We are IntechOpen,
the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Serum Leptin and Bone Turnover Markers in Postmenopausal Osteoporosis

Mehreen Lateef, Mukhtiar Baig and Abid Azhar

Additional information is available at the end of the chapter

1. Introduction

Osteoporosis is a very important health problem worldwide. It is defined as a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk [1]. Osteoporosis is a silent disease and the health and financial impact of the disease result from fracture, particularly hip fracture, for which subjects with osteoporosis are at an increased risk [2]. In the UK, one in two women and one in five men suffer a fracture after the age of 50, with an annual cost to the health services of around £2 billion [3,4].

In 1990, the number of osteoporotic fractures estimated in Europe was 2.7 million, with an estimated direct cost in 2004 of €36 billion (£24.5 billion), of which €24.3 billion (£16.6 billion) were accounted for by hip fracture. Costs are expected to rise to €76.8 billion (£52.4 billion) by the year 2050 [5]. Similar projections are made for many other regions of the world because of the increasing numbers of the elderly. In the USA, the annual cost of incident fractures due to osteoporosis or low bone mass is predicted to rise from $16.9 billion in 2006 to around $25.3 billion by the year 2025 [4]. The direct costs of medical care of hip fractures were over $65 million in 2004 [6].

There are many hormones involved in bone and mineral metabolism, such as oestrogens, testosterone and parathormone (PTH). The adipocyte also plays an important role in regulating bone metabolism by releasing estrogens, and the adipokines, like leptin, resistin, adiponectin, and many others. After the discovery of leptin receptors in bone many studies have been done to explore its involvement in bone metabolism. Some studies have shown that leptin is expressed and secreted from primary cultures of human osteoblasts during the mineralization period, and that it may stimulate osteogenesis in human bone marrow in vitro [7,8].

Furthermore, leptin may reduce ovariectomy-induced osteoporosis in rats and may also be involved in foetal and growing bone metabolism [9, 10].

Leptin, a fat-derived cytokine-like hormone, was discovered in 1994 by Friedman and colleagues [11]. A 16-kDa hormone, encoded by the OB gene, is predominantly expressed in adipose tissue [12] and circulates as a free and as a protein-bound entity. According to structural studies leptin belongs to the growth hormone four-helical cytokine subfamily. The leptin receptor was identified in the db locus of mouse chromosome 4. As a member of the IL-6 receptor family, the leptin receptor contains an extracellular-binding domain, a single transmembrane domain and a cytoplasmatic signaling domain [13]. Intracellular signaling is mediated through a non-covalently associated tyrosine kinase of the JAK kinase family [14]. Alternate gene splicing results in five known isoforms of the leptin receptor. The longest form of the receptor (ObR) is the only isoform capable of complete signal transduction. Conversely, the shorter isoforms of the leptin receptor have been suggested to participate in leptin clearance and/or to facilitate transport of leptin across the blood-brain barrier [14]. Circulating levels of leptin correlate with BMI and the content of fat mass. After crossing the blood–brain barrier, leptin reaches the hypothalamus, where it acts as a crucial regulator of feeding. Leptin is mainly regarded as a ''starvation-hormone'' signaling from the adipose tissue (AT) to the brain, indicating the size of the AT-stores [15].

Food intake and energy expenditure are controlled by leptin through an interaction with various neuropeptides in the hypothalamus. Neuropeptide Y (NPY) and agouti-related peptide (AGRP) expressions are inhibited, whereas pro-opiomelanocortin (POMC) expression is stimulated by leptin with increased food intake [16, 17]. Moreover, leptin interacts with neuromedin U (NMU); a novel and recently identified hypothalamic neuropeptide involved also in the regulation of appetite and locomotor activity [18]. Besides energy metabolism, leptin demonstrates pleiotropic effects in such areas as hematopoesis, blood pressure, T lymphocyte function, reproduction and bone mass regulation [14, 19]. Several endocrine and paracrine factors play a role in the fat-bone relationship. A number of local cytokines secreted by the adipose tissue, including leptin, have also been related to BMD variations [20]. Leptin because of its diverse role in bone is being considered one of the main functional connections between fat and bone.

Leptin, known to regulate appetite & energy expenditure may also contribute to mediate the effects of fat mass on bone. Interestingly, obesity seems to protect from osteoporosis. This observation led to researchers at bone formation in mouse models of obesity. Much effort has been dedicated to the relationship between leptin and bone. This interest stems from the well-founded knowledge that body weight is a major determinant of bone density [21]. It is known that obesity is generally accompanied by increased bone strength. Obese persons have stronger bones and lose bone tissue at a slower pace [22]. Leptin has been proposed to regulate increased body weight as well as increased bone density. Mice that have congenital absence of leptin (ob/ob) have been shown to be obese and have very high bone density. Leptin makes them lose both fat and bone [23]. The bone mass phenotype of ob/ob mice can be rescued by intracerebroventricular (ICV) infusion of leptin, suggesting that leptin exerts an indirect influence on bone mass. There is a re-

port which has shown that when leptin injected into the brain of animals it will inhibit bone formation at doses lower than those that cause loss of body weight [24]. A lot of studies have been done to explore the relationship of serum leptin with bone mass density and biochemical bone markers in osteoporosis. In this chapter, the mechanism of action of leptin on bone is reviewed and role of serum leptin in postmenopausal females is discussed with respect to its relation with bone mass density and biochemical bone markers.

2. Leptin and its mechanism of action on bone

Leptin acts on bone by two different mechanisms. The first is the indirect mechanism revealed by Ducy et al (2000) in mutant mice and rats that either cannot produce or cannot respond to leptin [25]. Leptin secreted from fat cells is carried by the ObRa receptors of vascular endothelial cells across the blood-brain-barrier where it activates ObRb receptors in the hypothalamus. These signals then stimulate expression of HOBIF (hypothalamic osteoblast inhibitory factor) which when released, lowers the matrix-making ability of osteoblasts [25-29] and because of this reason obese Ob (Lep)–/– mice, which should have low bone mass due to lack of leptin, and thus estrogen, actually have an abnormally high bone mass.

