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Original article

Body mass index and insulin resistance in healthy adults: Associations with plasma osteocalcin, phylloquinone levels, and dietary vitamin K intake

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Summary. The skeletal system is considered an endocrine organ today. Associations between bone Gla proteins, body mass index and insulin resistance are intriguing novel field due to being possible explanations for the interactions between bone and endocrine system. The aim of the present study was to investigate the associations between insulin resistance and body mass index (BMI) with plasma osteocalcin, phylloquinone levels and dietary vitamin K intakes in healthy non-obese adults. This cross-sectional study was conducted with 77 healthy non-obese adults. Anthropometric measurements and 24-hour food consumption record were taken from each individual. Blood glucose, insulin, osteocalcin (OC), undercarboxylated osteocalcin (ucOC), vitamin K levels were analyzed. The homeostasis model assessment for insulin resistance (HOMA-IR) value was calculated. Multiple linear regression models were performed using the backward method in order to determine the significant predictors of BMI and HOMA-IR. Mean age and BMI of the participants were 31.7±5.6 years and 24.6±3.04 kg/m^2 respectively. After multiple regression analysis, BMI, dietary vitamin K intake and phylloquinone were significant predictors of HOMA-IR. Furthermore, ucOC and triglyceride were significant predictors of BMI. No significant association between OC levels and HOMA-IR values were shown. In healthy non-obese adults, ucOC may be related to decreasing BMI. Our data do not support that increased OC has a beneficial role against insulin resistance. Dietary vitamin K intake may have a protective effect on insulin resistance. Further studies should examine the clinical importance of these findings.

Keywords: insulin resistance, body mass index, osteocalcin, vitamin K, phylloquinone

Introduction

The skeletal system is considered an endocrine organ (1). Osteocalcin (OC) is a bone-specific peptide, secreted by osteoblasts (2), and related to energy and glucose metabolism (3). Lee et al. have shown that OC deficient mice have higher blood glucose, higher insulin levels, impaired insulin sensitivity and elevated fat mass (3). In the circulatory system, OC is found in either a fully carboxylated (cOC) or undercarboxylated (ucOC) form (4). Previous research has focused on cOC as the biologically active form of OC involved in bone metabolism because of its high affinity for hydroxyapatite crystals (5). However, in recent years, ucOC activity has also been reported in relation to pancreatic beta cells and adiposities (6, 7). Yet, conflicting results have been shown for glucose and energy metabolism in cross-sectional human studies (6, 8-15).

Vitamin K is the general name given to compounds that have 2-methyl-1,4-naphthoquinone (16). Vitamin K1 (also known as phylloquinone) and vitamin K2 (also known as menaquinones) are forms of dietary vitamin K; dietary phylloquinone intake is the dominant source of dietary vitamin K. It is widely dis-

tributed in foods; however, the main dietary sources are dark green leafy vegetables, soy products and certain types of vegetable oils (17). In bone metabolism, vitamin K is responsible for carboxylation reactions of OC via its role as a carrier of selective glutamate residues to γ-carboxyglutamate. Therefore, plasma vitamin K level is one of the most important factors influencing levels of OC in circulation (18, 19). There are studies suggesting that vitamin K plays a role in glucose metabolism (20, 21). It is thought that vitamin K may affect glucose metabolism through its effect on OC metabolism (3, 22) or as a result of its anti-inflammatory properties (23, 24). However, the mechanism has not yet been clearly elucidated (25, 26).

The aim of the present study was to investigate the associations between 1) dietary vitamin K intake and plasma OC levels, insulin resistance, and body mass index (BMI); 2) plasma phylloquinone levels, insulin resistance and BMI; and 3) plasma OC levels, insulin resistance and BMI in healthy non-obese adults. To the best of our knowledge, this is the first cross-sectional study evaluating dietary vitamin K intake, plasma phylloquinone, OC levels, and ucOC levels together in healthy non-obese adults.

