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Metabolic Syndrome is More Common in Patients with 25 Hydroxy Vitamin D Levels Less than 10 ng/ml

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Abstract

The best known role of the vitamin D - parathyroid hormone (PTH) axis is to provide extracellular calcium homeostasis. Besides the classical functions of PTH and vitamin D, those hormones have been suggested to play important roles in the insulin resistance and synthesis, obesity, diabetes, and hypertension. The aim of this study was to investigate the association of vitamin D deficiency with metabolic syndrome frequency.

Methods: One hundred and two nonsmokers, premenopausal women aged more than 18 years old were recruited in this cross-sectional, observational study. Subjects were categorized into three groups according to their 25 hyroxyvitamin D levels. Categories were defined as "Vitamin D deficiency" (Group 1-Vitamin D level ≤ 10 ng/mL, n=32, mean age: 34,46 ± 6,77 years), as "Vitamin D insufficiency" (Group 2-Vitamin D level between 10,1-30 ng/mL, n=31, mean age: 32,32 ± 6,66 years) and as "Normal" (Group 3-Vitamin D level ≥ 30 ng/mL, n=39, mean age: 31,64 ± 5,34 years). Metabolic syndrome was determined by the definition of International Diabetes Federation.

Keywords: Hypovitaminosis D; Metabolic syndrome; Abdominal obesity; Disglycemia; Dislipidemia

Introduction

The best known role of the vitamin D-parathyroid hormone axis is to provide extracellular calcium homeostasis [1]. By the help of ultraviolet B (UVB) radiation, and less dietary supplements, vitamin D increases the intestinal absorption of calcium. Vitamin D is firstly converted to 25-hydroxy vitamin D (25(OH)D), which is the main indicator of the vitamin D status, and then to the active form of the vitamin D as 1,25-dihydroxy vitamin D ($25(OH)_2D$) [1].

Parathormon (PTH) regulates the metabolism of calcium by increasing 1,25(OH)2D formation and calcium reabsorbation in the kidney, and also calcium resorption in the bone. The effects of hypovitaminosis D are considered to be related to the decrease in intracellular calcium, and various target genes (for example, reduction in insulin secretion due to the decrease of the calcium deposits in islet cells [2], and reduction in renin gene expression and suppression [3], etc.). Besides the classical functions of PTH and vitamin D, those hormones play important roles in the development of metabolic syndrome, insulin resistance and synthesis [4,5], obesity [6], diabetes [7-9], and hypertension [10,11]. The reduction in 25 hydroxyvitamin D levels, and decreased consumption of daily milk and milk products were found as risk factors for metabolic syndrome [4,12,13]. In several studies, serum 25(OH)D levels in type 2 diabetics were found to be lower than those without diabetes [14]. Moreover, those without diabetes, but with high risk for diabetes have also significant differences compared to healthy controls [15]. The purpose of this study was to investigate the association of vitamin D deficiency with metabolic syndrome frequency.

Materials and Methods

Patients and control group

One hundred and two nonsmokers, premenopausal women aged more than 18 years old were recruited in the study at the Endocrinology and Internal Medicine outpatient clinics of Goztepe Training and Research Hospital between November 2008 and April 2009. Subjects were categorised into three groups according to their 25 hyroxyvitamin D levels. Categories were defined as “Vitamin D deficiency” (Group 1-Vitamin D level ≤ 10 ng/mL, n=32, mean age: 34,46 ± 6,77 years), as “Vitamin D insufficiency” (Group 2-Vitamin D level between 10,1-30 ng/mL, n=31, mean age: 32,32 ± 6,66 years) and as “Normal” (Group 3-Vitamin D level ≥ 30 ng/mL, n=39, mean age: 31,64 ± 5,34 years) [16]. Subjects with renal and hepatic insufficiency, metabolic bone disease, thyroid disorders, malignancy, gluten enteropathy, primer hyperparathyroidism, congestive heart failure, subjects on the treatment with supplemental calcium, vitamin D, anticonvulsant, hormone replacement, steroid, oral contraceptive, thiazide diuretic, betablocker, statin, and fibrate therapy, pregnant, and breast feeding women, and who are currently involved in a weight loss program were excluded from the study. Metabolic syndrome was determined by the definition of International Diabetes Federation (IDF) [17].