The second direct mechanism of leptin action is by promoting differentiation of bone marrow stromal cells into osteoblasts [8] and by inhibiting osteoclast generation [30]. Bone marrow stromal cells (BMSC) can differentiate into either adipocytes or osteoblast cell lineage. Bone marrow adipocytes may serve as a direct source of leptin, which can inhibits adipogenesis differentiation of BMSC and stimulates differentiation of osteoblasts [31] while Kim et al. (2003) have shown that very high leptin levels led to BMSC apoptosis [32]. Reseland et al. (2001) have found that human osteoblasts start making and secreting leptin when they are either in the late, matrix-mineralizing stage or when changing to osteocytes [7]. Leptin has also stimulates the proliferation of cultured human osteoblasts [33], and it has been shown to cause human bone marrow stromal cells to express alkaline phosphatase, collagen-I, and osteocalcin and to mineralize matrix [8]. These tissue culture experiments support the dual effect of leptin within the bone microenvironment depending on the local leptin concentration.

In the last decade Ducy et al. (2000a,b) [25,27] have not found any long isoforms of the leptin receptors (Ob-R) on osteoblasts, so they assumed that leptin acted centrally as a very potent inhibitor of bone formation. Although the long isoform of Ob-R is abundantly expressed in the hypothalamus, and in a large number of peripheral tissues [14]. BMSC, osteoblasts, osteoclasts and chondrocytes also express leptin receptors [8]. In osteoblasts, leptin acts through the osteoprotegerin (OPG)/RANKL (Receptor Activator for Nuclear factor κB Ligand) signaling pathway. Treatment with leptin changes the OPG/RANKL expression profile favoring OPG [30]. Consequently, osteoclastogenesis is very likely suppressed by leptin through the OPG/RANKL pathway. In agreement with the previous findings, Burguera et al [10] have also confirmed the previous findings that ad-

ministration of leptin reduced ovariectomy induced bone loss in rats by increasing osteo-protegerin mRNA in osteoblasts. Cornish et al in 2001 have found that leptin given peripherally increased bone strength in mice and also increased proliferation of osteo-blasts in vitro [34]. The results of these studies showed that direct peripheral action of leptin on bone is to enhance the strength of the bone in contrast to its central effect.

In order to evaluate its central effect, leptin was injected into the brain in the form of an intra-cerebelo-ventricular infusion [25, 27, 35]. Bone loss occurred in both wild-type mice and leptin deficient mice confirming that bone mass is partly regulated via the central, hypothalamic relay [25]. However, bone formation was inhibited at lower doses of leptin than those necessary to cause the loss of body weight. Ob/ob mice have low sympathetic activity, which led to the assumption that the central effect of leptin on bone is mediated by the sympathetic nervous system (SNS) [36]. The effect of leptin on the sympathetic nervous system is an important aspect in the regulation of energy homeostasis as well as several other physiological functions [37].

3. Serum leptin and Bone Mass Density (BMD)

It is widely recognized that BMD measurement can predict fracture risk in the same way as cholesterol predicts cardiovascular disease [38]. In fact, the strength of BMD measurement to predict fracture is approx 3 fold higher than strength of serum cholesterol to predict cardio-vascular disease [39]. Bone mass measurement has been found to be a single best predictor of fracture risk and is required to the early diagnosis of osteoporosis [37,38,39].

It is observed in a study by Lateef et al 2010 that BMD is found to be significantly lower in postmenopausal females with and without osteoporosis as compared to premenopausal females [40] and there is a negative correlation between age and BMD found in post meno-pausal ostreoporotic females indicating bone loss with age and menopause [41]. A rapid bone loss is commonly seen in elderly individuals and tends to worsen with advancing age. The aging population is inevitably proven to be more osteoporotic unless it is intervened first with diagnostic tools and after preventive therapy [42].

Another study of Lateef et al 2011 showed that plasma leptin levels were positively correlated with bone mineral density (BMD) values in osteoporotic females [43]. Some reports have suggested a correlation between serum leptin concentration and BMD while other showed no such association [44-48]. It has been shown that plasma leptin levels are positively correlated with BMD at all skeleton sites measured in postmenopausal osteoporosis [49]. It is interesting to note that the obese are usually protected against osteoporosis and have increased bone mineral density [50]. This has been attributed to the mechanical effects of their excessive weight on bone tissue. It has been shown that obese postmenopausal women have a tendency to have increased bone mineral density compared with lean women [51-53]. The study of Di Carlo et al. (2007) documented a significant correlation between serum leptin and BMD in early postmenopausal women but the correlation was lost during progression of the postmeno-pausal period [54]. Thomas et al. (2001) have observed that serum leptin correlated with BMD

in women but not in men [31]. Sato et al. (2001) have found a positive correlation between serum leptin and calcaneus BMD in men, but the relationship became inverse when adjusted for body weight [18]. Pasco et al. (2001) have demonstrated a significant positive association between BMD and serum leptin in non-obese women [55]. Results of Blain et al (2002) reported that leptin is an independent predictor of whole body and femoral neck BMD in postmenopausal women [56]. Nagy et al. (2001) found a negative correlation between serum leptin levels and radial and femoral BMD in postmenopausal women [57]. Hadji et al. (2001) reported that bone mass is not correlated with the serum leptin level in pre or postmenopausal women [58]. Rauch et al. (1998) also reported no correlation between bone mass and serum leptin levels by examining total and trabecular bone density at the distal radius in adult women [59]. In leptin literature, several studies have examined the relationship between serum leptin and BMD in various cohorts, but the results remain contradictory. This fact reflects the intricacy of the relationship of leptin and bone.

A study by Hamrick and Ferrari (2008) has documented that the effect of leptin is reduced with increased age and higher BMI in both humans and laboratory animals in spite of high serum leptin levels [60]. It has been postulated that the under-responsiveness to leptin, or leptin resistance, is mediated either by impaired transport of leptin through the blood-brain barrier, lower expression of leptin receptors and/or by the inhibition of the intracellular leptin signaling [61]. In plasma, leptin is bound to soluble leptin receptor (SLR), the product of an alternate splicing of leptin receptor mRNA or proteolytic cleavage [14]. Whereas serum leptin levels correlate positively with BMI, SLR is correlated negatively [14,62]. The inverse relationship between SLR and BMI reflects a feedback regulation between the body weight and leptin or leptin receptor expressions. It is observed in a study by Welt et al. (2004) when low serum leptin levels in women with hypothalamic amenorrhea (induced either by exercise or by low body weight) were treated with recombinant human leptin for three months, it led to an increase of osteocalcin, bone alkaline phosphates and IGF-1, whereas urinary N-telopeptide did not change [63].They have demonstrated that leptin administration in individuals with leptin deficiency appeared to improve the growth hormone axis and markers of bone formation [63].