Method

All non-obese healthy adults applied to Department of Nutrition and Dietetics, met the inclusion criteria in a year period and voluntary to participate were included to the study. Eventually, the present study comprised 77 healthy individuals (39 male, 38 female) aged between 25-50 years. We included healthy non-obese individuals who could recall their dietary intake for three consecutive days. Exclusion criteria were: having a chronic disease diagnosed by a physician (diabetes mellitus, high blood pressure, cardiovascular diseases, etc), taking hormone or anticoagulant treatment, using medication that could affect bone metabolism (calcitonin, biphosphonates, etc), or taking vitamin-mineral supplements. Moreover, female participants were excluded if they were postmenopausal, pregnant, or breastfeeding. The study protocol was approved by Gazi University, Faculty of Medicine, Clinical Research Ethics Council, and written informed consent was obtained from all volunteers, prior to participation in the study.

Anthropometric measurements

Body weight (kg) and height (cm) of participants was measured according to standart protocols. Height was measured with a stadiometer while the participants were in a Frankfort plane. The body weight were taken by a bioelectrical impedance analyzer (TBF-300, Tanita Corporation, Tokyo, Japan) after at least 4 hours fasting with minimal clothing. Body mass index (BMI) was calculated according to the following formula: body weight / height^2 (kg/m^2).

Food consumption records

In order to determine daily dietary vitamin K intake, food consumption was recorded for three consecutive days, one of which was a weekend day, in order to consider the variety of food consumed weekly. Daily dietary vitamin K intake was calculated using the Nutrition Information Systems (BeBIS) program (27).

Biochemical measurements

Blood samples for biochemical measurements were taken after eight hours of fasting. Blood samples were taken by a nurse while the participant was in a seated position in a comfortable environment. Samples were centrifuged and stored at -70˚C for analysis. From frozen blood samples, fasting glucose (mg/dL), total cholesterol (mg/dL), high density lipoprotein-cholesterol (HDL-C) (mg/dL), low density lipoprotein-cholesterol (LDL-C) (mg/dL), and triglyceride (mg/dL) were measured using enzymatic spectrophotometric methods. Insulin (μIU/mL) and parathyroid hormone (PTH) (pg/mL) levels were determined with electrochemiluminescence immunoassay. Vitamin D levels were measured with liquid chromatography/tandem mass spectrometry (LC-MS/MS). OC and ucOC levels were analyzed by sandwich enzyme-linked immunosorbent assay (ELISA) using commercial kits (Cusabio®). In order to determine vitamin K

levels, plasma phylloquinone was measured by high-pressure liquid chromatography (HPLC).

In order to evaluate insulin resistance, the homeostasis model assessment for insulin resistance (HOMA-IR) value was calculated using the following formula: fasting blood glucose (mmol/L) x fasting insulin (μU/mL) / 22.5 (28).

Statistical analysis

Numeric data were analyzed using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether they were normally distributed. For normally distributed data, mean ($\bar{\chi}$) ± standard deviation (SD) was calculated, and for non-normally distributed data, median ± interquartile range (IQR) was calculated. Pearson's correlations were performed to determine the relationships between BMI, HOMA-IR, and dietary vitamin K intake and biochemical parameters. Before advanced analysis, the logarithm (log) of non-normally distributed variables was calculated in order to obtain a normal distribution. Multiple linear regression models were performed using the backward method in order to determine the significant predictors of BMI and HOMA-IR. Statistical significance levels are given between 95% confidence intervals. All the analyses were performed using Statistical Package For Social Sciences (SPSS) for Windows, version 15 software (29).

Results

Anthropometric measurements, biochemical parameters, and dietary vitamin K intake are given in Table 1. Mean age of the participants was 31.7 ± 5.6 years. Dietary vitamin K intake of participants was 262.9 ± 125.7 mcg. Blood glucose, insulin, OC, ucOC and phylloquinone levels were 86.2±8.07 mg/dL, 7.6±3.45 μIU/mL, 1.2±0.55 ng/mL, 4.2±2.1 ng/mL and 0.6±0.68 ng/mL, respectively. The mean HOMA-IR value was 1.8 ± 0.9.