All the subjects were questioned about their normal physical activity and if they do exercise, they were also questioned about how often they exercise regularly. Regular exercise was defined as minimum 45 minutes walking, at least 4 days a week or its calorie equivalent [18].

Local Ethics Committee approval was obtained for the research (Date: 21.02.2008, Decision No: 44/E). Written informed consent was taken from all participants according to 1964 Helsinki Declaration.

Data collection

Clinical data and biochemical parameters (Fasting plasma glucose, triglyceride, HDL, LDL, parathormon, calcium, albumin, TSH and free T4) performed in the last week before the onset of the study were collected from the files of the subjetcs. Physical examination was

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performed by the same physician. During the physical examination, height (cm), weight (cm), waist and hip circumferences (cm) of the subjects were measured. BMI was calculated. Waist circumferences were measured at the plane between anterior superior iliac spines and lower costal margines at the narrowest part of the waistline while subjects were standing during slight expiration.

Subjects accepted to participate in the study were invited to the clinic in the next morning after 12 hour fasting duration. For measuring 25 (OH)D, venous blood samples were collected into plain tubes, and serum was separated and stored at -70°C until analysis for a week. Levels of 25 (OH)D were estimated using a kit 25 (OH)D-Ria-CT (Bruxelles-Belgium). The treated samples were then assayed using a competitive binding radioimmunuassay (RIA) technique.

Statistical analysis

All statistical analyses were made by using the software SPSS for Windows V13.0. Normality of distribution of variables was tested by Shapiro-Wilk and Kolmogorov-Smirnov tests. Subjects were compared for differences in anthropometric and biochemical data by two tailed Mann-Whitney U or Student's *t* test. Kruskal-Wallis test or Oneway ANOVA was performed for comparison of two or more independent samples. Correlation between variables were determined by Pearson correlation test or Spearman's Rho. Data are expressed as means ± SD. A *p* value below 0.05 (two tailed) was considered to be statistically significant.

Results

One hundred and two premenaposal women were recruited in the study between November 2008-April 2009. Age were similar among three groups (p=0.085). Anthropometric measurements of three groups can be seen on table 1.

Frequency of metabolic syndrome in vitamin D deficiency group was significantly more than that of the other groups (p=0.028; Figure 1). Number of metabolic syndrome criteria in Group 1 was more than that of Group 3 (p<0.0001; Table 2). Vitamin D level was negatively correlated with waist circumference, BMI, triglyceride and fasting plasma glucose, and positively correlated with HDL (r=-0.463, p<0.0001; r=-0.505, p<0.0001; r=-0.292, p=0.0028; r=-0.258, p=0.009; r=0.243, p=0.014, respectively; Figure 2). Among subjects without metabolic syndrome, vitamin D level in the group with more criteria was less than the other groups (p<0.0001; Table 3). Even we have taken only the subjects with waist circumference less than 88 cm, metabolic syndrome frequency in vitamin D deficiency group (n=4) was more than the other groups (p=0.001). Waist circumference was also greater in the vitamin D deficieny group (p<0.0001; Table 4).

		Group 1 (n=32)	Group 2 (n=31)	Group3 (n=39)	p
Age	year	34,47 ± 6,77	32,32 ± 6,68	31,64 ± 5,34	0,085
Systolic blood pressure	mmHg	114,44 ± 15,53	109,67 ± 12,64	116,79 ± 9,12	0,18
Diastolic blood pressure	mmHg	76,30 ± 9,26	71,67 ± 7,86	74,29 ± 4,75	0,14
Waist circumference	cm	89 ± 10,59	88,03 ± 12,69	74,72 ± 10,58	<0,0001
Weight	kg	71,72 ± 12,49	73,87 ± 14,71	57,22 ± 10	<0,0001
Hip circumference	cm	108,53 ± 8,74	108,05 ± 10,59	98 ± 7,07	<0,0001
BMI	kg/m²	28,51 ± 5,66	28,30 ± 5,76	21,92 ± 3,73	<0,0001

Group 1: "Vitamin D deficiency" (Vitamin D level ≤ 10 ng/mL); Group 2: "Vitamin D insufficiency" (Vitamin D level between 10,1-30 ng/mL); Group 3: "Normal" (Vitamin D level ≥ 30 ng/mL); BMI: Body Mass İndex

Table 1: Demographic and anthropometric values of three groups.

