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High Levels of Serum DPP-4 Activity Are Associated with Low Bone Mineral Density in Obese Postmenopausal Women

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Background: Dipeptidyl peptidase 4/CD26 (DPP-4) is a widely expressed cell surface serine protease. DPP-4 inhibitors, one of common anti-diabetic agents play a protective role in bone metabolism in recent studies. A soluble form of DPP-4 is found in serum, and exhibits DPP-4 enzymatic activity. However, the physiological role of serum or soluble DPP-4 and its relationship with DPP-4 enzymatic function remain poorly understood. The aims of current study were to determine the association between serum DPP-4 activity and bone mineral density (BMD) in postmenopausal women.

Methods: We recruited data and serum samples from 124 consecutive healthy postmenopausal women aged >50 years. We divided study subjects into obese (body mass index [BMI] ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2) postmenopausal women and examined the correlation between serum DPP-4 activity and clinical variables in each groups.

Results: A total of 124 postmenopausal women was enrolled, with a mean age of 59.9±7.1 years. The mean BMI of the study patients was 24.4±2.8 kg/m^2. Regarding bone turnover markers, serum DPP-4 activity was positively correlated with serum calcium concentrations, intact parathyroid hormone, and serum C-telopeptide levels in all of the study subjects. However, there was no association between serum DPP-4 activity and BMD in the spine or femoral neck in all of the study subjects. Serum DPP-4 activity was negatively correlated (R=−0.288, P=0.038) with BMD of the spine in obese postmenopausal women.

Conclusion: This study demonstrated for the first time that serum soluble DPP-4 activity was negatively correlated with BMD in obese postmenopausal women.

Keywords: Dipeptidyl peptidase 4; Bone mineral density; Postmenopause; Women

INTRODUCTION

Osteoporosis is a common disease in postmenopausal women and elderly people. Osteoporotic fractures are associated with disability, high healthcare costs, and an increased risk of morbidity and mortality. However, the appropriate medical treatment for osteoporosis improves patient survival and reduces fractures [1].

Dipeptidyl peptidase 4/CD26 (DPP-4) is a widely expressed cell surface serine protease that cleaves the N-terminal dipep-

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tide from peptide substrates that contain proline or alanine in the second position. Both membrane-anchored and soluble forms of the enzyme can perform this cleavage reaction [2-4]. In recent years, studies of DPP-4 enzymatic activity have mainly focused on the metabolic effects linked to glucagon-like peptide-1 (GLP-1) degradation [5], because DPP-4 inhibitors are commonly used as anti-diabetic agents to improve hyperglycemia in patients with type 2 diabetes.

Recent studies have also suggested that DPP-4 inhibitors play a protective role in bone metabolism [6]. For example, in diabetic rat models, sitagliptin treatment decreased the serum levels of a resorption marker and attenuated trabecular bone loss [7]. In a meta-analysis of 28 trials that included 11,880 and 9,175 patients receiving DPP-4 inhibitors and comparative agents, respectively, for a duration of at least 24 weeks, treatment with DPP-4 inhibitors was associated with a reduced risk of bone fractures compared to placebo or active drugs [8]. In another study, treatment with GLP-2 for 4 months in postmenopausal women resulted in increased bone mineral density (BMD) in the hip in a randomized clinical study [9]. Taken together, the above studies suggest that DPP-4 inhibitors might increase endogenous GLP-1 and GLP-2 expression, thereby decreasing osteoporotic fractures.

A soluble form of DPP-4 is found in serum, and exhibits DPP-4 enzymatic activity [10-12]. However, the physiological role of serum or soluble DPP-4 and its relationship with DPP-4 enzymatic function remain poorly understood because the mechanisms by which DPP-4 are produced and secreted remain unclear [13]. In the previous study, DPP-4 was known as a novel adipokine showing that the DPP-4 released from adipose tissue correlates with adipocyte size which was linking obesity [14]. There are currently no data regarding serum DPP-4 activity and BMD in humans. Therefore, we designed the current study to elucidate the association between serum DPP-4 activity and BMD in postmenopausal women and we made a subgroup analysis into obese and non-obese group in postmenopausal women because obesity was associated with DPP-4 activity and BMD.