4. Osteoporosis and bone turnover markers (BTMs)

Bone markers are product derived from the bone remodeling process. During this process, compounds are released either from bone or from the cells involved in the bone remodeling process (osteoblasts and osteoclasts.) Markers of bone turnover are biochemical products measured usually in blood or urine that reflect the metabolic activity of bone but which themselves have no function in controlling skeletal metabolism [64]. Biochemical markers of bone turnover are broadly divided into two categories: markers of bone resorption, which reflect osteoclast activity and are for the most part degradation products of type I collagen; markers of bone formation, which reflect osteoblast activity and are byproducts of collagen synthesis, matrix proteins or osteoblastic enzymes (Table 1) [65].

Bone formation	Detected in
Byproducts of collagen synthesis	
Procollagen type I C-terminal propeptides (P1CP)	Serum
Procollagen type I N-terminal propeptides (PINP)	Serum/Plasma
Matrix protein	
Osteocalcins (OC)	Serum/Plasma
Osteoblast enzyme	
Bone alkaline phosphatases (BALP)	Serum
Bone resorption	Detected in
Collagen degradation products	
Hydroxyprolin	Urine
Pyridinolin(PYD)	Urine
Deoxypyridinoline (DPD)	Urine
Cross-linked telopeptides of type I collagen	
N-terminal cross-linked telopeptide (NTX)	Urine and serum/plasma
C-terminal cross-linked telopeptide (CTX)	Urine and serum/plasma
Osteoclast enzymes	
Tartrate-resistant acid phosphatases (TRACP)	Serum

Table 1. List of important biochemical markers of bone turnover

5. Markers of bone formation

Bone formation markers are direct or indirect products of active osteoblasts expressed during different phases of osteoblast development and reflecting different aspects of osteoblast function and bone formation. All markers are measured in serum or plasma [66].

5.1. Alkaline phosphatase

Alkaline phosphatase (ALP) is a ubiquitous enzyme that plays an important role in osteoid formation and mineralization. The total ALP serum pool consists of several dimeric isoforms which originate from various tissues such as liver, bone, intestine, spleen, kidney and placenta. In adults with normal liver function, approximately 50% of the total ALP activity in serum arises from liver and 50% arise from bone [67].

5.2. Bone specific alkaline phosphatase

Bone specific alkaline phosphatase (BALP) is one of several isoenzymes of the alkaline phosphatase (ALP) family. The entire family is encoded by four gene loci, three tissue specific genes (bone,kidney,liver and other tissues). Although the nonspecific ALPs are the products of a single gene, the ioenzymes present in tissues such as bone, kidney or liver vary greatly because of variations in their carbohydrate side chains. These post translational modifications are exploited to distinguish the various ALP-isoforms from each other, employing methods including gel electrophoresis, heat denaturation, chemical inhibition or binding through specific monoclonal antibodies [68]. For therapeutic monitoring of patients, B-ALP measurements are good indicators of the metabolic activity of bone. Rising ALP concentrations may indicate estrogen deficiency [69,70].

5.3. Osteocalcin

Osteocalcin (OC) is a small, hydroxyapetite-binding protein synthesized by osteoblasts and to a lesser extent by hypertrophic chondrocytes. It contains three gamma- carboxyglutamic acid (Gla) residues which are responsible for calcium binding properties of protein. The precise function of osteocalcin has yet to be determined but recent studies suggest that OC is involved in bone remodeling via a negative mechanism. Serum osteocalcin is considered as a specific marker of osteoblast function, as its levels correlate with bone formation rates. However, the peptide is rapidly degraded in serum and both intact peptides and OC fragments of various sizes coexist in the circulation [70]. Osteocalcin is normally considered as bone formation marker. However, because it is released during bone formation from bone forming cells and during bone resorption from bone matrix, it reflects the overall turnover of bone. Assays have been developed to detect the intact protein and or the main breakdown product called N-mid fragment. OC serum levels follow a circadian rhythm with high values in early morning, but usually not influenced by food intake. Serum osteocalcin levels reportedly vary significantly during the menstrual cycle with the highest level observerd during luteal phase [71].

5.4. Amino & carboxyterminal procollagen propeptides of type I collagen

The amino and carboxy terminal procollagen propeptides of type I collagen (PINP, PICP) are cleaved by specific extracellular endopeptidases from newly translated collagen type I pepetide. As these extension peptides are generated in a stoichiometric relationship with collagen biosynthesis, they are considered quantitative measures of newly formed type I collagen. However, because type I collagen is also a component of several soft tissues (fibrocartilage, tendon, skin, gingival, intestine, heart valve, and large vessels) there is potential contribution to circulating procollagens from soft tissue synthesis of type I collagen. Both PICP and PINP demonstrate a cardian rhythm with peak values in the early morning, and are usually not influenced by food intake. Serum levels of amino and carboxy terminal procollagen propeptides of type I collagen (PINP, PICP) are measured by type and site specific immunoassays [66]. Moderate correlations between serum PICP levels and the rate of bone formation have been reported [72].

5.5. Markers of bone resorption

Most biochemical markers of bone resorption are degradation products of bone collagen, but noncollagenous proteins such as bone sialoprotein or tartarate resistant acid phosphatase have also been investigated [73].

5.6. Hydroxy proline

Hydroxyproline is an amino acid common to and characteristic of all forms of collagen, and urinary hydroxyproline excretion is the oldest test of bone resorption. However, this test lacks specificity for bone resorption because excreted hydroxyproline also comes from other tissues, particularly from skin collagen (which can turn over rapidly in certain disorders), from newly synthesized collagen that is not incorporated into tissue, and from dietary collagen and gelatin. Because it is less specific than newer tests, it is no longer widely used [74].

5.7. Pyridinoline (Pyr) and Deoxypyridinoline (DPD)

The pyridinum crosslinks pyridinoline (PYD) and deoxypyridinolin (DPD) are the main crosslinks in skeletal tissues but act as stabilizers of mature croslinks in type I, II & III collagens of all major connective tissues (bone, dentin, ligaments, tendons, vascular walls, muscle and intestine) except skin. While PYD predominates in most tissues, DPD is most abundant in bone and therefore is considered the more specific marker [75].

