Relationships between serum Omentin-1 levels and bone mineral density in older men with osteoporosis

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Received 14 October 2015
Available online 6 April 2016

Abstract

Objective: To investigate the correlation between serum Omentin-1 levels and the presence of osteoporosis in older men.

Methods: Serum Omentin-1, bone turnover biochemical markers, and bone mineral density (BMD) were determined in 45 older men with osteoporosis or 45 older men without osteoporosis (65–70 years old).

Results: Omentin-1 levels were increased in older men with osteoporosis, and the differences remained significant after controlling for fat mass. Omentin-1 was negatively correlated with BMD. In a multiple linear stepwise regression analysis, Omentin-1, lean mass, but not fat mass, were independent predictors of BMD for the combined group. Significant negative correlations between Omentin-1 and bone-specific alkaline phosphatase (BAP) and bone cross-linked N-telopeptides of type I collagen (NTX) were found. Omentin-1 was also independently associated with BMD and bone turnover markers in older men with osteoporosis and control groups that were considered separately.

Conclusions: Omentin-1 is an independent predictor of BMD in older men with osteoporosis, and it is negatively correlated with bone turnover biochemical markers. It is suggested that Omentin-1 may exert a negative effect on bone mass through the regulation of the osteoblast differentiation in the older men with osteoporosis.

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Keywords: Omentin-1; Bone mineral density; Osteoporosis

Introduction

Osteoporosis, is a metabolic bone disease, characterized by low bone mass and microarchitectural deterioration of bone tissue.1 Compared with osteoporosis in post-menopause, osteoporosis in older men has higher risks of fracture and fatality.2,3 But the mechanism remains unclear. Although the relationship between lean mass and bone mineral density (BMD) is well known,4,5 the relationship between fat-dependent factors and

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Peer review under responsibility of Chinese Medical Association.
BMD is less clear. On the other hand, BMD is affected by various factors like sex, genetics, and regional risk factors.

Fat mass plays an important role in bone metabolism. It has been demonstrated that certain adipokines, such as leptin, adiponectin and Omentin-1, can modulate bone metabolism in vitro and in vivo.6–11 Adiponectin has been found to be related to the decreased BMD in older men.12

Omentin-1 (also intelectin-1) is a novel visceral adipose tissue-derived cytokine. The level of circulating Omentin-1 is high in plasma and is decreased in patients with obesity and increased after weight loss. It correlates positively with adiponectin and negatively with body mass index (BMI) and the leptin level.13,14 Omentin-1 has been reported to inhibit osteoblast differentiation in vitro.15,16 In co-culture systems of osteoblasts and osteoclast precursors, Omentin-1 reduced osteoclast formation by stimulating osteoprotegerin (OPG) and inhibiting the receptor activator for nuclear factor κB ligand (RANKL) production in osteoblasts. This suggested that Omentin-1 may play a pivotal role in the dynamic balance of bone formation and bone resorption.

The present study was undertaken to investigate whether Omentin-1 levels were associated with BMD and bone turnover biochemical markers in older men with osteoporosis. Serum Omentin-1, adiponectin, leptin and 25-hydroxyvitamin D and the bone turnover markers such as BAP and NTX were measured to investigate the relationship of these factors and BMD in older men with osteoporosis.

Methods

Subjects

We enrolled 45 older men with osteoporosis who met the World Health Organization (WHO) criteria for osteoporosis and 45 older men without osteoporosis were enrolled as controls. The older men with osteoporosis and controls were recruited from the patients in Hunan Province Geriatric Hospital during 2012 and 2013 in Changsha (China). The patients who had secondary osteoporosis diseases or who had previously taken any special medicine which could affect bone metabolism, such as glucocorticoids, or any treatment for osteoporosis were excluded from the study. Any patients with severe heart, brain and kidney diseases were not included in the study.

All subjects were screened through a detailed questionnaire, medical history and physical examination. Information on dietary intake through a food frequency questionnaire, as well as habitual physical activity were recorded. Body height and weight were measured using a stadiometer and a standardized balance-beam scale, respectively.

This study was approval by the South China University Research Ethics Committee, and all subjects and their family gave their informed consent to participate.