METHODS

Study subjects

We recruited data and serum samples from 124 consecutive healthy postmenopausal women aged >50 years as part of a subset of a study performed from June 2009 to October 2010 at Kangwon National University Hospital, South Korea [15]. Menopause was defined as the absence of menstruation for at least 1 year. Women who had been taking glucocorticoids and estrogen for more than 3 months, and had diseases that could affect bone metabolism such as Graves disease or Cushing syndrome, or conditions such as diabetes mellitus were excluded from the study. Hysterectomized and premenopausal bilaterally ovariectomized women were also excluded.

A self-administered questionnaire, interviews, and anthropometric measurements were used to collect data regarding lifestyle, physical activity, and previous medical and fracture histories. Previous fragility fractures were defined as low-trauma fractures involving the femur, spine, and other sites such as the wrist, ankle, foot, and ribs.

Areal BMD (g/cm^2) values were determined in the spine, right femoral neck, and total hip in all of the subjects using a Lunar Prodigy Vision dual-emission X-ray absorptiometry system (Lunar Corp., Madison, WI, USA). According to the World Health Organization definition, osteoporosis was determined as a T-score ≤ -2.5 standard deviations (SDs) at any site. One investigator performed the densitometry tests and analyses in all of the subjects. The precision of the equipment, presented as the coefficient of variation, was 0.90% and 1.14% for the lumbar spine and femoral neck, respectively, in 20 volunteers at Kangwon National University who were not enrolled in the study.

Serum DPP-4 activity was measured using a human DPP-4/CD26 immunoassay kit (R&D Systems, Minneapolis, MN, USA). The serum levels of C-terminal telopeptide of type I collagen (C-telopeptide), and intact parathyroid hormone (PTH) were measured by Molecular Analytics (Roche, Mannheim, Germany). The serum levels of osteocalcin and 25-(OH) vitamin D3 were measured using a Y-counter (Packard, Meriden, CT, USA). We examined the association between serum DPP-4 activity and BMD in obese and non-obese groups.

Ethics statement

The Institutional Review Board of Kangwon National University Hospital approved the study protocol (IRB number 09–07). Written informed consent was obtained from each individual.

Statistical analysis

Pearson correlation coefficients were calculated to analyze the relationship between serum DPP-4 levels and clinical parameters, including BMD. Student *t* tests or chi-square tests were used to compare the baseline characteristics between obese and non-obese menopausal women. Serum DPP-4 activity was nor-

mally distributed variable. Statistical analyses were performed using SPSS version 21.0 (IBM Co., Armonk, NY, USA). All *P* values were two-tailed, and $P<0.05$ was considered statistically significant.

RESULTS

A total of 124 postmenopausal women were enrolled, with a mean age of 59.9±7.1 years. The mean body mass index (BMI) of the study patients was 24.4±2.8 kg/m^2, and the mean age at menopause was 50.8±3.6 years. Table 1 shows the baseline clinical characteristics of study subjects. Obese patients have a higher blood pressure and higher BMD of spine and total hip compared to non-obese patients (Table 1).

Serum DPP-4 activity was negatively correlated with age and systolic blood pressure and serum DPP-4 activity was positively correlated with corrected calcium, C-telopeptide and intact PTH in the whole study population (Table 2). However, there was no association between serum DPP-4 activity and BMD in the spine or femoral neck in all of the study subjects. We divided study subjects into obese (BMI ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2) postmenopausal women.

In the non-obese group, there was positive correlation between serum DPP-4 activity and corrected calcium ($R=0.316$, $P=0.007$) or C-telopeptide ($R=0.284$, $P=0.016$) but there was no correlation between serum DPP-4 activity and BMD of spine or femoral neck (Table 3).