5.8. Crosslinked Telopeptides

The term "crosslinked telopeptides" refers to the measurement of collagen degradation products associated with the crosslink regions in type I collagen. Fragments derived from the C terminus are also released into circulation as a result of the osteoclast-mediated degradation of type I collagen and can be measured by various assays [76, 77]. The immuno reactive epitopes are located on peptide fragments derived from the N terminal (NTX-1) and C terminal (CTX-1 and ICTP) telopeptides of the collagen type I molecule. The NTX-1 and CTX-1 epitopes can be measured in both serum and in urine [78, 79].

6. Tatartarate Resistant Acid Phosphatase (TRACP)

Tartarate resistant acid phosphate is synthesized and secreted by osteoclasts during active bone resorption. The process of resorption occurs after the attachment of osteoclasts to the bone surface and follows the secretion of acid and enzymes into a space created between the osteoclast and the bone. The acidic environment is produced by the action of carbonic anhydrase and an H-ATPase proton pump. TRACP, one of the enzymes secreted into this space, has been located in the adjacent osteoclast membrane (known as the ruffled border) [80]. Its activity in serum reflects bone resorption rates and more recently it has been possible to measure the isoenzyme by very specific immunoassays

The use of biochemical markers of bone remodeling in the monitoring of patients on treatment for osteoporosis is generally well-recognized [81,82]. However, optimum treatment targets specific to various therapies and the benefits of monitoring in terms of improvement in fracture outcomes or in adherence to oral therapies are not established [83].

The changes in BMD and BTMs following the initiation of osteoporosis treatment independently correlate with fracture risk reduction [84]. The advantage of BTM over BDM is that the change in BTMs following treatment explains a greater proportion of treatment as compared to BMD does, in terms of fracture risk reduction [85,86]. Also, the change in BMD is small and slow whereas the changes in BTMs are large and occur early after initiation of therapy. Repeat BMD is not advocated within 12 months after initiation of therapy as the changes do not generally attain significance within that time, and in fact 18-24 months may be appropriate for repeat BMD measurements [87]. BTMs on the other hand show significant change by 3-6 months. For example, bone resorption markers can be measured 3 months after initiation of oral bisphosphonates, and bone formation markers 6 months after start of therapy [88, 89]. Changes in BTMs may be useful in monitoring osteoporosis treatment to confirm compliance with oral therapies and efficacy of treatment [90].

There are many studies which have demonstrated BTMs and their contribution to fracture risk, but the results of these studies have been inconsistent [91-95]. Many studies which have shown positive results with BTMs included bone resorption markers, with increased resorption marker predicting an increased fracture risk. While for BTMs to predict fracture risk independently of BMD, it is needed to clarify their relationships to other established risk factors.

The changes in BTMs following therapy are well documented. There is a decrease in BTMs following initiation of anti-resorptive therapy, reflecting inhibition of osteoclastic activity [96-100]. For example, with bisphosphonate treatment, there is a decrease in bone resorption markers within days following intravenous therapy, and within weeks following oral therapy.

Vasikaran et al [83] supports the role of BTMs in the management of patients with osteoporosis and also emphasized on the adoption of international reference standards for enhancing laboratory consistency and to facilitate their inclusion in routine clinical practice.

The problem in BTMs use is their wide biological and analytical variability, Glover et al [101] emphasized that reference ranges should be defined and standardized with emphasis on sample size and age range of the population. Sandhu & Hampson (2011) describe that the best established clinical use for BTMs is in monitoring treatment efficacy and compliance [102]. In a study by Kim et al observed that BMT can be used to determine BMD response to antiresorptive therapy in Korean postmenopausal osteoporotic females [103].

The Scientific Advisory Council of Osteoporosis Canada including multidisciplinary working group stated about the bone turnover markers in the management of postmenopausal osteoporosis that as far as potential uses of bone turn over markers (BTMs) are concerned, they can be used to predict bone loss and fracture in untreated postmenopausal women. They can also be used to monitor osteoporosis therapy, and up to some extent enhance the adherence to therapy but BTMs should not be used for diagnosis of osteoporosis as s separate and

independent factor. Similarly it must not be used to select the most appropriate type of osteoporotic therapy for the treatment. [104].

7. Relationship of leptin with bone markers in post menopausal osteoporotic females

Data in the literature are inconsistent and conflicting about the relationship of leptin with bone markers in post menopausal osteoporotic females. The study of Goulding & Taylor (1998) was the first to examine relationships among plasma levels of leptin, and dynamic biochemical markers of bone cell activity in postmenopausal women [46]. This study demonstrated no association between circulating plasma levels of leptin and biochemical markers of either osteoclastic or osteoblastic activity. They concluded that leptin itself does not play any significant direct role in controlling bone cell activity in postmenopausal women.

Scariano et al reported positive association between serum leptin and bone specific alkaline phosphatase in postmenopausal women and elderly men after adjustment for BMD, age and BMI [105]. The association of circulating leptin levels with bAP, a specific marker of osteoblast activity suggests that leptin levels influence osteoblast activity in vivo in elderly women and men. In a cross sectional study by Filip R & Raszewski G (2009) a positive association between leptin and osteocalcin in older patients with hip fracture [106]. Rauch et al. and Lateef et al also found no relationship between plasma leptin level and bone turnover markers in adult women and postmenopausal osteoporotic females respectively [40,59]. Filip & Raszewski et al, found no correlations of serum leptin with lumber spine BMD, femoral neck BMD, biochemical markers of bone turnover with leptin, in overweight and obese postmenopausal women, even after stratification of the study group by BMI ratio value (25–29 9, 30–39 9 and ≥ 40), or by waist: hip ratio (WHR), ratio value (< 0 85 and ≥ 0 85) [106]. In a small study, Iwamoto et al. (2000) found correlations between serum leptin and bone remodelling markers only in premenopausal women [107]. Peng et al (2008) reported no association between serum leptin and bone turnover biochemical markers in men [108].

