Leptin is a diverse 16 kDa peptide hormone, which belong to the family of helical cytokine with lengthy chain (figure 3) [64]. Leptin is an important member of adipokine family that helps in regulation of food intake, energy homeostasis, reproduction, metabolism, immune function, bone physiology, tissue remodeling, neuroendocrine function and others [65].

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Research has shown that leptin plays significant role in the regulation of body weight and BMD. Experimental evidence in mice showed that they appeared obese and have increased bone density when they were congenitally absent in leptin (ob/ob), indicating that leptin has a role in loss of bone density as well as fatty tissue [66].

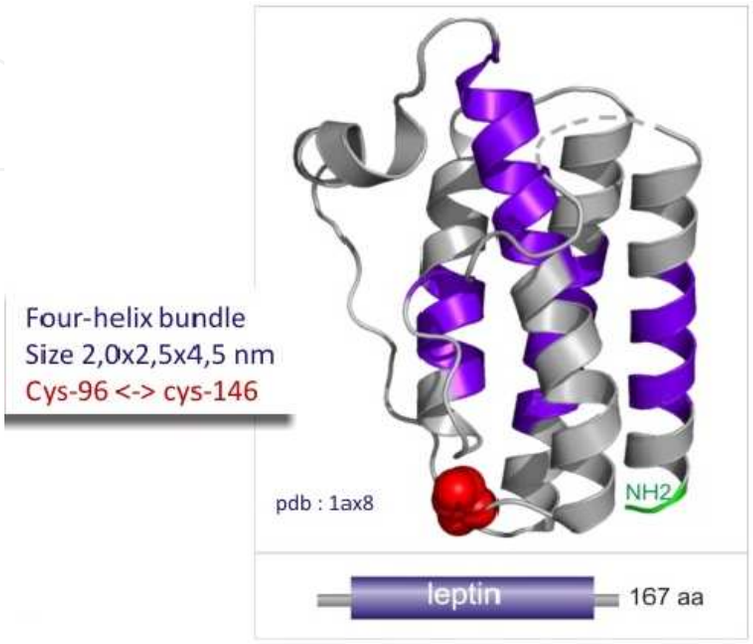


Figure 3. Leptin structure [64]

In a study, leptin replacement demonstrated the improvement of abnormalities in ob/ob mice in the form of decreasing food intake, energy loss, and temperature of body, infertility and immune function [67]. Since then, the knowledge which has been obtained from various studies indicating that leptin is not only important in control of body weight but also play imperative role in angiogenesis, hematopoiesis, blood pressure, immune function, lymphoid organ homeostasis, T lymphocyte systems, fertility, and bone formation [68].

Leptin is produced primarily from adipocytes according to adipose tissues quantity in the body. Brown fat tissue, stomach, placenta, ovary, bone marrow, liver, pituitary and mammary epithelial cells also secrete leptin [69]. Researchers observed that leptin is encoded by ob gene (LEP) (ob - obese and LEP - Leptin), according to the name that was first proposed, 'leptos', derived from the Greek word meaning thin, as ob protein is considered to be one of the molecules that regulates energy balance in mice [70].

4.1. Leptin receptor

Leptin's receptors were first isolated by cloning from mouse choroid plexus, these receptors belong to the cytokine family. There are six leptin receptors, which are divided into secretory (ob-Re), long (ob-Rb), and short forms (four short form receptors) [71-72]. The molecular receptor structure of the leptin and helical cytokine (class I) is similar. These homodimer

receptors are able to activate the Janus kinase (JAK), and JAK is capable of starting as an activator of STAT – signal transducer and activator of transcription (Figure 4) [73]. Leptin signals through the activator system of JAK transcription, are associated with the form obRb (isoform long form) that would alter the expression of hypothalamic neuropeptides [74-75]. The ob-Rb is found in high levels in the hypothalamic nuclei [71] and its activity helps in mediating signal transduction by leptin in the hypothalamus, while the other leptin receptor activity (short form) is not strong enough in the functioning of leptin [72].

