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VITAMIN D STATUS AND ITS ASSOCIATION WITH FAT TISSUE AND ADIPOKINE CONCENTRATION IN REPRODUCTIVE AGE WOMEN

KARONOVA T. L.[1], BELYAEVA O. D.[2], BYSTROVA A. A.[3], BUDANOVA M.V.[4] & GRINEVA E.N.[5]

[1,2,3,4,5]Federal North-West Medical Research Centre, St. Petersburg, Russia

[1,2,3]Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia

ABSTRACT

Recent studies have suggested an association between obesity and low serum 25-hydroxyvitamin D (25(OH)D) level but the underlying mechanisms of this interlink are still unknown.

Design and Methods

We examined 460 healthy women of reproductive age resident in North-West Russia. Serum 25(OH)D was analyzed by chemiluminiscentic method. Adipokines and parathyroid hormone (iPTH) concentrations were measured by ELISA. The amount and distribution of fat was assessed by Dual-energy X-ray absorptiometry with software for «total body scan».

Results

Vitamin D deficiency was revealed in 61.3% of participants. Serum 25(OH)D level inversely correlated with body weight, waist circumference, body mass index and amount of fat. Women with vitamin D deficiency had higher risk of obesity compared to women with normal Vitamin D status (OR 2.25 [1.05-4.85]; CI95%). Both leptin and adiponectin levels correlated with fat amount. No association between serum 25(OH)D level and adipokines concentration was found.

Conclusions

Our study showed close association between vitamin D deficiency and obesity, both conditions being very common in reproductive age women residents of North-West Russia.

KEYWORDS: Adiponectin, Leptin, Obesity, Vitamin D Deficiency

INTRODUCTION

Increasing attention has been recently paid on the common association between obesity and vitamin D deficiency. Obesity prevalence has achieved an epidemic rate and, according to the World Health Organization data, the number of overweight patients is continuously growing [1]. It has been demonstrated that obese patients often have low levels of vitamin D [2-6,7]; thus vitamin D deficiency is supposed to contribute to fat accumulation [8,9,10-13]. Therefore, a close association between low vitamin D level and fat accumulation seems quite evident though the cause-and-effect relations are still to be investigated. Given the lack of data concerning Russian population, this problem has become extremely relevant in Russia.

Thus, the objective of our study was the assessment of serum 25(OH)D levels in relation to the quantity and distribution of fat as well as to adipokine levels in healthy women of reproductive age resident in Saint Petersburg.

DESIGN AND METHODS

The study was carried out at Almazov Federal Heart, Blood and Endocrinology Centre and Pavlov Saint Petersburg State Medical University, Department of Internal Diseases №1 during the period from 2009 until 2012. We enrolled women of reproductive age who signed an informed consent, without clinically significant pathology of liver, kidney, and gastrointestinal tract that could adversely affect metabolism of vitamin D. Exclusion criteria were the following: regular insolation, intake of the drugs containing calcium and/or vitamin D. Study period lasted from September to May excluding summer time.

Anthropometric examination included height, weight, waist circumference (WC) measurement by standard methods, body mass index (BMI) calculation by the A. Quetelet's formula: weight/height^2 (kg/m^2). The body mass was considered normal if BMI was 18.5-24.9 kg/m^2, overweight – if BMI was 25-29.9 kg/^{2}, obesity was diagnosed when BMI was ≥30 kg/m^2. Abdominal obesity was diagnosed according to the Guidelines of International Diabetes Federation [14], if WC was >80 cm; the latter was measured at the midpoint between the lower rib margin and the iliac crest (parallel to the floor).

Dual-energy X-ray absorptiometry with the use of the software for «total body scan» (GE Lunar Prodigy DXA, USA) was performed in 190 subjects to assess the amount and distribution of fat [15]. Based on the parameters of total adipose tissue volume fat mass index (FMI) was calculated [16].

The serum 25(OH)D level was measured by chemiluminiscentic method on AbbottArchitect 8000, USA) with Abbot reagents (USA). According to the Endocrine Society (2011) criteria the normal vitamin D level is considered serum 25(OH)D≥75 nmol/l, lack of vitamin D is considered when the 25(OH)D level is from 50 to 75 nmol/l; values 25(OH)D below 50 nmol/l indicate vitamin D deficiency [17]. However, the use of these thresholds might result in the overdiagnosis of vitamin D deficient states. Therefore, considering the low vitamin D level (>50 nmol/l) that is sufficient for the majority of its effects to be apparent, the criteria and the thresholds require to be revised. According to the recommendations of the Institute of Medicine (IOM, 2011), the serum level of 25(OH)D≥50 nmol/l can be considered normal, the levels <30 nmol/l are regarded as vitamin deficient, and the values ranging from 30 to 50 nmol/l indicate the lack of vitamin D [18].

Serum parathyroid hormone (iPTH) level was detected using ELISA (Access) and commercial immunoassay kits (Beckman Coulter, USA).

Adiponectin and leptin levels were measured by ELISA with the use of ImmunoChem-2100 device and reagents (DRG Diagnostics, Germany).