In postmenopausal osteoporotic patients with increased bone turnover, serum leptin concentration is not correlated with BMD or with the biomarkers of bone formation or bone resorption [109]. According to few studies performed in China no correlation found between serum leptin and bone turnover biochemical markers in post-menopausal Chinese women [110-112]. Similarly, no correlation observed between leptin and bone turnover markers in Chinese adolescent dancers and control group in one more study (101) Blain, et al (2002) reported that serum leptin level was positively correlated with weight, fat mass, BMI, E2, creatinine clearance, and BAP level and inversely correlated with urine CTx [56]. They supported the suggestion that circulating leptin exerts its protective effect on bone through limiting the excessive bone resorption coupled with bone formation that is associated with bone loss after menopause.

Prouteau et al (2006) suggested a regulatory role of leptin on type I collagen metabolism [113]. The negative association between bone resorption (CTx levels) and serum leptin levels observed at baseline (stable body weight) was further confirmed by the biochemical changes

occurring in responses to weight loss and weight regain. The drop in leptin levels was strongly related to the increase in bone resorption marker occurring in response to weight loss. Similarly, after weight regain the rise in leptin levels was associated with a concomitant decrease in bone resorption. The reasons for these discrepancies need to be clarified.

8. Conclusion

The relationship of leptin and bone turnover markers in post menopausal osteoporosis has not yet been clarified. Although several studies have been done but still there is need to explore their exact connection. Many studies have recommended that in the treatment of the post-menopausal women, biochemical markers of bone turnover may be useful as adjuncts to BMD and other diagnostic tests. They can be mainly used to monitor response to treatment and also used as relatively economical tools for studying bone metabolism. The exact roles of BTM need to be established in clinical practice. It is suggested that repeated measurements of bone markers during anti-resorptive therapy may help to improve the management of osteoporotic patients.

Both a peripheral and a central action of leptin on bone metabolism have been suggested. Peripherally, leptin is thought to exert positive effects on bone formation, whereas it is thought to reduce bone formation via a central control mechanism when binding to its specific receptors located on the hypothalamic nuclei [26]. It has been suggested that circulating leptin may act positively to maintain bone mass but these effects of serum leptin are not mediated due to these biochemical markers. Despite a preliminary understanding of leptin–bone mass interactions, the exact roles of leptin on bone metabolism have not yet been elucidated.

The role of BTMs in monitoring osteoporosis treatment to confirm compliance with oral therapies, and efficacy of treatment has been established. Further studies with reference to serum leptin and BTMs in post menopausal osteoporotic females are needed to clarify their association and significance of that association in treatment targets for various therapies and optimal monitoring regimes.

Author details

Mehreen Lateef[1*], Mukhtiar Baig[2] and Abid Azhar[3]

*Address all correspondence to: meher_khan555@hotmail.com; drmukhtiarbaig@yahoo.com; abid.azhar@kibge.edu.pk

1 Pharmaceutical Research Centre, Pakistan Council of Scientific and Industrial Research Complex Laboratories Complex, PCSIR, Karachi, Pakistan

2 Department of Biochemistry, Bahria University Medical and Dental College (BUMDC), Karachi, Pakistan

3 Karachi Institute of Biotechnology and Genetic Engineering (KIBGE), Karachi, Pakistan

References

[1] Consensus Development Conference Diagnosis, prophylaxis and treatment of osteoporosis. American Journal of Medical Sciences 1993; 94:646–65.

[2] Davey DA. Osteoporosis, osteopenia and fracture risk: Widening the therapeutic horizons. South African Medical Journal 2012; 102: 285-288.

[3] Dennison E, Cole Z, Cooper C, et al. Diagnosis and epidemiology of osteoporosis. CurrentOpinion ofRheumatology 2005; 17:456-461.

[4] Burge RT. The cost of osteoporotic fractures in the UK: Projections for 2000-2020. Journal of Medical Economics 2001;4: 51.

[5] Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. Osteoporosis International 2005; 16:229–238.

[6] Lim S, Koo BK, Lee EJ, Park JH, Kim MH, Shin KH, et al. Incidence of hip fractures in Korea. Journal of Bone & Mineral Metabolism 2008; 26: 400-405.

[7] Reseland J, Syversen U, Bakke I. et al. Leptin is expressed in and secreted from primary cultures of human osteoblasts and promotes bone mineralization. Journal of Bone & Mineral Research 2001;16:1426–1433.

[8] Thomas T, Gori F, Khosla S, Jensen MD, Burguera B, Riggs BL. Leptin acts on human marrow stromal cells to enhance diff erentiation to osteoblasts and to inhibit differentiation to adipocytes. Endocrinology 1999; 140:1630–1638.

[9] Steppan CM, Crawford DT, Chidsey-Fink KL, et al.Leptin is a potent stimulator of bone growth in ob/ob mice. Regulatory Peptides 2000; 92, 73–78.

[10] Burguera B, Hofbauer LC, Thomas, T. et al. Leptin reduces ovariectomy-induced bone loss in rats. Endocrinology 2001; 142, 3546–3553.

[11] Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-432.

[12] Coen G. Leptin and bone metabolism. Journal of Nephrology 2004;17: 187-189.

[13] Tartaglia LA, Dembski M, Weng X,et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995; 83: 1263-1271.

[14] Zhang F, Chen Y., Heiman M, et al. Leptin: structure, function and biology. Vitamins & Hormones 2005; 71: 345-365.

[15] Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. European Journal of Nutrition 2012;51:513–528.

[16] Wardlaw SL. Obesity as a neuroendocrine disease: lessons to be learned from proopiomelanocortin and melanocortin receptor mutations in mice and men.Journal ofClinicalEndocrinology andMetabolism 2001; 86: 1442.

[17] Patel MS, Elefteriou F. The new field of neuroskeletal biology. CalcifedTissue International 2007; 80: 337-347.

[18] Sato S, Hanada R, Kimura A, et al. Central control of bone remodelling by neuromedin U. NaturalMedicine 2007; 13: 1234-1240.

[19] Sirotkin AV, Mlynček M, Makarevich AV, et al. Leptin affects proliferation-, apoptosis- and protein kinase A-related peptides in human ovarian granulosa cells. PhysiologicalResearch 2008; 57:437-442.

[20] Reid I. Relationships among body mass, its components, and bone. Bone 2002; 13: 547-555.