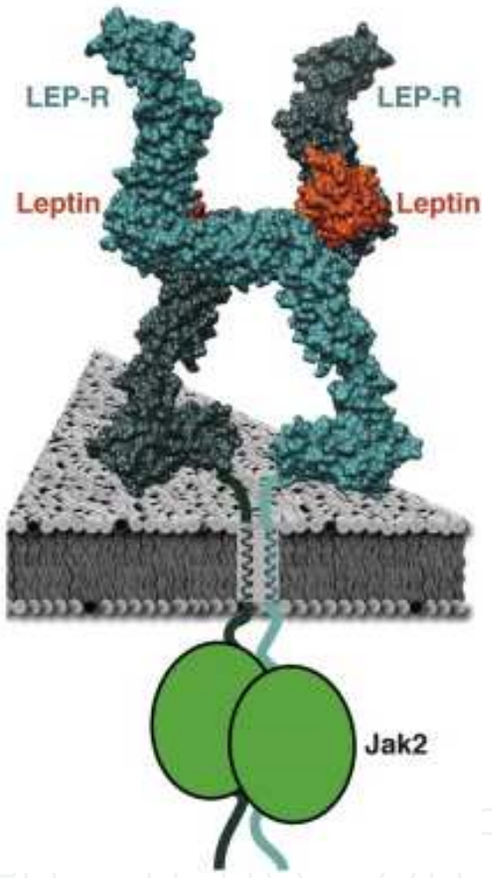


Figure 4. Leptin receptor [73]

4.2. Leptin and bone interaction: conflicts and evidences

Bone mass has been said to be regulated by leptin. The interaction of leptin with bone is multifaceted, related with location of bone. It also depends on the fact that whether leptin has a direct action on osteoblasts through receptors or it acts indirectly through the hypothalamus, it has the ability to both stimulate and inhibit bone formation [76-79]. Reduction in serum leptin levels are linked with decreased intake of food that might results

in reduction in formation of bone and growth especially in children and adolescence [80-81]. In mice, lack of leptin also causes loss of bone and increased adiposity in bone marrow [82]. Leptin's enhanced levels and bone mass are associated with each other in obesity [83]. Leptin instead of supporting adipocyte phenotype of bone marrow stromal cells (BMSCs) supports osteoblast demonstrated by in vitro studies [78, 84-85]. Similarly, in vitro studies have demonstrated that in ovariectomized rats there was reduction in bone loss and suspension of tail after leptin treatment [86-87].

A study in Caucasian woman demonstrated that serum leptin had an inverse relationship with BMD, another study observed a positive connection [88-89]. A large-scale study established that serum leptin has no association with BMD [90]. Similarly, in another study no relation established between leptin and BMD [91]. Furthermore, it was suggested that leptin might be a forecaster of BMD in females with low BMD [92]. Recently, in Pakistan, we investigated correlation of serum leptin with BMD in postmenopausal osteoporotic females but no relationship was found [31].

In vitro data shows that serum leptin supports the segregation and development of the osteoblast lineage cells and controls development of osteoclast [92-93]. Some clinical data have shown an inverse relationship between bone resorption markers and serum leptin concentrations in postmenopausal women [89, 94] while other found a negative relationship [95-96].

Recently, Scotece et al., (2014) described that leptin level could be a valuable risk marker for osteoporosis [97]. A study by Suh et al., (2013) found that changes in serum osteocalcin were linked with leptin levels. It seems that there is connection between adipose tissue and bone [98]. On the other hand, Mohiti-Ardekani et al., (2014) reported that there is no correlation of circulating leptin concentrations with BMD and bone biochemical markers including osteocalcin [99].

4.3. Indirect role of leptin in bone metabolism

Leptin has both direct and indirect effects on bone. Indirect mechanisms have been revealed by experimental studies in mutant rats and mice that cannot synthesize leptin or do not have receptors for it. Leptin is carried across the blood brain barrier (BBB) by special receptors, which are located on the endothelial cells, the obRa receptors. In the brain leptin binds with obRb receptors which are located in hypothalamus and activates them. Binding of leptin with its receptors stimulate the expression of a hypothalamic osteoblast inhibitory factor (HOBIF) that lowers the ability of osteoblast to make bone matrix [76-77, 100-101]. And because of this mechanism, obese ob (Lep)–/– mice, due to lack of leptin have an unusually elevated bone mass.