BMD measurements and body composition measurements

BMD was measured by dual energy X-ray absorptiometry (DXA) using a Lunar device (Lunar, MA, USA) as previously described.17–19 Supine position with the hip and knee fixed in flexion immobilization by means of supports were standard positions for the measurement. Total body, lumbar spine L2-L4, and total hip BMD were expressed in g/cm². Body fat mass and lean body mass were measured using DXA.

The precision of the DXA was evaluated over three repeated measurements of different BMD values in 75 subjects, and gave a mean coefficient of variation (CV) for all regions of 0.58 ± 0.20% (mean ± SD; range: 0.40–1.00%). A control spine phantom scan was performed everyday with a long-term (more than nine years) CV of 0.30–0.41% and the root-mean-square coefficient of variation was 0.37% (degrees of freedom (df) = 1576).19

Serum Omentin-1, adiponectin, leptin measurement

Blood samples were collected between 7:00 A.M. and 9:00 A.M. after fasting overnight and the samples were allowed to clot. Thereafter, the samples were centrifuged and divided into aliquots and stored at −70 ºC until assayed. The levels of Omentin-1 in human serum were determined using an Omentin-1 enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, Inc., Belmont, CA, USA). The levels of adiponectin in human serum were determined using an adiponectin ELISA kit (Phoenix Pharmaceuticals, Inc.). Serum leptin was detected using an ELISA kit (Phoenix Pharmaceuticals). The intra- and inter-assay coefficients of variation were 5.0% and 6.0% for Omentin-1, 5.6% and 7.0% for adiponectin, and 6.0% and 7.1% for leptin.

Hormone assays

The serum estradiol level was determined with a competitive immunoassay that uses direct chemiluminescence (Automated Chemiluminescence
System 180 Estradiol-6 Assay, Bayer HealthCare LLC Diagnostics, Tarrytown, NY, USA). The 25-hydroxyvitamin D was measured with an ELISA kit (Biomedica Medizinprodukte GmbH & Co KG, Vienna, Austria). The intra- and inter-assay CVs were 6.0% and 6.7% for estradiol and 5.2% and 7.1% for 25-hydroxyvitamin D respectively.

**Bone turnover biochemical markers measurement**

The serum concentration of bone alkaline phosphatase (BAP) as the marker of bone formation were measured with an ELISA kit (BAP from Metra™ BAP EIA kit, Quidel Corporation, USA). As a marker of bone resorption, serum cross-linked N-telopeptides of type I collagen (NTX) were measured using an ELISA kit (Osteomark, Ostex, Inc., Seattle, WA, USA). The intra- and inter-assay CVs were 5.1% and 7.0% for BAP, 5.3% and 7.9% for NTX, respectively.

**Statistical analysis**

SPSS 17.0 was used for the statistical analyses. The results were provided as mean and standard deviation (Mean ± SD). The correlations between Omentin-1, adiponecctin, leptin and BMD, and bone turnover biomarkers were made using Pearson's correlation analysis and partial correlation analysis. Multivariate linear stepwise analysis was performed to determine how much of the variance in BMD at various skeletal regions could be explained by age, BMI, fat mass, lean mass, 25-hydroxyvitamin D, estradiol, serum Omentin-1, adiponecctin, and leptin.

**Results**

**Clinical characteristics of the study participants**

The characteristics of the participant are summarized in Table 1. Omentin-1 levels were significantly higher in older men with osteoporosis subjects than controls.

**Relationships between serum Omentin-1, adiponecctin and leptin levels and BMD**

Table 2 showed that there were significant negative correlations between Omentin-1 and BMD for the total body, lumbar spine, and total hip determinations, and they remained significant after adjustment for age and fat mass. There were significant negative relationships between adiponecctin and BMD for the total body, lumbar spine, and total hip determinations that disappeared after adjustment for age and fat mass. There existed significant positive relationships between leptin and BMD for the total body, lumbar spine, and total hip determinations that

Table 1
Subject characteristics, and bone and biochemical parameters of 45 older men with osteoporosis and 45 control group men (n = 90).