[21] Mazess RB, Barden, HS, Ettinger M, Johnston C, Dawson-Hughes B, Baran D, Powell, M. &Notelovitz, M. Spine and femur density using dual-photon absorptiometry in US white women. Journal of Bone and Mineral Research 1987; 2: 211-219.

[22] Tremollieres F, Pouilles JM,Ribot C.Vertebral postmenopausal bone loss is reduced in overweight women: a longitudinal study in 155 early postmenopausal women. Journal of ClinicalEndocrinology & Metabolism 1993; 77: 683-686.

[23] Elias CF, Purohit D. Leptin signaling and circuits in puberty and fertility. Cellular and Molecular Life Sciences 2012.DOI 10.1007/s00018-012-1095-1(Accessed 12 August 2012).

[24] Mundy GR. Secondary osteoporosis: the potential relevance of leptin and low body weight. Annals of Internal Medicine 2000; 21: 828-830.

[25] Ducy P, Amling M, Takeda S. Leptin inhibits bone formation through a hypothalamic relay. Cell 2000; 100:197–207.

[26] Amling M, Takeda S, Karsenty GA. Neuro(endo)crine regulation of bone remodeling. Bioessays 2000; 22: 970–975.

[27] Ducy P, Schinke T, Karsenty G. The osteoblast: a sophisticated fibroblast under central surveillance. Science 2000; 289:1501–1504.

[28] Karsenty G. Leptin controls bone formation through a hypothalamic relay. Recent ProgHorm Res 56:401–415, 2001.

[29] Takeda S &Karsenty G. Central control of bone formation. Journal ofBone& MineralMetabolism 2001;19:195–198.

[30] Holloway WR, Collier FM, Aitken CJ, Myers DE, Hodge JM, Malakellis M, et al.. Leptin inhibits osteoclast generation. Journal of Bone and Mineral Research 2002; 17:200–209.

[31] Thomas T, Burguera B, Melton LJ. 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.

[32] Kim GS, Hong JS, Kim SW, et al. Leptin induces apoptosis via ERK/cPLA2/cytochrome c pathway in human bone marrow stromal cells. Journal of Biological Chemistry 2003; 13: 21920-21929.

[33] Evans BAJ, Elford C, Gregory JW. Leptin control of bone metabolism; direct or indirect action? Bone 2001; 28:149.

[34] Cornish J, Callon KE, Bava U. The direct actions of leptin on bone cells increase bone strength in vivo: an explanation of low frequency fracture rates in obesity. Bone 2001;28:S88.

[35] Karsenty G. Convergence between bone and energy homeostasis: leptin regulation of bone mass. Cell Metabolism 2006; 4: 341-348.

[36] Takeda S, Elefteriou F, Levasseur R, et al. Leptin regulates bone formation via the sympathetic nervous system. Cell 2002; 111: 305-317.

[37] Harlan SM. Rahmouni K. Neuroanatomical determinants of the sympathetic nerve responsesevoked by leptin. Clinical Autonomic Research Doc 10.1007/s10286-012-0168-4 (Accessed June 2012).

[38] Sergio RagiEIS, LewiecklME. Peripheral bone densitometry: clinical applications. ArquivosBrasileiros de Endocrinologia&Metabologia2006; 50 :596-602.

[39] Marshall D, Johnell O, Wedel H. Meta-analysis of how well measured of bone mineral density predict occurrence of osteoporotic fractures. British Medical Journal 1996; 312: 1254-1259.

[40] Lateef M, Baig M, Azhar A. Estimation of osteocalcin and telopeptide-C in postmenopausal osteoporotic females. Osteoporosis International 2010;21:751-755.

[41] Hans D, Fuerst T, Lang T, Majumdar S, Lu Y, Genant HK & Gluer C.How we can measure bone quality? Bailliers Clinical Rheumatology 1997; 11: 495-515.

[42] Gluer CC. Quantitative ultrasound techniques for the assessment of osteoporosis: expert agreement and current status. Journal of Bone & Mineral Research 1997; 12: 1280-1288.

[43] Lateef M, Baig, M, Azhar A. Relationship of leptin with BMD in postmeopausal osteoporosis. In Kanis JA &Lindlay A. (eds) Osteoporosis International: Abstracts of 1st IOF-ESCEO Preclinical Symposium and ECCEO-IOF Congress, 22-23 March 2011, Valencia, Spain.

[44] Ensurd, KE, Palermo, L, Black DM.Cauley, J, Jergas, M, Orwoll, ES, Nevitt, MC, Fox KM. & Cummings SR. Hip and calcaneous bone loss increase with advancing age:

longitudinal results from the study of osteoporotic fractures. Journal of Bone and Mineral Research 1995; 10: 1778-1787.

[45] Miller PD,Zapalowski, C, Kulak CA. &Bilezikian JP.Bone Densitometry: the best way to detect osteoporosis and to monitor therapy. Journal of Clinical Endocrinologyand Metabolism 1999;84: 1867-1871.

[46] GouldingA,Taylor RW. Plasma Leptin values in relation to bone mass and density and to dynamic biochemical markers of bone resorption and formation in postmenopausal women. Calcified Tissue International 1998; 63: 456 -458.

[47] Rouch F, Blum WF, Klein K. Allolio, B. &Schonau, E. Does leptin have an effect on bone in adult women? Calcified Tissue International 1998; 63: 453-455.

[48] Iwamoto I, Douchi T, Kosha S, Murakami, M. Fujino T. & Nagata Y. Relationship between serum leptin level and regional bone mineral density, bone metabolic markers in healthy women. ActaObstetriciaetGynecologicaScandinavica 2000; 79: 1060-1064.

[49] Yamauchi M, Sugimoto T, Yamaguchi T. Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women. ClinicalEndocrinology 2001; 55:341–347.

[50] Albala C, Yanez M, Deveto E, Sostin C, Zeballos, L. & Santos JL. (1996). Obesity as protective factor for postmenopausal factor postmenopausal osteoporosis. International Journal of Obesity and Related Metabolic Disorders 1996; 20:1027-1032.

[51] Riggs BL, Melton J. Involutional osteoporosis. New EnglandJournal ofMedicine 1986; 314: 676-685.

[52] Ribot C, Tremollierrs F, Pouilles JM, Bonneu M, Germain F,Louvet JP. Obesity and postmenopausal bone loss: the influence of obesity on vertebral density and bone turnover in postmenopausal women. Bone 1987; 8: 327-331.