Leptin stimulates bone formation via beta-1-adrenergic receptors and stimulation of the somatotropin-IGF-1 system [102]. Leptin inhibits activity of osteo-catabolic neuropeptide Y (NPY) and stimulates activity of osteo-anabolic systems, such as cocain and amphetamine-regulating transcript, via hypothalamic relays [103]. Moreover, leptin suppresses bone formation through beta-2-adrenergic receptors located in bone and inhibits serotonin production in the brain that result in loss of trabecular bone formation [104].

4.4. Direct role of leptin in bone metabolism

This is achieved by directly inhibiting the BMSCs to generate osteoclast while stimulating them to differentiate into osteoblasts [84, 93]. The BMSCs can be discriminated mainly into adipocytes or osteoblast cell family. These adipocytes in bone marrow provide leptin, which is able to inhibit adipogenesis discrimination of BMSC. It can excite discrimination of osteoblasts [84] while another study have pointed out that extremely elevated level of leptin causes apoptosis of BMSCs. A study reported that human osteoblasts, can begin producing and secreting leptin in the delayed matrix-mineralizing stage or shifting to osteocytes [85]. Proliferation of cultured human osteoblasts is also stimulated with leptin and it causes human BMSCs to express collagen-I, osteocalcin & alkaline phosphatase, and matrix mineralization [84,105]. These in vitro studies demonstrated that effects of leptin are dual in the microenvironment of bone and it also depends on presence of the leptin levels locally.

In the last decade, researchers proposed leptin to be a strong inhibitor of synthesis of bone because they could not find that osteoblast have long isoforms of the leptin receptors (ob-R) [76, 100]. In hypothalamus, and in many peripheral tissues expression of a large number of long isoform of ob-R have been confirmed [69].

Leptin receptors are also expressed by BMSCs, osteoblasts, osteoclasts and chondrocytes [84]. The signaling pathway in osteoblast, by which leptin acts, is osteoprotegerin (OPG)/RANKL (Receptor Activator for Nuclear factor κB Ligand). There was alteration found in the OPG/RANKL expression profile after treatment with leptin [93]. Burguera et al., (2001) have also established that bone loss in ovariectomized rats is reduced by elevating osteoprotegerin mRNA in osteoblasts [87].

For verifying the central effect, infusion of leptin was given into the brain and it was found that leptin also inhibits the bone formation through central nervous system. One important finding was that the lower doses inhibited the bone formation as compared to the doses which was essential for the loss of body weight [100-101]. It was observed in the experimental ob/ob mice that this central effect is due to activation of sympathetic part of autonomic nervous system. This activation of sympathetic system by leptin is very important in controlling energy homeostasis and numerous physiological functions [100].

In mice, food restriction decreased longitudinal growth and bone mass, but administration of leptin restored skeletal growth, in spite of low energy intake and raised serum osteocalcin, that is a bone formation marker [106].

In patients of hypothalamic amenorrhea, who have relative leptin deficiency, recombinant leptin treatment improves markers of bone formation [107]. It seems that leptin affects bone centrally through the sympathetic nervous system, which is a main downstream mediator [108]. Leptin deficiency seems to reduce adrenergic tone [109] and to influence the discharge of noradrenaline from sympathetic nerve fibers [110]. Noradrenaline binds to α -adrenergic receptors on osteoblasts and restrains formation of bone [108-109,111].

For observing direct and indirect or central and peripheral effects in vitro/in vivo, many researchers used supraphysiological doses of leptin in their studies [78,84,85,87], so it's difficult to draw accurate conclusion from these studies.

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The mechanism of leptin function is highly intricate, because of the several receptor isoforms, localized expression and activation of leptin. Still, the role of leptin is not completely understood and the heterogeneity in its functions and its involvement in several body systems make its role challenging, particularly in the field of metabolism and endocrinology, and generally in medicine. Further studies are essentially needed for better understanding the role of leptin in several metabolic and non-metabolic functions that may also elucidate its role in health and disease and particularly in the pathophysiology of osteoporosis.