The data are presented as the ratio percent or as Mean±standard error. For statistical analysis STATISTICA version 9.0 for Windows was used. Non-parametric statistics, χ^2-test were applied to compare frequencies of qualitative variables. Quantitative variables were analyzed by ANOVA. The Pearson correlation analysis was applied to find the associations between studied variables.

RESULTS AND DISCUSSIONS

In total, 460 females were enrolled in the study, aged from 30 to 52 years, mean age was 43.4±0.3 years. The characteristics of the participants are presented in Table 1.

Table 1: Characteristics of Women with Different Body Mass Index

Parameters	All Study Population (N=460)	Women With BMI<25 Kg/M² (N=101) 1	Women With BMI 25-29.9 Kg/M² (N=134) 2	Women With BMI>30 Kg/M² (N=225) 3	P
Age, years	43.42 ±0.3	42.7±0.9	44.3±0.6	44.5±0.5	>0.05
Weight, kg	77.7±.06	60.9±0.7	73.6±0.6	93.9±0.9	$p_{1-2,1-3}$ <0.001
BMI, kg/m²	28.7±0.2	22.3±0.2	27.3±0.1	34.9±0.3	$p_{1-2,1-3}$ <0.01
FMI, kg/m²	12.5±0.3	10.1±0.5	11.9±0.4	14.3±0.4	p_{1-2} <0.01 p_{1-3}<0.001
WC, cm	90.4±0.6	81.4±1.3	90.3±0.9	101.1±0.8	$p_{1-2,1-3}$ <0.001
HC, cm	108.2±0.5	99.8±1.3	107.9±0.8	116.2±0.7	$p_{1-2,1-3}$ <0.001
Adipose tissue amount, kg	33.9±0.8	27.4±1.6	32.2±1.2	38.7±1.2	p_{1-2} <0.01 p_{1-3}<0.001
Fat amount, %	42.2±0.5	38.1±1.1	41.9±0.7	44.7±0.6	p_{1-2} <0.01 p_{1-3}<0.001
% abdominal fat	43.6±0.6	37.9±1.4	43.8±0.8	46.7±0.7	$p_{1-2,1-3}$ <0.01
25(OH)D, nmol/l	48.5±0.9	52.5±2.8	48.7±2.2	44.8±2.0	p_{1-3}<0.05
iPTH, pg/ml	42.0± 1.2	39.4±2.1	44.8±2.7	42.1±2.1	>0.05
Adiponectine, μg/ml	20.7±0.8	21.6±1.5	21.5±1.4	19.8±1.3	>0.05
Leptin, ng/ml	48.6±1.9	33.4±3.4	43.1±2.8	56.7±2.6	p_{1-2} <0.05 p_{1-3}<0.001

Depending on the BMI values all subjects were divided into 3 groups: with normal body mass (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥30.0 kg/m^2). One hundred-one (22%) females had normal weight, 359 (78%) were either overweight or obese. Abdominal type of obesity with WC >80 cm was diagnosed in 300 participants (83.6%). Dual-energy X-ray absorptiometry confirmed both overweight/obesity in 87.7% females and android type of fat distribution. ROC-analysis showed a positive correlation between BMI and FMI (R_γ=+0.98).

Serum 25(OH)D level varied from 6.2 to 134.0 nmol/l, mean values were 48.5±0.9 nmol/l. The lack of vitamin D or its deficiency was found in 417 (90.6%) females, if the serum 25(OH)D level ≥75 nmol/l is considered normal, and only 43 (9.4%) subjects had it. Applying the IOM criteria, we found normal 25(OH)D levels ≥50 nmol/l in 178 (38.7%) females, the lack of vitamin D – in 238 (51.7%), and its deficiency – in 44 (9.6%) subjects. Thus, 29.3% females had normal levels of vitamin D instead of its deficiency according to the last recommendations. The detailed characteristics are shown in Table 2. It should be stated that the 25(OH)D levels did not differ significantly by season: 48.4±2.4 nmol/l in autumn, 47.1±1.8 nmol/l in winter and 49.9±2.3 nmol/l in spring (p>0.05).

Table 2: Characteristics of Women with Different Serum 25(OH)D Level

Parameters	All Study Population (N=460)	Normal 25(OH)D (N=178)1	Viatamin D Insufficiency (N=238) 2	Vitamin D Deficiency (N=44) 3	P
Age, years	43.42 ±0.3	42.9±0.5	44.3±0.4	43.2±1.2	>0.05
Weight, kg	77.7±.06	72.7±1.2	75.2±1.1	77.7±2.81	$p_{1-2,1-3}$<0.05
BMI, kg/m²	28.7±0.2	27.8±0.4	28.0±0.4	28.5±1.0	$p_{1-2,1-3}$<0.05
FMI, kg/m²	12.5±0.3	12.1±0.4	12.7±0.4	13.2±1.3	>0.05
WC, cm	86.1±1.1	81.4±1.3	88.1±0.9	90.9±2.6	>0.05
HC, cm	108.2±0.5	105.5±0.8	106.4±0.7	108.8±1.8	p_{1-3}<0.05
Adipose tissue amount, kg	33.9±0.8	32.8±1.3	34.3±1.2	36.2±3.3	>0.05
Fat amount, %	42.2±0.5	41.1±0.7	42.9±0.7	44.7±0.6	p_{1-2}<0.05
% abdominal fat	43.6±0.6	42.8±0.8	44.1±0.9	44.1±0.7	>0.05