| Items            | OP (n = 45) | Control (n = 45) | P |
|------------------|-------------|------------------|---|
| Age, years       | 66.35 ± 0.83| 66.28 ± 0.79     | NS |
| BMI, kg/cm²      | 20.33 ± 0.54| 20.99 ± 0.68     | NS |
| Fat mass (kg)    | 9.27 ± 0.64 | 8.67 ± 0.64      | <0.001 |
| Lean mass (kg)   | 32.31 ± 0.64| 32.26 ± 1.46     | NS |
| LS BMD (g/cm²)   | 0.802 ± 0.049| 0.973 ± 0.040   | <0.001 |
| Hip BMD (g/cm²)  | 0.821 ± 0.040| 0.942 ± 0.041   | <0.001 |
| T-BMD (g/cm²)    | 0.831 ± 0.049| 1.041 ± 0.049   | <0.001 |
| BAP (µg/ml)      | 30.16 ± 3.09 | 34.90 ± 2.73     | <0.001 |
| NTX (nmol/BCE)   | 28.11 ± 2.50 | 31.78 ± 2.90     | <0.001 |
| Omentin-1 (ng/ml)| 263.93 ± 22.88| 183.91 ± 22.91 | <0.001 |
| Adiponecctin (µg/ml)| 10.50 ± 1.13| 10.90 ± 0.74     | <0.001 |
| Leptin (ng/ml)   | 7.89 ± 0.49  | 9.29 ± 0.95      | <0.001 |
| Estradio (pmol/L)| 17.08 ± 0.82 | 19.16 ± 0.84     | <0.001 |
| 25-hydroxyvitamin D (ng/ml) | 32.83 ± 1.38 | 34.87 ± 1.59 | <0.001 |

Values are presented as Mean ± SD. BMI: body mass index; BAP: bone alkaline phosphatase; LS BMD : lumbar spine bone mineral density; T-BMD: thoracic spine bone mineral density; NTX: Cross-linked N-telopeptides of type I collagen; Omentin-1 levels were significantly higher in older men with osteoporosis subjects than controls.

Table 2
Correlation coefficients of serum Omentin-1, adiponecctin, leptin levels and BMD in the group as a whole (n = 50).

| Items    | T-BMD | LS BMD | Hip BMD |
|----------|-------|--------|---------|
|          | Unadjusted | Age and fat mass adjusted | Unadjusted | Age and fat mass adjusted | Unadjusted | Age and fat mass adjusted |
| Omentin-1| -0.513** | -0.497** | -0.622** | -0.601** | -0.679** | -0.636** |
| Adiponecctin| -0.263* | -0.291* | -0.304* | -0.406* | -0.323* | -0.446* |
| Leptin   | 0.367** | 0.338** | 0.384** | 0.352** | 0.409** | 0.388** |

BMD: bone mineral density; T-BMD: total BMD; LS BMD: lumbar spine BMD; Pearson's correlation coefficients and Partial correlation coefficients after adjustment for age and fat mass in the group as a whole are shown. **P < 0.01, *P < 0.05.
remained significant after adjustment for age and fat mass.

**Multiple regression analyses identified as predictors of BMD**

Regression modeling to eliminate confounding variables was performed for the group as a whole and also for the individual groups. The parameters identified as significant and independent determinant factors of BMD for the group as a whole are shown in Table 3 by a multiple linear regression analysis. The dependent variables were BMD of the total body, lumbar spine, and total hip. Several independent variables were entered in the regression analysis models, including age, BMI, fat mass, lean mass, 25-hydroxyvitamin D, estradiol, serum Omentin-1, adiponectin, and leptin. In the model with total body BMD as the dependent variable, the significant independent variables were Omentin-1, lean mass, Vitamin D, BMI, and adiponectin, and these explained 25.6% of the total body BMD variance ($R^2 = 0.256$). In the model with the lumbar spine BMD as the dependent variable, the significant independent variables were Omentin-1, lean mass, Vitamin D, and BMI, and these explained 26.8% of the lumbar spine BMD variance ($R^2 = 0.268$). In the model with total hip BMD as the dependent variable, the significant independent variables were Omentin-1, lean mass, Vitamin D, and BMI, and these explained 24.9% of the total hip BMD variance ($R^2 = 0.249$). These results show that Omentin-1, lean mass, Vitamin D, BMI, and adiponectin are the significant predictors for BMD.