The correlations between HOMA-IR, BMI, and dietary vitamin K intake and biochemical parameters are given in Table 2. HOMA-IR was positively correlated with age, BMI, glucose, insulin, total cholesterol, LDL-C, triglyceride, PTH, and phylloquinone, and negatively correlated with dietary vitamin K intake and HDL-C (see Table 2). The multiple regression model was established with HOMA-IR as the dependent variable and age, gender, BMI, vitamin K intake, phylloquinone and parathyroid hormone as the independent variables. BMI, dietary vitamin K intake and phylloquinone were significant predictors of HOMA-IR (Table 3).

BMI was positively correlated with age, glucose, insulin, HOMA-IR, total cholesterol, LDL-C, and triglyceride, and negatively correlated with HDL-C and ucOC ($p < 0.05$) (Table 2). The multiple regression analysis revealed that ucOC and log_triglyceride were significant predictors of BMI (Table 4).

Table 1. Anthropometric measurements, biochemical parameters and dietary vitamin K intakes of the individuals

Parameters	Subjects (n:77) $\bar{\chi}$±SD or median±IQR
Gender (male/female)	39/38
Age (year)	31.7±5.61
BMI (kg/m²)	24.6±3.04
Dietary vitamin K intake (mcg)	262.9±125.69
Glucose (mg/dL)	86.2±8.07
Insulin (μIU/mL)	7.6±3.45
HOMA-IR	1.5±0.77
Total cholesterol (mg/dL)	173.0±31.27
LDL-C (mg/dL)	108.6±29.13
HDL-C (mg/dL)	55.3±15.04
Triglyceride (mg/dL)	80.0±63.0
PTH (pg/mL)	41.0±12.37
Vitamin D (ng/mL)	16.4±6.55
OC (ng/mL)	1.2±0.55
ucOC (ng/mL)	4.2±2.05
Phylloquinone (ng/mL)	0.6±0.68

Bold values are normally distributed ($\bar{\chi}$±SD), and the others are not normally distributed (median±IQR)
BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, PTH: Parathyroid hormone, OC: osteocalcin, ucOC: undercarboxylated osteocalcin

Table 2. The correlations of BMI and HOMA-IR with dietary vitamin K intake and biochemical parameters in adults (n=77)

Parameters	HOMA-IR		BMI	
	Correlation coefficient[a]	p	Correlation coefficient	p
Age (years)	**0.294**	**0.009**	**0.331**[b]	**0.003**
BMI (kg/m^2)	**0.268**	**0.018**	-	-
Vitamin K intake (mcg)	**-0.247**	**0.030**	-0.124[b]	0.284
Glucose (mg/dL)	**0.527**	**<0.001**	**0.309**[b]	**0.006**
Insulin (μIU/mL)	**0.974**	**<0.001**	**0.297**[a]	**0.038**
HOMA-IR	-	-	**0.268**[a]	**0.018**
Total cholesterol (mg/dL)	**0.400**	**<0.001**	**0.259**[b]	**0.023**
LDL-C (mg/dL)	**0.403**	**<0.001**	**0.378**[b]	**0.001**
HDL-C (mg/dL)	**-0.324**	**0.004**	**-0.472**[b]	**<0.001**
Triglyceride (mg/dL)	**0.537**	**<0.001**	**0.400**[a]	**<0.001**
PTH (pg/mL)	**0.228**	**0.046**	0.036[b]	0.758
Vitamin D (ng/mL)	0.042	0.717	0.060[b]	0.599
OC (ng/mL)	0.214	0.062	0.020[b]	0.862
ucOC (ng/mL)	-0.106	0.357	**-0.302**[b]	**0.008**
Phylloquinone (ng/mL)	**0.289**	**0.011**	0.096[a]	0.404