Table 2: Contd.,

25(OH)D, nmol/l	48.5±0.9	67.2±1.3	39.2±0.4	18.2±0.9	p_{1-2} <0.001 p_{1-3}<0.001
iPTH, pg/ml	42.0± 1.2	42.3±2.1	44.1±1.9	32.6±0.3	>0.05
Adiponectine, μg/ml	20.7±0.8	20.8±1.3	20.5±2.0	17.6±3.1	>0.05
Leptin, ng/ml	48.6±1.9	40.9±3.9	44.8±3.5	34.4±4.7	p_{1-2}<0.05

When correlated to the anthropometry and absorptiometry parameters serum 25(OH)D level was higher in women with normal BMI than those with overweight and obesity (52.5±2.8 and 44.8±2.0 nMol/L, p<0.05). Analysis showed a negative correlation between 25(OH)D and BMI (r=-0.35, p<0.01). Moreover, 25(OH)D was negatively associated with waist circumference (r=-0.12, p<0.05), body mass (r=-0.14, p<0.05), and fat amount (r=-0.14, p<0.05). We found that vitamin D deficiency was higher in abdominal obese population than with normal BMI and WC parameters (χ^2=6.80, p<0,01). The risk of obesity, in particular the higher degrees, was higher in both females with serum 25(OH)D level <50 nmol/l (OR 2.25[1.05-4.85]; CI95%) and in subjects with 25(OH)D serum level <75 nmol/l (OR 1.86[0.88-3.95]; CI95%), compared to the women with 25(OH)D level exceeding the threshold of 75 nmol/l.

Serum iPTH was within normal range in all study population, mean values were 42.0±1.2 pg/ml. However, it tended to increase in subjects with the low 25(OH)D level. In the whole sample there was no correlation between these parameters (r=0.35, p=0.30), although a weak negative association between iPTH and 25(OH)D was found in a obese women (r=-0.2, p=0.08). Serum iPTH concentration positively correlated with waist circumference (r=0.31, p=0.04), and FMI (r=0.34, p=0.04), suggesting that the higher the level of iPTH, the higher the fat amount.

Leptin and adiponectin levels were associated with the body mass that corresponds to the data from other studies [19-22]. Thus, leptin positively correlated to body mass (r=0.36, p<0.001), BMI (r=0.37, p<0.001) and fat amount (r=0.43, p<0.001). At the same time fat amount negatively correlated to adiponectin level (r=-0.26, p=0.008). There was no significant correlation between adiponectin, leptin concentrations and serum 25(OH)D level.

We secondary examined 40 women after 3 month of diet and physical activity. 26 subjects (65%) lost more than 5% of previously body mass and 14 person (35%) lost up to 5%. Serum 25(OH)D level in women with significant weight losing became higher (from 55.2±2.8 to 66.7±3.3 nmol/l, p<0.01). This changing in 25(OH)D level in women with stable body mass did not find.

Obesity, and in particularly, its abdominal type, is known to play an important role in the development of type 2 diabetes mellitus, arterial hypertension, and atherogenic dyslipidemia [23, 24]. At the same time the causal effects and relations between vitamin D and obesity are not fully understood. Several pathways link obesity and the lack of vitamin D. First of all, sedentary lifestyle affects the synthesis of pre-vitamin D in the skin – cholecalciferol [25]. However, most of the scientists agree that the main effects are associated with the accumulation and storage of 25(OH)D in adipose tissue leading to the decrease of serum circulating vitamin D and enhanced catabolism of its metabolite calcidiol in the adipose tissue converting it to the inactive form of 24,25-dihydroxyvitamin D [26, 27]. Non-alcoholic fatty liver disease should be also considered as a possible cause in obese patients. There are some data proving that 25(OH)D level is negatively associated with the severity of liver steatosis, fibrosis and inflammation [28]. Adipose tissue is now considered to be an active endocrine organ releasing a variety of adipokines, including leptin [19-22]. Leptin regulates several stages of vitamin D synthesis. It is known to affect negatively the activity of 1-alpha-hydroxilase in kidney, peripheral tissues, including adipose tissue, resulting in reduced concentration of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) that is an active

metabolite of vitamin D [29-32].

At the same time, the concept of obesity developing secondarily to vitamin D deficiency is also known and it is caused by the presence of vitamin D receptors in adipocytes. Being a steroid, $1,25(OH)_2D$ binds its specific nuclear receptors activating them and acting as a transcription factor, thus widely controlling gene expression and regulating lipogenesis, lipolysis and adipogenesis [8,11,12,13,29,30]. Therefore, vitamin D deficiency state is associated with the coexistence of lipogenesis stimulation and lipolysis reduction that contributes to fat accumulation.

In conclusion, our study showed that obesity and vitamin D deficiency are very common and closely interrelated in females of reproductive age.

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