In older men in the osteoporosis group, BMI, Omentin-1, lean mass, and adiponectin were also significant and independent determining factors. In the model with total body BMD as the dependent variable, the significantly independent variables were Omentin-1, lean mass, Vitamin D, and BMI, and these explained 4.6% of the total body BMD variance ($R^2 = 0.046$). In the model with lumbar spine BMD as the dependent variable, the significant independent variables were Omentin-1, lean mass, Vitamin D, BMI, and adiponectin, and these explained 2.0% lumbar spine BMD variance ($R^2 = 0.020$). In the model with total hip BMD as the dependent variable, the significant independent variables were Omentin-1, lean mass, BMI and adiponectin, and these explained 1.5% of total hip BMD variance ($R^2 = 0.015$).

**Association between serum Omentin-1 and bone turnover biochemical markers**

Serum BAP as a bone formation marker and serum NTX as a bone resorption marker were assayed. In both of the individual groups there was a significant negative correlation between Omentin-1 and NTX, BAP. The correlations were still significant after adjustment for age and fat mass. The $R$ values in the whole group, in the older men with osteoporosis group, and in the control group are shown in the Table 4.

**Discussion**

Older men with osteoporosis have low bone mineral density (BMD). Recent studies have shown that cytokines secreted by adipose tissue participate in bone

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**Table 3**

Parameters identified as significant and independent predictors of BMD in the group as a whole ($n = 90$).

| Parameters   | T-BMD ($R^2 = 0.256$) | LS BMD ($R^2 = 0.268$) | Hip BMD ($R^2 = 0.249$) |
|--------------|------------------------|------------------------|------------------------|
|              | $\beta$-coefficient $P$ | $\beta$-coefficient $P$ | $\beta$-coefficient $P$ |
| Omentin-1    | $-0.189$ 0.000         | $-0.124$ 0.006         | $-0.162$ 0.002         |
| BMI          | 0.328 0.000           | 0.209 0.012           | 0.297 0.008           |
| Lean mass    | 0.523 0.000           | 0.466 0.000           | 0.431 0.000           |
| VD           | 0.209 0.003           | 0.197 0.000           | 0.174 0.012           |
| Adiponectin  | $-0.115$ 0.010        | $-0.136$ 0.008        | $-0.153$ 0.006        |

Multiple regression analyses in the group as a whole ($n = 90$); BMD: bone mineral density; BMI: body mass index; VD: 25-hydroxyvitamin D.
Thus, we investigated the relationship between serum levels of ‘adipokines’ and BMD, including biochemical bone turnover markers in older men with osteoporosis. Our results showed that Omentin-1 was significantly associated with BMD for the total body, the lumbar spine, and the total hip in older men with osteoporosis, and this association was independent of age, fat mass, and other hormonal factors. Moreover, Omentin-1 was negatively correlated with BAP and NTX in both older men in the osteoporosis group and those in the control group. Our study showed that Omentin-1 correlated negatively with markers of bone turnover in both older men with osteoporosis and those in the control group. It suggested that Omentin-1 played a role both in older men with osteoporosis and those in the control group. But the Omentin-1 level in older men with osteoporosis was higher than in the men in the control group, which indicated Omentin-1 might played a role in the decreased BMD of older men with osteoporosis. This finding suggested that Omentin-1 played a significant role in regulating bone mass in older men with osteoporosis via suppressing bone formation.

In the simple correlation analysis, significant negative correlations were found between Omentin-1 and BMD at various skeletal regions in the group as a whole and also in the individual groups. Significant predictors for BMD, as assessed by multivariate linear regression analysis, were BMI, lean mass, and Omentin-1, but not fat mass. These results showed that Omentin-1 was an independent predictor of BMD in older men with osteoporosis and that this was independent of fat mass.

Fat mass was not the significant predictor for BMD, suggesting that the effects of Omentin-1 on BMD were independent of fat mass. This data was consistent with recent reports from others showing that fat mass was not a determinant of BMD. Furthermore, the results showed that Omentin-1 levels were negatively correlated with NTX and BAP even after adjustment for age and fat mass. Thus, Omentin-1 may exert a negative effect on bone metabolism not by inhibiting bone resorption associated with bone loss in older men with osteoporosis.