Table 4 shows the correlation between serum DPP-4 activity and clinical variables in obese patients ($n=52$). In Serum DPP-4 activity was negatively correlated with systolic and diastolic BP in obese subjects. Serum DPP-4 activity was also negatively correlated ($R=-0.288$, $P=0.038$) with BMD in the spine (Fig. 1).

Table 1. Baseline Clinical Characteristics of the Study Subjects ($n=124$)

Variable	Total	Non-obese group	Obese group	*P* value[a]
Number	124	72	52	
Age, yr	59.9±7.1	59.6±7.4	60.2±6.7	0.641
Body mass index, kg/m^2	24.4±2.8	22.4±1.5	27.1±2.0	<0.001
Systolic blood pressure, mm Hg	123.9±16.0	120.2±15.2	128.8±16.0	0.003
Diastolic blood pressure, mm Hg	75.8±10.5	72.5±9.6	80.0±10.3	<0.001
Age at menopause, yr	50.8±3.6	51.0±3.3	50.5±4.0	0.455
No. of years since menopause	9.1±7.6	8.7±7.9	9.7±7.2	0.430
Serum DPP-4 activity, ng/mL	616.7±127.4	623.6±128.3	607.1±126.7	0.479
Calcium, mg/dL	9.5±0.3	9.5±0.3	9.5±0.3	0.985
Phosphate, mg/dL	3.8±0.5	3.9±0.5	3.8±0.5	0.289
Albumin, g/dL	4.3±0.3	4.3±0.3	4.3±0.2	0.973
Creatinine, mg/dL	0.6±0.1	0.6±0.1	0.6±0.1	0.835
Osteocalcin, ng/mL	12.6±2.7	12.5±2.5	12.7±3.1	0.676
C-telopeptide, ng/mL	0.78±0.36	0.80±0.42	0.75±0.26	0.378
Intact PTH, pg/mL	0.092±0.050	0.098±0.059	0.084±0.032	0.108
25-Vitamin D3, ng/mL	6.1±3.3	6.3±3.4	5.8±3.2	0.440
BMD (g/cm^2) by DXA				
BMD of spine	0.993±0.150	0.950±0.135	1.053±0.151	<0.001
BMD of femoral neck	0.081±0.107	0.786±0.108	0.823±0.103	0.061
BMD of total hip	0.886±0.124	0.859±0.117	0.924±0.124	0.003
Total fragility fracture history				
Total fracture history	23 (18.5)	14 (19.4)	9 (17.3)	0.099
Spine fracture history	1 (0.8)	0	1 (1.9)	0.311
Hip fracture history	0	0	0	0.159

Values are expressed as mean±SD or number (%).
DPP-4, dipeptidyl peptidase 4; PTH, parathyroid hormone; BMD, bone mineral density; DXA, dual-emission X-ray absorptiometry.
[a]*P* value was measured between non-obese and obese group.

Table 2. Correlation between Serum DPP-4 Activity and Other Variables in the Whole Study Population (n=124)

Variable	*R*	*P* value
Age, yr	−0.182	0.043
Body mass index, kg/m^2	−0.030	0.741
Systolic blood pressure, mm Hg	−0.229	0.001
Diastolic blood pressure, mm Hg	−0.115	0.203
Corrected calcium, mg/dL	0.256	0.013
Phosphate, mg/dL	0.085	0.835
Creatinine, mg/dL	−0.092	0.311
Osteocalcin, ng/mL	0.003	0.975
C-telopeptide, ng/mL	0.253	0.005
Intact PTH, pg/mL	0.220	0.014
25-Vitamin D3, ng/mL	0.171	0.058
BMD of spine, g/cm^2	−0.076	0.403
BMD of femoral neck, g/cm^2	0.038	0.676
BMD of total hip, g/cm^2	0.008	0.933

DPP-4, dipeptidyl peptidase 4; PTH, parathyroid hormone; BMD, bone mineral density.