[a] Spearman's correlation test, [b] Pearson correlation test, bold values are statistically significant (p<0.05 or p<0.001)
BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, PTH: Parathyroid hormone, OC: Osteocalcin, ucOC: Undercarboxylated osteocalcin

Table 3. Multiple linear regression analysis of the factors related with HOMA-IR (n=77)

Parameter	R^2	Variable	β	95% Cl	p
log_HOMA-IR	0.258	Constant	-	-0.484, 0.197	0.402
		BMI	0.323	0.007, 0.033	0.002
		log_phylloquinone	0.266	0.039, 0.298	0.011
		Vitamin K intake	-0.249	-0.001, 0.000	0.018

Dependent variable: log_homeostasis model assessment of insulin resistance (log_HOMA-IR), **independent variables:** Age, BMI, vitamin K intake, log_ phylloquinone, parathyroid hormone

Discussion

In the present study, associations between dietary vitamin K intake, plasma OC levels, HOMA-IR (as an indicator of insulin resistance) and BMI were investigated. We found no significant relationship between OC levels and HOMA-IR values in the present study. Several studies have found that the level of OC in circulation is related to a decrease in insulin resistance and an increase in insulin sensitivity (9, 10, 12, 13, 15, 30). However, the reports in the literature are conflicting. In one study, OC was an independent contributor to improving glycaemic control in the long term, but did not have any reducing effect on insulin resistance in Type 2 diabetes mellitus (DM) (31). In another study low plasma OC levels did not predict the development of diabetes after three years of follow-up (32). Furthermore, Aoki et al. found that the level of OC in circulation was increased in individuals with impaired glucose intolerance compared to individuals with normal glucose tolerance (14).

One possible reason for the variability between the current study and previous reports is that healthy non-obese adults were investigated in the present study. In most studies where OC was found to be inversely associated with HOMA-IR, obese participants were included. For this reason, we suggest that the effect of OC on HOMA-IR seems to be mediated by adipose

Table 4. Multiple linear regression analysis of the factors related to BMI (n=77)

Parameter	R^2	Variable	β	95% Cl	p
BMI	0.250	Constant	-	10.146, 21.384	0.000
		log_triglyceride	0.401	2.728, 8.233	0.000
		ucOC	-0.270	-0.697, -0.102	0.009

Dependent variable: Body mass index (BMI), independent variables: Age, log_homeostasis model assessment of insulin resistance (log_HOMA-IR), log_triglyceride, undercarboxylated osteocalcin (ucOC)

tissue hormones such as adiponectin and leptin. It is known that leptin mRNA is increased in obese individuals, and plasma leptin levels are higher in obese than non-obese individuals (33, 34). Moreover, studies have shown that leptin levels are associated with insulin resistance, and HOMA-IR values increase as plasma leptin levels increase (35, 36). Decreases in circulating adiponectin levels have been shown to result in decreased insulin sensitivity and increased insulin resistance (37). In a study of individuals of different ethnicities with and without metabolic syndrome, plasma OC levels were shown to be positively associated with leptin levels and negatively with adiponectin levels (38). Therefore, future studies will benefit from the examination of leptin and adiponectin levels in order to understand the exact mechanisms involved in normal and overweight healthy adult populations.

In the present study, we found that as plasma phylloquinone levels increase, insulin resistance increases. Furthermore, plasma phylloquinone levels were found to be a significant predictor of insulin resistance. As previously mentioned, vitamin K is an indicator of the degree of carboxylation (39). Therefore, an increase in plasma phylloquinone levels is related to increased plasma OC levels (19). Although, a significant positive association was found between plasma phylloquinone levels and OC (data are not shown), as we expected, OC was not found as a predictor of plasma phylloquinone levels in the current study (data not shown). Furthermore, there was no significant association between OC and HOMA-IR in the current study. Studies have shown that there are numerous other determinants of blood phylloquinone levels (40). Given the fact that triglyceride-rich lipoproteins serve as carries of phylloquinone in the blood circulation, positive associations behind the phylloquinone levels and HOMA-IR can be explained that it is mediated by triglyceride levels rather than bone metabolism.