Omentin-1 participates in the regulation of bone metabolism and its influence may be negative. Recently, a study demonstrated that Omentin-1 inhibited osteoblastic differentiation in vitro. Omentin-1 also reduces osteoclast formation in coculture systems through stimulating OPG and inhibiting RANKL production in osteoblasts via the PI3K/Akt signaling pathway. RANKL promotes osteoclast formation and activation, suppresses osteoclast apoptosis, and OPG has been shown to directly block all RANKL-mediated actions. In our research, increased Omentin-1 levels were negatively correlated with BMD and bone turnover markers in older men with osteoporosis. Thus, it suggested Omentin-1 could be exerting its negative effect on bone metabolism by inhibiting bone-formation in older men with osteoporosis.

Combined with the previous research, our results suggested two distinct actions of Omentin-1 on bone formation. One action was reducing osteoclast formation indirectly through stimulating OPG and inhibiting RANKL production in osteoblasts. The other action was directly inhibiting osteoblast differentiation. Compared with the control group, the bone turnover marker levels in older men with osteoporosis were lower, while Omentin-1 levels were higher. This indicates that there is a suppressive effect of Omentin-1 on bone turnover and bone mass. Our present observations showed that Omentin-1 exerts a negative effect on BMD in older men with osteoporosis with decreased bone turnover makers. Previous studies have found that lean mass and some other factors were greatly correlated with BMD, and this could explain why these parameters were independent predictors of BMD in older men with osteoporosis and controls. In addition, our data showed that Omentin-1 was also an independent predictor of BMD in healthy controls. It indicated that high Omentin-1 levels were a negative factor for BMD in the whole group. The level of

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Table 4
Correlation coefficients of serum Omentin-1, BAP and NTX in the whole group, older men with osteoporosis and control groups.

| Item   | BAP Unadjusted | BAP Age and fat mass adjusted | NTX Unadjusted | NTX Age and fat mass adjusted |
|--------|----------------|-------------------------------|----------------|-------------------------------|
| Total  | -0.815*        | -0.734*                       | -0.706*        | -0.698*                       |
| OP     | -0.553*        | -0.437*                       | -0.402*        | -0.390*                       |
| Control| -0.552*        | -0.621*                       | -0.446*        | -0.470*                       |

Pearson’s correlation coefficients and Partial correlation coefficients after adjustment for age and fat mass in the three groups were shown; BAP: bone alkaline phosphatase; NTX: Cross-linked N-telopeptides of type I collagen; OP: osteoporosis; *P < 0.05.
Omentin-1 was higher than that of healthy group (45 older men without osteoporosis were enrolled as controls), which might explain why the BMD level was lower than that of healthy group. Thus, our data showed that Omentin-1 might weaken more bone formation than bone resorption, therefore decreasing bone mass.

In the multiple linear regression analysis, adiponectin showed a negative relationship with BMD and was an independent determinant factor for BMD. A previous study has reported that adiponectin was independently associated with lumbar spine and femoral neck-bone BMD. But our recent study found that estrogen suppressed the effect of adiponectin on bone metabolism via blocking the activation of adiponectin-induced p38 MAPK. So, in older men with osteoporosis, the decreased estrogen levels promoted the action of adiponectin on bone mass.

Leptin was not a significant predictor for BMD in our study. The relationship between serum leptin and BMD was ambiguous. Previous study showed that serum leptin was inversely associated with BMD, while other studies showed a positive correlation. Our data showed that leptin had a positive association with BMD in the simple correlation, but this relationship disappeared in the regression model. These differing results may depend on the inverse functions of leptin on BMD through binding at the ObRs receptor in the central nervous system (CNS) and at various peripheral tissues. This showed complex interactions between hormones and body composition in determining bone metabolism.

The serum 25(OH)VD was positively correlated with the T score of the neck, ward, greater trochanter of the femur and vertebral lumbar. In our study, 25(OH)VD showed a positive relationship with the lumbar spine and total hip BMD which coincides with the previous finding. Therefore, a 25(OH)VD deficiency may be an independent predictor for BMD.

In conclusion, the present study provided evidence that Omentin-1, a novel visceral adipose tissue-derived cytokine, was an independent predictor of BMD both in older men with osteoporosis and control. And it showed a negative correlation with bone turnover markers. It suggested that Omentin-1 may exert a negative effect on bone mass by inhibiting bone formation in older men with osteoporosis.

Acknowledgments

This work was supported by Hunan provincial natural science foundation grant 13JJ4119 from China and Hunan health special foundation grant A2014-02. We thank Dr. Peng Cheng for helpful discussions and comments on the manuscript.

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