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Serum 25-hydroxyvitamin D and Osteocalcin Levels and Insulin Sensitivity in Young Women

Do Kyeong Song*, Hyejin Lee and Yeon-Ah Sung

Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, Korea

Correspondence author: Do Kyeong Song, M.D., Ph.D., Department of Internal Medicine, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea; Tel: +82-2-2650-6158, Fax: +82-2-2650-5235; **E-mail:** sdkhope@hanmail.net

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Abstract

Introduction

Vitamin D and osteocalcin have been reported to affect insulin secretion and sensitivity in the elderly. This study aimed to investigate whether the levels of 25-hydroxyvitamin D [25(OH)D] and osteocalcin were associated with insulin sensitivity in young Korean women.

Methods

One hundred and twenty-eight healthy women (16–38 yrs) were recruited and divided into obese (BMI ≥ 25 kg/m^2) and non-obese (BMI < 25 kg/m^2) groups according to their body mass index (BMI). The serum 25(OH)D level was measured by radioimmunoassay, total osteocalcin was measured by electrochemiluminescence immunoassay, and carboxylated osteocalcin was measured by enzyme immunoassay. The standard 75-g oral glucose tolerance test was performed, and the metabolic clearance rate was calculated as an index of insulin sensitivity: [MCR = 18.8 – (0.271 × BMI) – (0.0052 × $Insulin_{120}$) – (0.27 × $Glucose_{90}$)].

Results

The median levels of 25(OH)D were below 20 ng/ml in both obese and non-obese subjects. Obese women had higher serum 25(OH)D ($P < 0.01$) levels, but the total and carboxylated osteocalcin levels did not differ between the two groups ($P > 0.05$). Multiple linear regression analysis showed that 25(OH)D was significantly negatively associated with the MCR after adjustment for age, total osteocalcin, and carboxylated osteocalcin ($\beta = -0.333$, $P < 0.01$).

Conclusion

Most of the participants had vitamin D deficiency. A low vitamin D level interferes with conclusions regarding the relationship between osteocalcin and metabolic parameters. Further prospective studies will be needed to confirm the different effects of vitamin D/osteocalcin on insulin sensitivity according to age.

Keywords: *25-hydroxyvitamin D; Osteocalcin; Insulin sensitivity*

Introduction

Most Koreans have low levels of 25-hydroxyvitamin D [25(OH)D] and a high prevalence of vitamin D insufficiency. The prevalence of vitamin D insufficiency is higher in young adults than in elderly people [1]. Additionally, the prevalence of type 2 diabetes mellitus is rapidly rising. Low insulin sensitivity is associated with type 2 diabetes mellitus [2]. Vitamin D and osteocalcin have been reported to affect insulin secretion and insulin sensitivity [3,4]. Vitamin D deficiency has been associated with impaired insulin secretion in humans and in animal models [5]. The concentration of 25(OH)D was lower in patients with type 2 diabetes mellitus than in nondiabetic controls [6].

Total osteocalcin is synthesized by osteoblasts and undergoes a posttranslational vitamin K-dependent modification in which 3 glutamic acid residues are carboxylated. Total osteocalcin and carboxylated osteocalcin synthesis are directly regulated by 1, 25-dihydroxyvitamin D and parathyroid hormone [7]. In animal models, osteocalcin-deficient mice have obesity, hyperglycemia, glucose intolerance, and insulin sensitivity [4,8]. In humans, serum total osteocalcin is inversely associated with measures of insulin sensitivity and fat mass [3]. In a cross-sectional study of nondiabetic older adults, elevated carboxylated osteocalcin is associated with lower insulin sensitivity [7].

However, increasing numbers of studies have suggested that there is ambiguity and inconsistency between the rodent studies and results in humans. Few studies have confirmed a link between energy metabolism of the adipose tissue and skeleton. There have been multiple studies in young and normoglycemic populations, even in Asians reporting the lack of a relationship or ambiguity between vitamin D/osteocalcin and insulin sensitivity [9–13]. Furthermore, the interaction between vitamin D and insulin sensitivity in the general population has not been adequately determined. Many

previous studies on the association of vitamin D/osteocalcin and insulin sensitivity were performed in older adults [6,7]. Therefore, we aimed to evaluate whether a low vitamin D status was associated with insulin sensitivity in young Korean women.