Table 3. Correlation between Serum DPP-4 Activity and Other Variables in Non-Obese Subjects (n=72)

Variable	*R*	*P* value
Age, yr	−0.177	0.138
Body mass index, kg/m^2	0.045	0.707
Systolic blood pressure, mm Hg	−0.094	0.433
Diastolic blood pressure, mm Hg	0.039	0.744
Corrected calcium, mg/dL	0.316	0.007
Phosphate, mg/dL	0.157	0.189
Creatinine, mg/dL	−0.051	0.721
Osteocalcin, ng/mL	−0.087	0.466
C-telopeptide, ng/mL	0.284	0.016
Intact PTH, pg/mL	0.221	0.062
25-Vitamin D3, ng/mL	0.211	0.076
BMD of spine, g/cm^2	0.125	0.296
BMD of femoral neck, g/cm^2	0.102	0.395
BMD of total hip, g/cm^2	0.085	0.480

DPP-4, dipeptidyl peptidase 4; PTH, parathyroid hormone; BMD, bone mineral density.

Regarding bone turnover markers, serum DPP-4 activity was positively correlated with serum calcium concentrations, intact PTH, and serum C-telopeptide levels in all of the study subjects (Table 2). There was also a positive correlation between serum DPP-4 activity and serum C-telopeptide levels in non-obese subjects (R=0.284, P=0.016, n=76) (Table 3). However, there was no correlation between serum DPP-4 activity and bone turnover markers such as C-telopeptide or osteocalcin in the obese subjects (Table 4).

Table 4. Correlation between Serum DPP-4 Activity and Other Variables in Obese Subjects (n=52)

Variable	*R*	*P* value
Age, yr	−0.185	0.190
Body mass index, kg/m^2	0.028	0.842
Systolic blood pressure, mm Hg	−0.391	0.004
Diastolic blood pressure, mm Hg	−0.280	0.044
Corrected calcium, mg/dL	0.102	0.471
Phosphate, mg/dL	−0.032	0.824
Creatinine, mg/dL	−0.051	0.721
Osteocalcin, ng/mL	0.111	0.434
C-telopeptide, ng/mL	0.189	0.179
Intact PTH, pg/mL	0.223	0.111
25-Vitamin D3, ng/mL	0.102	0.472
BMD of spine, g/cm^2	−0.288	0.038
BMD of femoral neck, g/cm^2	−0.027	0.847
BMD of total hip, g/cm^2	−0.053	0.708

DPP-4, dipeptidyl peptidase 4; PTH, parathyroid hormone; BMD, bone mineral density.

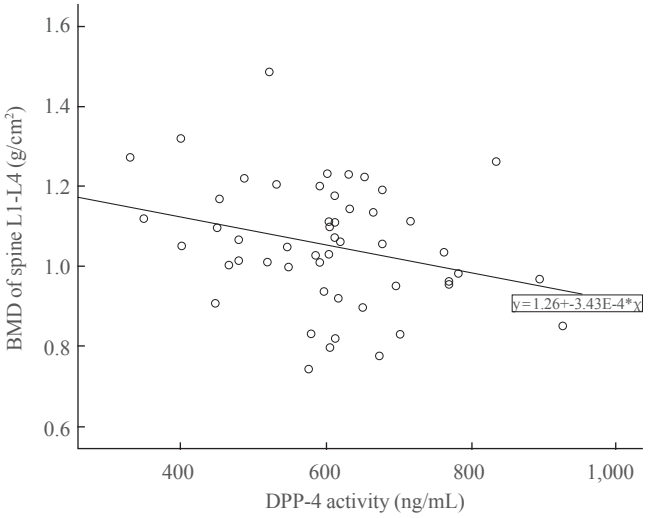

Fig. 1. Correlation analysis showing the association between bone mineral density and serum dipeptidyl peptidase 4/CD26 (DPP-4) activity levels in obese postmenopausal women (n=52). BMD, bone mineral density.

DISCUSSION

The current study demonstrated for the first time that serum soluble DPP-4 activity was negatively correlated with spine BMD in obese postmenopausal women. However, there was no significant association between serum DPP-4 activity and BMD in non-obese postmenopausal women. It is unclear why serum DPP-4 activity was only associated with BMD in obese postmenopausal women.