Conclusion

It was found that increased frequency of metabolic syndrome was associated with vitamin D deficiency independent of hyperparathyroidism. As a result, vitamin D deficiency may be an independent risk factor for metabolic syndrome.

Discussion

It was shown in this study that metabolic syndrome frequency was increasing with vitamin D deficiency. Moreover, vitamin D level was

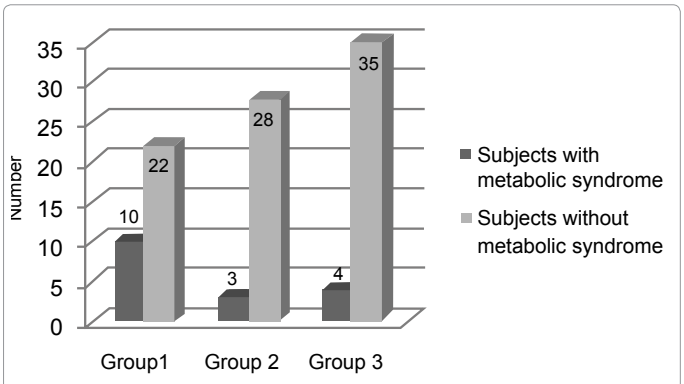

Figure 1: Metabolic syndrome frequency in three groups.

Criteria number		Vitamin D groups		
		Group 1	Group2	Group3
0	n (%)	5 (15,63)	7 (22,58)	22 (56,41)
1	n (%)	7 (21,88)	12 (38,71)	13 (33,33)
2	n (%)	10 (31,25)	9 (29,03)	0
3	n (%)	9 (28,13)	3 (9,68)	3 (7,69)
5	n (%)	1 (3,13)	0	1 (2,56)

Group 1: "Vitamin D deficiency" (Vitamin D level ≤ 10 ng/mL); Group 2: "Vitamin D insufficiency" (Vitamin D level between 10,1-30 ng/mL); Group 3: "Normal" (Vitamin D level ≥ 30 ng/mL)

Table 2: Criteria number of metabolic syndrome among three groups.

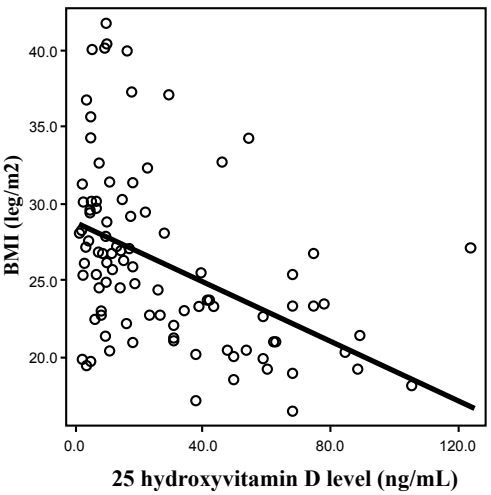

Figure 2: Correlation of vitamin D with BMI.

	Criteria number			
	0	1	2	p
Vitamin D level (ng/ml) ± SD	42,51 ± 29,08	32,59 ± 29,49	10,9 ± 6,4	<0,0001

Table 3: Vitamin D levels of patients without metabolic syndrome according to the presence of metabolic syndrome criteria number.

	n	Ortalama ± SD
Group 1	14	79,8 ± 6,0
Group 2	16	77,6 ± 4,3
Group 3	34	71,6 ± 6,1

Group 1: "Vitamin D deficiency" (Vitamin D level ≤ 10 ng/mL); Group 2: "Vitamin D insufficiency" (Vitamin D level between 10,1-30 ng/mL); Group 3: "Normal" (Vitamin D level ≥ 30 ng/mL)

Table 4: Mean waist circumferences of the patients with waist circumference less than 88 cm.

negatively correlated with waist circumference, BMI, triglyceride and fasting plasma glucose and positively correlated with HDL.