Methods

We performed a survey to identify genetic markers for polycystic ovary syndrome in the Korean population [14]. Subjects were excluded if they had been on medication which had effect on calcium metabolism and vitamin D levels, such as calcium, vitamin D, and anticonvulsant drugs or if they had a condition causing malabsorption of nutrients such as inflammatory bowel disease. Subjects who had been diagnosed with type 2 diabetes mellitus or who had any missing data due to the inadequate sample volume were excluded. Finally, of 2000 women under 40 years of age who voluntarily participated in the survey between 2008 and 2010, we enrolled 128 healthy young women. Throughout the year, we invited volunteers to visit our hospital on the morning after an overnight fast of at least 8 h. Based on their Body Mass Index (BMI), subjects were divided into two groups. The BMI was categorized as < 25 kg/m^2 or ≥ 25 kg/m^2, which was suggested as the cut-off point for obesity in Asian populations [15]. Written informed consent was obtained from all participants or their parents if the participants were younger than 18 years of age. The institutional review board of Ewha Womans University Mokdong Hospital approved this study.

Height, weight, and waist circumference were measured. The waist circumference was measured on bare skin at the narrowest indentation between the 10^{th} rib and iliac crest at midrespiration. BMI, defined as body weight in kilograms divided by the square of height in meters (kg/m^2), was used as an index of obesity. The blood pressure was calculated as the mean of two manual sphygmomanometer readings with the patient in the seated position.

We stored the frozen serum samples, which were drawn after overnight fasting, at −80°C until analysis and instantly kept the frozen serum sample at -20°C for measurement. The serum 25(OH)D was measured by radioimmunoassay (Parkard, CA, USA), and the mean inter- and intraassay coefficients of variation (CV) were 7.3% and 8.1%, respectively. Total osteocalcin was measured using an electrochemiluminescence immunoassay (Roche, MA, USA), and the mean inter- and intraassay CVs were 1.5% and 0.7%, respectively. Carboxylated osteocalcin was measured by enzyme immunoassay (Takara Bio, Shiga, Japan), and the mean inter- and intraassay CVs were 1.4% and 3.7%, respectively. The 75-g oral glucose tolerance test (OGTT) was performed in the morning after an 8-hr overnight fast. Blood for measuring the insulin and glucose levels was collected at 0, 30, 60, 90, 120 minutes. Glucose levels were measured by the glucose oxidase method (Beckman Model Glucose Analyzer 2, CA, USA), and insulin levels were measured by radioimmunoassay (BioSource, Nivelles, Belgium). The homeostasis model assessment-estimated insulin resistance (HOMA-IR) index was calculated as the product of the fasting insulin level (mIU/L) and fasting glucose level (mg/dL) divided by 405. The metabolic clearance rate (MCR) was calculated as an index of insulin sensitivity by the Stumvoll Method: [MCR (mL/kg·min) = 18.8 – (0.271 × BMI) – (0.0052 × $Insulin_{120}$) – (0.27 × $Glucose_{90}$)] [16].

The statistical analyses were performed using SPSS 18.0 software package for Windows (IBM Corporation, Chicago, IL, USA). Because 25(OH)D, total osteocalcin, carboxylated osteocalcin, and MCR had a markedly skewed distribution, logarithmic transformation of these values was performed before regression analysis. Quantitative variables were reported as the means ± standard deviations. Variables with a skewed deviation were reported with medians and interquartile ranges. Two groups with different parameters were compared using Student's *t* test or Mann-Whitney *U* test, depending on the data distribution. To investigate the association of the serum 25(OH)D, total osteocalcin, and carboxylated osteocalcin with insulin sensitivity, multiple linear regression analyses were performed. The considered covariates were age, total osteocalcin, and carboxylated osteocalcin. Statistical significance was defined as $P < 0.05$.

Results

Table 1 shows the clinical characteristics of the subjects. Age was comparable between obese and non-obese women. The mean BMI ($P < 0.01$), waist circumference ($P < 0.01$), systolic blood pressure ($P < 0.01$), diastolic blood pressure ($P < 0.01$), and 2-hour post-load glucose ($P < 0.01$) were higher in obese women than in non-obese women. The MCR was significantly lower, and fasting plasma insulin and HOMA-IR were higher in obese women than in non-obese women (*Ps* < 0.01, Table 1).