DPP-4 substrates are proline- or alanine-containing peptides including chemokines, neuropeptides, and vasoactive peptides such as interleukin 2 (IL-2), IL-1β, and GLP-1 [16]. It is widely distributed in the placenta, kidney, liver, intestine, brain, lymphocytes, endothelial cells, and lungs [3,16,17]. DDP-4 enzyme activity regulates the postprandial availability of different gut hormones that might affect bone metabolism, including GLP-1, GLP-2, glucose-dependent insulinotropic peptide, and peptide YY [18]. Therefore, additional beneficial effects on bone health could be achieved using DPP-4 inhibitors compared to those achieved using GLP-1 receptor agonists [18]. Therefore, the current study suggests that the activity of serum soluble DPP-4 might influence a variety of gut hormones that regulate bone metabolism in obese postmenopausal women.

Several studies have revealed a positive relationship between DPP-4 inhibitors and bone metabolism [6-8]. However, another study showed that the use of DPP-4 inhibitors was not associated with fracture risk [19]. In addition, the DPP-4 inhibitor MK-0626 showed neutral effects on the bone in diabetic muscle-lysine-arginine (MKR) mice or during osteoblast differentiation [20].

The current study showed that serum DPP-4 activity was positively correlated with serum C-telopeptide levels in non-obese subjects (n=76) and the entire study population (n=124), suggesting that there is a possible correlation between serum DPP-4 activity and bone resorption markers. Interestingly, serum DPP-4 levels were correlated with serum intact PTH levels and corrected calcium levels in all of the study subjects, but not in the obese group. Interestingly, previous reports have demonstrated that PTH is a DPP-4 inhibitor [21,22]. Our study showed no association between DPP-4 and osteocalcin such as bone formation marker but recent study demonstrated that increased plasma DPP-4 activity was positively associated with C-telopeptide and osteocalcin and negatively with active GLP-1 and BMD [23].

Nevertheless, further studies with a sufficient sample size in the obese group are needed to clarify the association between serum DPP-4 activity and serum C-telopeptide concentrations or intact PTH levels.

Recently, Nishida et al. [23] demonstrated that blocking DPP-4 signaling inhibits the development of human osteoclasts, suggesting that there is an association between DPP-4 and bone resorption. Zheng T et al. also showed that postmenopausal women with the highest quartile of DPP-4 activity showed lower BMD compared with whose in the lowest quartile [24]. Another study showed that $Dpp4^{-/-}$ ovarectomized female mice exhibited reductions in femoral geometry and femoral structural properties [25]. However, another study showed that treatment with vildagliptin (100 mg daily) for 1 year did not change postprandial serum C-telopeptide levels in a single center, double blinded randomized clinical trial of 59 patients with drug-naïve type 2 diabetes [26].

In the recent years, DPP-4 activity was regarded as a new adipokine highly expressed and released from adipocytes and DPP-4 concentrations are higher in obese subjects suggesting the linking between type 2 diabetes and atherosclerosis [14]. However, our study demonstrated there was no significantly difference of the DPP-4 activity between obese and non-obese postmenopausal women and we showed the inverse association between DPP-4 activity and BMD of spine only in obese postmenopausal women. Further study with larger study population is need to clarify above discrepancies.

One of the limitations of this study is that it is not population-based, and is a single center study with a small sample size. Second, it is a cross-sectional study that failed to identify a causal relationship between serum DPP-4 activity and BMD. Third, the study subjects are postmenopausal women, and we did not clarify the interaction between serum DPP-4 activity and estrogen levels (menopausal status). Additional prospective studies are needed with a larger sample size to obtain sufficient statistical power to demonstrate the association between DPP-4 activity and bone metabolism.

In conclusion, we demonstrated that serum DPP-4 activity was negatively associated with BMD of the spine in obese postmenopausal women. These findings have implications for increasing our understanding of serum soluble DPP-4 activity on bone metabolism, and give clues for future prospective studies to help clarify causality of DPP-4 activity and advance this area of research.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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