Bone component	Effect	Mechanism
Osteoblast	Increase directly	By inhibiting GSK-3β and thus promote differentiation of osteoblast and mineralization of primary cultures of VSMC [112]
Osteoblast	Decrease indirectly	By binding and activating obRb receptors, in hypothalamus. It stimulates the expression of a HOBIF that lowers the ability of osteoblast to make bone matrix [76-77, 100-101]
Osteoclast	Decrease	By inhibiting osteoclast generation by RANKL/RANK/OPG system [93]
Bone Matrix	Decrease	By inhibiting matrix mineralization. Endochondral ossification at the growth plate mediated by the leptin signaling[113]
Osteocalcin	Increase	By elevating osteoblast-specific osteocalcin release through a hypothalamic relay [114]
Osteopontin	Increase	By increasing up regulation of osteopontin by stimulating OPN mRNA and protein expression in these cells [115]

GSK glycogen synthase kinase, **VSMC** vascular smooth muscle cells **BBB** Blood Brain Barrier, **HOBIF** Hypothalamic osteoblast inhibitory factor, **OPG** osteoprotegrin, **RANKL** receptor activator of nuclear factor-κB ligand, **OPN** Osteopontin

Table 2. Effects of leptin on different Bone components

4.5. Expectations

Leptin replacement therapy in animals and humans has shown promising results, but, whether in postmenopausal osteoporotic patients, its use as a drug or drug target may give some therapeutic benefits; it's a basic question that is yet to be explored.

Therefore, in future, it could be expected that administration of some therapeutic agents that target the leptin secretion would contribute in decreasing the severity of the disease in postmenopausal women. Future studies may elucidate such agents and their role in alleviating progression and spread of osteoporosis. Serum leptin effects on bone metabolism are inconsistent and intricate, so there is still need to investigate the precise effects of leptin on bone by designing some clinical trials and longitudinal studies. Such studies would improve our understanding regarding the mechanisms underlying leptin role in bone metabolism and how it could be targeted particularly to treat osteoporosis or other bone disorders. Still, several venues need to be explored to explicate its undiscovered functions in human body especially, its role in terms of agonist and/or antagonist for the bone forming cells.

5. Conclusion

Evidences, shown by the results of several studies have clearly exhibited the role and involvement of leptin and Hcy in pathophysiology of osteoporosis at various levels but still their exact role, generally in bone metabolism and particularly in osteoporosis is not clear. We still need well designed experimental and clinical studies to validate the specific involvement of these two biochemical agents in bone pathophysiology or as a diagnostic & therapeutic markers, and also their precise involvement in osteoporosis and their synergistic, antagonists and/or agonists' influences on bone forming or destroying cells and other bone proteins.

It seems in future, leptin and Hcy could be the emerging therapies and new targets for treatment of osteoporosis. However, it would be too early to validate the role of Hcy and leptin in osteoporosis before addressing some important queries: like identifying their actual mechanism of action, site/s of their targets in the body for influencing bone metabolism, the effects of presently available anti-resorptive treatment on Hcy and leptin levels. Although, various studies have revealed mechanism of Hcy and leptin action, still further clarification regarding bone specific receptors, peripheral or central or both actions and their interaction with osteoporotic risk factors need to be investigated.

Numerous basic and clinical studies are available which are helping us to understand their role in health and diseases but still these are far from completion. Our future research should be focused on these important questions that whether bringing change in their level and/or activity may help us in preventing and treating osteoporosis, and interaction of Hcy and leptin with several other hormones and peptides and consequences of their increased/decreased levels at various tissues and organs level. Such questions require to be addressed for establishing their precise role in bone metabolism. Therefore, further studies are needed to reveal their character as novel therapeutic agents and/or targets.

6. Few key points

- Homocysteine (Hcy) and leptin are new risk factor for primary osteoporosis.
- Hcy interacts with bone by enhancing osteoclastic and reducing osteoblastic activity, reducing bone blood supply and directly interacting with bone matrix.
- Hcy level could be modulated by nutritional conditions, and physical activity.
- Each μmol/L raise in Hcy level augments 4% fracture risk.
- Serum leptin supports the segregation and development of the osteoblast lineage cells and control development of osteoclast.
- Leptin stimulates bone formation via beta-1-adrenergic receptors and stimulation of the somatotropin-IGF-1 system
- Leptin directly inhibits the BMSCs to generate osteoclast and stimulate them to differentiate into osteoblasts.

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- BMSCs, osteoblasts, osteoclasts and chondrocytes have leptin receptors.
- The mechanism of leptin function is highly intricate, because of the several receptor isoforms, localized expression and activation of leptin.
- Leptin and Hcy role as diagnostic & therapeutic markers in osteoporosis needs further exploration.
- Further well-designed experimental and clinical studies are needed to validate the specific involvement of these two biochemical agents in bone pathophysiology.

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