Table 2 shows the bone metabolism parameters of subjects according to BMI. Obese women had higher serum 25(OH)D ($P < 0.01$) levels; however, the total and carboxylated osteocalcin levels did not differ between the two groups ($P > 0.05$). The median 25(OH)D levels were below 20 ng/ml in both obese and non-obese subjects (Table 2).

Multiple linear regression analysis showed that 25(OH)D was negatively associated with MCR ($\beta = -0.333$, $P < 0.01$) and positively associated with the 2-hour post-load glucose ($\beta = 0.254$, $P < 0.01$) after adjusting for age, total osteocalcin, and carboxylated osteocalcin (Table 3).

Discussion

In this study, the 25(OH)D levels were low in both obese and non-obese subjects. Most of the participants had vitamin D deficiency. Obese women had higher serum 25(OH)D levels. The total and carboxylated osteocalcin levels did not differ between the two groups. Additionally, a higher 25(OH)D level was negatively associated with insulin sensitivity.

Vitamin D is acquired through diet and cutaneous synthesis in sunlight. It is called vitamin D_3 (cholecalciferol) after its formation in the skin and vitamin D_2 or D_3 when obtained from dietary sources that undergo hydroxylation in the liver, resulting in formation of 25(OH)D, the chief circulating form of vitamin D [17].

In contrast to previous reports [6,18], a higher 25(OH)D level was negatively associated with insulin sensitivity in this study. Hypovitaminosis D has long been suspected as a risk factor for glucose intolerance [19]. Vitamin D status has been inversely associated with diabetes mellitus in epidemiological studies [5,20]. Several clinical

intervention studies support that vitamin D supplementation may affect glucose homeostasis or insulin sensitivity [21,22]. Significant improvements in the FPG, insulin, and homeostasis model assessment-insulin sensitivity after treatment with vitamin D were reported in a study of 100 patients with type 2 diabetes mellitus who were between 30 to 70 years old [22]. A potential explanation for the association between a low 25(OH)D level and impaired glucose tolerance has focused on the direct effects of vitamin D on pancreatic ß-cell insulin secretion. Vitamin-D receptors and vitamin D-binding proteins are known to exist in pancreatic tissues. In *in vitro* studies, 1, 25-dihydroxyvitamin D_3, the active form of vitamin D, induced increased transcription and protein expression of insulin receptors [23].

Table 1. Clinical characteristics of the subjects

	Total subjects (n = 128)	Non-obese (n = 74)	Obese (n = 54)	*P* value
Age (years)	25 ± 4	25 ± 3	25 ± 5	0.620
BMI (kg/m^2)	22.6 ± 4.3	19.2 ± 0.7	27.3 ± 2.3	<0.001
Waist circumference (cm)	76.4 ± 11.2	68.3 ± 4.7	87.4 ± 7.4	<0.001
Systolic BP (mmHg)	109 ± 11	104 ± 9	115 ± 11	<0.001
Diastolic BP (mmHg)	71 ± 9	68 ± 8	75 ± 9	<0.001
FPG (mg/dl)	84 ± 8	84 ± 9	85 ± 7	0.240
2-h PPG (mg/dl)	102 ± 23	96 ± 22	111 ± 21	<0.001
FPI (U/ml)	7.6 (5.8, 10.2)	7.3 (6.0, 9.0)	9.6 (5.4, 15.3)	0.005[a]
2-h PPI (U/ml)	36.6 (19.5, 68.1)	35.8 (22.3, 66.7)	38.0 (13.4, 92.4)	0.948[a]
MCR (mL/kg·min)	9.6 (8.3, 10.7)	10.6 (9.6, 11.3)	8.3 (5.4, 9.2)	<0.001[a]
HOMA-IR	1.5 (1.2, 2.2)	1.4 (1.2, 1.8)	2.1 (1.1, 3.2)	0.004[a]

Plus-minus values indicate the means ± SD.

Values before parentheses are medians, and values in parentheses are interquartile ranges.

P values were calculated with the Mann-Whitney *U* test.

P values, non-obese subjects vs obese subjects.