[53] Dequeker J,Boonen S. Extraskeletal Risk and Protective Factors for fractures In Geuseus P.(ed)Osteoporosis in clinical practice In *Springer*: London; 1998. p55-58.

[54] Di Carlo C, Tommaselli GA, Gargano V, Sammartino A, Bifulco G, Tauchmanova L et al. Effects of estrogen-progestin therapy on serum levels of RANKL, osteoprotegerin, osteocalcin, leptin, and ghrelin in postmenopausal women. Menopause 2007; 14:7–9.

[55] Pasco JA, Henry MJ, Kotowicz J A, et al. Serum leptin levels are associated with bone mass in no obese women. Journal of Clinical Endocrinology andMetabolism; 86: 1884-1887.

[56] Blain H, Vuillemin A, Guillemin F,et al. Serum leptin level is a predictor of bone mineral density in postmenopausal women. Journal of Clinical Endocrinology and Metabolism 2002; 87, 1030–1035

[57] Nagy Z, Speer G, Takács I, Bajnok Č, Lakatos P. Serum leptin levels and bone mineral density in postmenopausal women In Journal ofBone andMineral Research: Pro-

gram and abstracts from the Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research; October 12–16, 2001; Phoenix, Arizona.

[58] Hadji P, Bock K, Gottschalk M, Kalder M, Emons G, Shulz KD. The influence of serum leptin concentrations on bone mass assessed by quantitative ultrasonometry (QUS) in pre- and postmenopausal women In Journal ofBone andMineral Research: Program and abstracts from the Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research, October 12–16, 2001; Phoenix, Arizona.

[59] Rauch F, Blum WF, Klein K, Allolio B, Schönau E. Does Leptin Have an Effect on Bone in Adult Women? Calcified Tissue International 1998;63:453–455.

[60] Hamrick MW, Ferrari SI. Leptin and the sympathetic connection of fat to bone. Osteoporosis International 2008; 19:905-912.

[61] Munzberg H, Bjornholm M, Bates SH, et al. Leptin receptor action and metabolisms of leptin resistance. Cellullar& MolecularLife Sciences 2005; 62: 642-652.

[62] Anderlová K, Křemen J, Doležalová R, et al., The influence of very-low-calorie-diet on serum leptin, soluble leptin receptor, adiponectin and resistin levels in obese women. Physiological Research 2006; 55: 277-283.

[63] Welt CK, Chan JI, Bullen J, et al. Recombinant human leptin in women with hypothalamic amenorrhea. New England Journal of Medicine 2004; 351: 987-997.

[64] VasikaranS, Eastell R, Bruyère O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporosis International 2011; 22: 391–420.

[65] Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. Proceedings of the Nutrition Society 2008; 67:157-162.

[66] Delmas PD. Markers of bone turnover for monitoring treatment of osteoporosis with antiresorptive drugs. Osteoporosis International 2000;11::S66- 76.

[67] Green S, Antiss CL, Fishman WH. Automated differential isoenzyme analysis II. The fractionation of serum alkaline phosphatase into liver, intestinal and other components. Enzymologia 1997; 41: 9 -26.

[68] Seibel MJ. Biochemical markers of bone metabolism in the assessment of osteoporosis: useful or not? EndocrinologicalInvestigation 2003; 26: 464-471.

[69] Gundberg CM,Nishimoto SK. InSeibel MJ, Robbins SP, Bilezzikian, JP, (eds) Vitamin K dependent proteins of bone and cartilage. Dynamics of bone and cartilage metabolism In Academic Press, San Diego; 1999;p43-58.

[70] Vesper HW. Analytical and preanalytical issues in measurement of biochemical bone markers. Laboratory Medicine 2005; 36: 424-429.

[71] Gundberg CM, Markowitz ME, Mizruchi M, Rosen JF. Osteocalcin in human serum: a circadian rhythm. *Journal ofClinical andEndocrinologicalMetabolism*1985;60:736-739.

[72] Parafitt AM, Simon LS, Villanueva AR, &Krane SM. Procollagen type I carboyterminal extension propeptide in serum as a marker of collagen biosynthesis in bone.Journal ofBone & Mineral Research 1987; 5: 427 -436.

[73] Risteli J, Risteli L. Products of bone collagen metabolism. In: Seibel MJ, Robbins SP, Bilzekian JP, eds. *Dynamics of Bone and Cartilage Metabolism: Principles and Clinical Applications*. London: Academic Press; 1999:275-287.

[74] Singer FR, Eyre DR. Using biochemical markers of bone turnover in clinical practice. Cleveland Clinic Journal of Medicine 2008; 75: 739-750.

[75] Calvo MS, Eyre DR, Gundberg CM. Molecular basis and clinical applicationof biological markers of bone turnover. Endocrinol Review 1996;17:333–368.13.

[76] Garnero P, Gineyts E, Riou JP, Delmas PD. Assessment of boneresorption with a new marker of collagen degradation in patients with metabolic bone disease. Journal of Clinical andEndocrinologyMetabolism 1994;79:780–785.

[77] Christgau S, Rosenquist C, Alexandersen P, et al. Clinical evaluationof the Serum CrossLaps One Step ELISA, a new assay measuring theserum concentration of bone-derived degradation products oftype I collagen C-telopeptides. ClinicalChemistry 1998; 44:2290–2300.

[78] Hanson DA, Weis MA, Bollen AM, Maslan SL, Singer FR, Eyre DR. A specific immunoassay for monitoring human bone resorption:quantitation of type I collagen cross-linked N-telopeptides in urine.Journal ofBone MineralResearch 1992; 7:1251–1258.

[79] Clemens JD, Herrick MV, Singer FR, Eyre DR. Evidence that serumNTx (collagen-type I N-telopeptides) can act as an immunochemicalmarker of bone resorption. ClinicalChemistry 1997; 43:2058–2063.

[80] Price CP. Tartarate Resistant Acid Phosphatase as a marker of bone resorption. Clinical Chemistry1995; 41: 641-643.

[81] Brown JP, Albert C, Nassar BA, Adachi JD, Cole D, Davison KS, Dooley KC, Don-Wauchope A, Douville P et al., Bone turnover markers in the management of post-menopausal osteoporosis. Clinical Biochemistry 2009; 42:929–942.