Low levels of vitamin D are affecting the cellular functions negatively in most tissues. In that manner, pancreas is one of those tissues. Vitamin D deficiency may deteroriate the effect of insulin on adipose tissue. In a study of Reis et al., vitamin D deficiency was found to be related to abdominal obesity, metabolic syndrome, insulin resistance and type 2 diabetes [19]. Various mechanisms are responsible from this associaton. First, anormal calcium metabolism is related with weight gain [20]. Increase in intracellular calcium was shown to activate lipogenesis and to inhibit lipolysis [21]. Increased levels of intracellular calcium leads to accumulation of triglyceride in adipocytes and activation of lipogenesis and obesity. High calcium intake was investigated in the study of Zemel et al. according to this hypothesis and it was found that obesity risk is decreasing with high calcium intake in mice [20]. Other mechanisms related to that is associated with TNF-α (Tumor necrosis factor) interferon (IFN)- γ, and expression of adipocyte uncoupling protein 2 (UCP-2). Vitamin D decreases production of important cytokines in lipogenesis and lipolysis such as IFN - γ which has been determined to regulate fat inflammation, and TNF-α which has been determined to promote lipogenesis and induce lipolysis in mice. Moreover, 1, 25(OH)2D has been reported to inhibit the expression of UCP-2 which can stimulate lipogenesis and inhibit lipolysis [22]. In a study of Konradsen et al. conducted with 2187 patients, BMI was negatively correlated with 25(OH)D and 1,25(OH)D levels [23]. As similar with the results of Rodriguez et al. [24], BMI was negatively correlated with 25(OH)D in our study.

The relationship of abdominal obesity and vitamin D deficiency is well known, so it should not be the only aspect for metabolic syndrome. The number of patients without metabolic syndrome having 3 criteria of metabolic syndrome other than waist circumference according to IDF was more in vitamin D deficiency group in our study. It may prove that vitamin D deficiency is not only related to abdominal obesity but also with the other components of metabolic syndrome such as dyslipidemia and abnormal glucose metabolism. Chiu et al. also found that frequencies of metabolic syndrome and insulin resistance are more in hypovitaminosis D [4].

Serum parathyroid concentrations have an important role in the mechanism of insulin resistance. Lee et al. shown that vitamin D levels are negatively correlated with metabolic syndrome frequency independent of serum parathyroid levels [25]. Hyperparathyriodism secondary to decrease in serum 25(OH)D levels was thought to be the main mechanism causing insulin resistance [26]. In a study conucted with 1017 morbid obese, Caucasian, male and female subjects, parathormone levels were found to be the only predictor of metabolic syndrome rather than vitamin D levels [27]. However, there are some studies showing that metabolic syndrome development is decreasing with high calcium and vitamin D intake [28].

As an interesting, important and different finding from the other studies, we found that the parathormone and calcium levels were similar in three groups in our study, even the frequency of metabolic syndrome was higher in vitamin D deficiency group. Therefore we suggest that vitamin D deficiency may be associated with metabolic syndrome independent of hyperparathyroidism. Having no significant differences among serum parathormone levels of vitamin D sufficient, insufficient and deficient subjects can be explained by blunted parathyroid hormone response to vitamin D deficiency by hypomagnesemia, which means that parathyroid hormone levels are often normal when 25-hydroxyvitamin D level falls below 20 ng/ml [29]. However, we did not determine serum magnesium levels of the subjects and this was the weakness of our study. The strong side of our study was that all conditions affecting weight gain, waist circumference, serum lipid, calcium and vitamin D levels were excluded and our findings were independent of hyperparathyroidism which is one of the reasons for obesity and lipogenesis. However, we should be careful while applying the result on the whole population.

Increasead frequency of metabolic syndrome was associated with vitamin D deficiency independent of hyperparathyroidism in our study. Therefore, we suggest that vitamin D deficiency may be an independent risk factor for metabolic syndrome. Vitamin D administration especially at winter time to vitamin D deficient people with metabolic syndrome is a subject worth investigating especially for the countries like ours whose food products are not supplemented with vitamin D.

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