Non-obese: BMI < 25 kg/m^2

Obese: BMI ≧ 25 kg/m^2

BMI: Body Mass Index

BP: Blood Pressure

FPG: Fasting Plasma Glucose;

2-h PPG: 2-hour Post-Load Glucose

FPI: Fasting Plasma Insulin

2-h PPI: 2-hour Post-Load Insulin

MCR: Metabolic Clearance Rate

HOMA-IR: Homeostasis Model Assessment-Estimated Insulin Resistance

Table 2. Bone metabolism parameters of the subjects

	Total subjects (n = 128)	Non-obese (n = 74)	Obese (n = 54)	*P* value
25(OH)D (ng/ml)	16.1 (13.6, 19.0)	15.5 (12.4, 18.0)	17.0 (14.9, 22.6)	0.002
Carboxylated osteocalcin (ng/ml)	6.4 (3.7, 9.3)	5.9 (3.3, 8.5)	6.9 (4.2, 9.9)	0.186
Total osteocalcin (ng/ml)	15.9 (13.4, 18.9)	16.3 (14.0, 19.7)	15.2 (12.5, 18.5)	0.189

Values before parentheses are medians, and values in parentheses are interquartile ranges.

P values were calculated with the Mann-Whitney *U* test

P values, non-obese subjects vs obese subjects

Non-obese: BMI < 25 kg/m^2

Obese: BMI ≧ 25 kg/m^2

25(OH)D: 25-hydroxyvitamin D

Table 3. Association of bone metabolism parameters and insulin sensitivity indices

	FPG		2-h PPG		HOMA-IR		MCR	
	Standardized coefficients (beta)	*P* value	Standardized coefficients (beta)	*P* value	Standardized coefficients (beta)	*P* value	Standardized coefficients (beta)	*P* value
Age	0.160	0.097	0.160	0.086	-0.038	0.697	0.247	0.007
25(OH)D	-0.046	0.607	0.254	0.004	-0.005	0.952	-0.333	<0.001
Total osteocalcin	-0.081	0.410	-0.002	0.987	-0.096	0.331	-0.043	0.640
Carboxylated osteocalcin	0.020	0.847	0.165	0.101	0.131	0.212	0.061	0.533

FPG: Fasting Plasma Glucose

2-h PPG: 2-hour post-load glucose

HOMA-IR: The Homeostasis Model Assessment-Estimated Insulin Resistance

MCR: Metabolic Clearance Rate

25(OH)D: 25-hydroxyvitamin D

The MCR, 25(OH)D, total osteocalcin, and carboxylated osteocalcin were analyzed after log transformation.

In this study, obese women had higher levels of serum 25(OH)D. This is not consistent with the associations reported in previous studies. In the Korea Third National Health and Nutrition Examination Survey of 8,421 men and women, an inverse association between the 25(OH) D level and metabolic syndrome risk, particularly for abdominal obesity, was reported [24]. Obese individuals have low concentrations of 25(OH)D [25]. In a large cohort of 302 healthy adults in the USA, the serum 25(OH)D level was negatively correlated with the BMI and body fat mass [26]. Sequestration of vitamin D in body-fat stores and its consequent reduced bioavailability have been suggested as an explanation for this association [27].

Risk factors for hypovitaminosis D include older age, female sex, lower latitude, winter season, and darker skin pigmentation as well as factors that determine sunlight exposure, such as clothing, cultural practices, and dietary habits. In Canada, young women of Asian and African descent had lower levels of vitamin D than white Canadian women. Additionally, in Australia, Middle Eastern and Asian immigrants had lower vitamin D levels than white Australian and European women [28]. These studies indicate that ethnic differences play a role in the circulating level of serum vitamin D. The sunlight exposure time is different according to the time of year. When we adjusted the sampling time of year because the subjects in our study had a low vitamin D status, there was no effect of the difference of the sampling time on the results. Therefore, the difference in the sampling time may not affect the vitamin D levels in our study.

In general, older age has been suggested as a risk factor for vitamin D insufficiency because cutaneous synthesis of vitamin D_3 declines with age [29]. However, in Korea and Canada, vitamin D insufficiency is more prevalent among young adults than in the older population [1]. In the Korea National Health and Nutrition Examination Survey from 2008, the serum 25(OH)D level increased with age in those between 20–29 and 60–69 years of age in both sexes, and vitamin D insufficiency was most prevalent in the 20–29 age group. These observations may be due to behavioral factors, including an indoor lifestyle, sunscreen use, outdoor activity, and dietary habits [29]. It is unclear why the associations between 25(OH)D and insulin sensitivity and between 25(OH)D and obesity in this study were different from the results of previous reports. Ethnic differences and low vitamin D status in our subjects may provide an explanation for the different relationship of 25(OH)D.