[82] Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. International Journal of Clinical Practise 2009; 63:19-26.

[83] VasikaranS, Eastell R, Bruyère O et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporosis International 2011; 22:391–420.

[84] Riggs BL, Melton LJ, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. Bone 1996; 18:197S-201S.

[85] Delmas PD,Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone 2004; 34:599-604.

[86] Delmas PD. Markers of bone turnover for monitoring treatment of osteoporosis with antiresorptive drugs. Osteoporosis International 2000; 11:S66- 76.

[87] Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men (RACGP) 2012 http://www.racgp.org.au/guidelines/musculoskeletaldiseases/osteoporosis (accessed on Feb 2010)

[88] Chung SH, Kim TH, Lee HH. Relationship between Vitamin D level and bone mineral density in postmenopausal women from Bucheon area. Jounal ofKorean Society of Osteoporosis 2009; 7:198-202.

[89] Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. New England Journal ofMedicine 2004; 50:459-468.

[90] Lee J, Vasikaran S. Current Recommendations for Laboratory Testing and Use of Bone Turnover Markers in Management of Osteoporosis. Annals ofLaboratory Medicine 2012; 32:105-112.

[91] Tromp AM, Ooms ME, Popp-Snijders C, Roos JC, Lips P. Predictors of fractures in elderly women. OsteoporosisInternational 2000; 11:134-140.

[92] Chapurlat RD, Garnero P, Bréart G, Meunier PJ, Delmas PD. Serum type I collagen breakdown product (serum CTX) predicts hip fracture risk in elderly women: the EPIDOS study. Bone 2000; 27:283-286.

[93] Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover,endogenous hormones and the risk of fractures in postmenopausal women: the OFELY Study. Journal of Bone& Mineral Research 2000; 15: 1526-1536.

[94] Garnero P, Cloos P, Sornay-Rendu E, Qvist P, Delmas PD. Type I collagen racemization and isomerization and the risk of fracture in postmenopausal women: the OFELY prospective study. Journal of Bone& Mineral Research 2002; 17:826-33.

[95] Meier C, Nguyen TV, Center JR, Seibel MJ, Eisman JA. Bone resorption and osteoporotic fractures in elderly men: the dubbo osteoporosis epidemiology study.Journal of Bone& Mineral Research 2005; 20:579-587.

[96] Garnero P, Shih WJ, Gineyts E, Karpf DB, Delmas PD. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. Journal of ClinicalEndocrinology & Metabolism 1994; 79:1693-1700.

[97] Bell NH, Bilezikian JP, Bone HG, Kaur A, Maragoto A, Santora AC. Alendronate increases bone mass and reduce bone markers in postmenopausal African-American women.Journal of ClinicalEndocrinology & Metabolism 2002; 87:2792- 2797.

[98] Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. Journal of ClinicalEndocrinology & Metabolism 1998; 13: 1431-1438.

[99] Garnero P, Gineyts E, Arbault P, Christiansen C, Delmas PD. Different effects of bisphosphonate and estrogen therapy on free and peptide-bound bone cross-links excretion. Journal of ClinicalEndocrinology & Metabolism1995; 10:641-649.

[100] Rosen HN, Moses AC, Garber J, Ross DS, Lee SL, Greenspan SL. Utility of biochemical markers of bone turnover in the follow-up of patients treated with bisphosphonates. CalcifedTissue International 1998; 63:363-368.

[101] Glover SJ, Garnero P, Naylor K, et al. Establishing a reference range for bone turnover markers in young, healthy women. Bone 2008; 42:623 -630.

[102] Sandhu KS, Hampson G. The pathogenesis, diagnosis, investigation and management of osteoporosis. Journal of ClinicalPathology 2011; 64:1042-1050.

[103] Kim SW, Park DJ, Park KS et al. Early changes in biochemical markers of bone turnover predict bone mineral dnsity response to antiresorptive therapy in Korean postmenopausal women with osteoporosis. Endocrine Journal 2005;52:667-674.

[104] Brown JP, Albert C, Nassar BA, Adachi JD, Cole D, Davison KS, et al. Bone turnover markers in the management of postmenopausal osteoporosis. Clinical Biochemistry 2009; 42:929-442.

[105] Scariano JK, Garry PJ, Montova GD et al. Serum leptin levels, bone mineral density and osteoblast alkaline phosphatase activity in elderly men and women. Mechanism of Ageing and Development 2003; 24:281-286.

[106] Filip R &Raszewski G. Bone mineral density and bone turnover in relation to serum leptin, -α ketoglutarate and sex steroids in overweight and obese postmenopausal women. Clinical Endocrinology 2009; 70, 214–220.

[107] Iwamoto I, Douchi T, Kosha S, et al. Relationships between serum leptin level and regional bone mineral density, bone metabolic markers in healthy women. ActaObstetriciaetGynecologicaScandinavica2000; 79: 1060-1064.

[108] Peng XD, Xie H, Zhao Q, et al.Relationships between serum adiponectin, leptin, re-sistin, visfatin levels and bone mineral density, and bone biochemical markers in Chinese men. ClinicaChimicaActa 2008; 387: 31-35.

[109] Shaarawy M, Abassi AE, Hassan H, et al.Relationship between serumleptinconcen-trations and bonemineraldensity as well as biochemicalmarkers of boneturnover in women with postmenopausalosteoporosis. Fertility & Sterility 2003; 79: 919-924.

[110] Zhang H, Xie H, Zhao Q et al. Relationships between serum adiponectin, apelin, lep-tin, resistin, visfatin levels and bone mineral density, and bone biochemical markers in post-menopausal Chinese women. Journal of Endocrinological Investigation 2010; 33:707-711.

[111] Wu N, Wang QP, Li H, et al. Relationships between serum adiponectin, leptin con-centrations and bone mineral density, and bone biochemical markers in Chinese women. ClinicaChemicaActa 2010; 411:771-775.

[112] Yang LC, Lan Y, Hu J et al. Correlation of serumleptinlevel with bonemineraldensity and boneturnovermarkers in Chineseadolescentdancers. Biomedicaland Enviromen-talScience; 2009; 22:369-373.

[113] Prouteau S, L Benhamou L, Courteix D. Relationships between serum leptin and bone markers during stable weight, weight reduction and weight regain in male and female judoists. European Journal of Endocrinology 2006; 154: 389–395.