Elevated dietary vitamin K intake was a significant predictor of decreased insulin resistance in the present study. Vitamin K intake has a role in the acute insulin response (20, 41) and is related to insulin sensitivity and Type 2 DM (25, 26). Furthermore, a beneficial role of phylloquinone in glucose homeostasis was shown in men and women (26). In another study, high vitamin K intake was related to a decrease in the risk of developing Type 2 DM after a 10.3 year follow up (25). Recently, vitamin K intake or supplementation was investigated in detail, and the authors suggested that it could be a novel therapy to improve glucose metabolism (42). It has been suggested that the mechanism behind the impact of vitamin K intake on glucose metabolism is either through OC metabolism (3, 22) or through its anti-inflammatory effects (43, 44). However, in the present study, dietary vitamin K intake was not associated with plasma OC levels. For this reason, as previous studies have suggested, anti-inflammatory effects of vitamin K might have contributed to this finding (22, 44), or increased dietary vitamin K intake could be a demonstration of a healthy dietary pattern, given that vitamin K rich foods include dark green leafy vegetables; however, we could not investigate these possibilities in the present study.

Another significant finding of the present study was that increased plasma ucOC levels were related to reduced BMI. Multiple regression analysis revealed that ucOC was a significant negative predictor of BMI, along with triglyceride (a positive predictor). ucOC is a known regulator of energy metabolism in mice (3); our results suggest that ucOC may be related to energy metabolism in humans too. However, the results of human studies in the literature are contradictory (6-8, 11). Several clinical studies have suggested that ucOC levels are negatively associated with obesity in humans (6, 7). In male participants, plasma ucOC levels were shown to be negatively correlated

with BMI, body fat percentage and subcutaneous fat area, and body fat percentages were found to reduce as plasma ucOC levels increased in female participants (6). Overweight and obese patients have been shown to have lower plasma ucOC levels, and two types of OC can be released from both omental adipose tissue and sub-surface skin *in vitro* (7). However, there are other studies suggesting that plasma ucOC levels are not associated with BMI (8, 11). Recently, weight and body fat loss were not found to be associated with OC types under vitamin D and vitamin K supplementation (8).

There is a number of limitations in our study. First, we could not determine causality because of the cross-sectional nature of the study. Furthermore, the sample size was small. Although, we included healthy non-obese adults in our study, vitamin D levels of participants were mostly deficient. This situation is expected because vitamin D deficiency is very common in our country. In The Turkish Diabetes, Hypertension, Obesity and Endocrine Disease Survey (TURDEP-II) (n = 9560), 93% of adults in Turkey were found to have vitamin D deficiency (≤20 ng/ml) (45). Vitamin D is a determinant of OC expression (4), and correction of vitamin D deficiency has been shown to improve insulin sensitivity, but not to alter plasma OC levels (46). Yet, other studies have suggested that correction of vitamin D levels does not improve insulin secretion and sensitivity after 12 weeks ergocalciferol supplementation (47) and that vitamin D supplementation does not have any effect on insulin resistance (48). Therefore, we think our study is an important contribution given that we investigate a sample that comprises participants with vitamin D deficiency, which is a common situation in our society.

Beyond limitations, in this study we investigated healthy non-obese individuals and, to the best of our knowledge, this is the first assessment to evaluate plasma OC, ucOC, phylloquinone levels, and dietary vitamin K intake together. Most available studies do not take into consideration the effect of dietary vitamin K intake on BMI and glucose metabolism.

In conclusion, our results suggest that ucOC may be related to decreased BMI in healthy non-obese adults. Our data do not support the contention that increased OC has a beneficial role against insulin resistance. Because of the presence of other factors affecting plasma phylloquinone levels, plasma phylloquinone levels do not appear to be an improving marker for insulin resistance. However, dietary vitamin K intake may have a protective effect on insulin resistance. Further studies should examine the underlying mechanisms and clinical importance of these findings.

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