Contrary to the associations seen in previous studies, the total osteocalcin levels did not differ between the obese and non-obese women in this study. As previously described in detail [30], total osteocalcin is the most abundant noncollagenous protein of the bone matrix, and it has been used as a marker of bone formation. Carboxylated Gla residues are related to calcium and hydroxyapatite binding, allowing for deposition of total osteocalcin in mineralized bone matrix. Uncarboxylated osteocalcin is more easily released into the circulation; however, both the carboxylated and uncarboxylated forms can be detected in blood.

A study in elderly Swedish men showed that the plasma total osteocalcin was a strong negative predictor of fat mass and plasma glucose [31]. Additionally, in the investigation of postmenopausal women, the serum total osteocalcin levels were shown to have a statistically significant negative- correlation with BMI [32]. Total osteocalcin was particularly inversely related to visceral obesity in Korean obese and overweight men [33]. Additionally, the relationship between vitamin D/osteocalcin and insulin sensitivity was weak in young adults [9–12].

The serum total osteocalcin level was significantly negatively correlated with FPG and Hemoglobin A1c in both men and postmenopausal women with type 2 diabetes mellitus [34,35]. Additionally, hyperglycemia influences the response of osteoblasts to parathyroid hormone and 1, 25-dihydroxyvitamin D [36]. In animal models, chronic hyperglycemia decreased total osteocalcin [37]. Circulating levels of total osteocalcin were lower in animals on a high-fat diet, with a larger reduction in those that were under-expressing the insulin receptor [38]. In some studies, the serum total osteocalcin level had no correlation with insulin sensitivity [39,40]. Of note, the total or carboxylated osteocalcin levels were not associated with insulin sensitivity indices in our study.

In nondiabetic older adults, an elevated carboxylated osteocalcin level was associated with lower insulin sensitivity [7]. However, in the present study, carboxylated osteocalcin did not differ between the obese and non-obese groups. Levels of carboxylated and uncarboxylated osteocalcin are influenced by the vitamin K status, while the total circulating concentration of osteocalcin is independent of vitamin K [30]. Factors influencing the levels of carboxylated osteocalcin, such as the vitamin K status, should be considered in explaining the relationship of carboxylated osteocalcin with obesity and insulin sensitivity. In this study, the vitamin K status was not measured. The proportion of carboxylated osteocalcin was lower than in previous studies. The difference of the standardization of methods for measuring osteocalcin, sample stability or handling, and the biological variability may affect the levels of carboxylated osteocalcin. We used an enzyme immunoassay to measure carboxylated osteocalcin; however, a two-sited immunofluorometric assay was used in a previous study [12].

With this study population being limited to young Korean women, confounding factors affecting bone metabolism according to ethnicity and age could be controlled. However, there are some limitations in this study. First, due to the small sample size, generalization of the results is difficult. Therefore, additional research is necessary to determine the patterns in other age and ethnic groups. Second, measurements of physical activity were not made in this study. Comparison of this information between the obese and non-obese groups would be helpful to further understand the mechanism behind the differences in 25(OH)D status between the two young age groups. Finally, most subjects in this study had vitamin D deficiency [defined as 25(OH)D of less than 20 ng/ml, n = 102 (80%)] or insufficiency [25(OH)D from 20 to less than 30 ng/ml, n = 21 (16%)]. Considering that the obese group had only 9% (n = 5) with a sufficient 25(OH) D level, it was difficult to analyze the relationship between 25(OH)D and obesity. Additionally, other bone turnover markers and vitamin K statuses should be considered to confirm the status of bone turnover in these vitamin D-deficient subjects. The results may reflect overall bone formation because we did not measure other bone formation markers, especially the bone resorption markers.

Conclusion

In conclusion, the levels of 25(OH)D were low in our subjects. Unlike in previous reports, a higher 25(OH)D level was negatively associated with insulin sensitivity in young Korean women, suggesting that the low vitamin D levels interfere with conclusions on the relationship between osteocalcin and metabolic parameters. Further studies on subjects of different ages and a prospective study in young women of the same age will be needed to confirm the different effects of vitamin D/osteocalcin on insulin sensitivity according to age.

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