



OCCURRENCE OF VITAMIN 25(OH)D₃ INSUFFICIENCY IN YOUNG WOMEN WITH METABOLIC SYNDROME

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Abstract

Vitamin D insufficiency is prevalent and may be associated with higher risk for metabolic syndrome. Low serum 25-hydroxyvitamin D₃ is known to perturb cellular function in many tissues, including the endocrine pancreas, which are involved in the pathogenesis of obesity and type 2 diabetes.

This study examined the vitamin 25(OH)D₃ concentration and its relationship with the metabolic syndrome among 52 young women aged 20-40 yrs with overweight and obese. As defined by revised International Diabetes Federation (IDF 2005) criteria, 27 of the 52 women had the metabolic syndrome (52%). Women with MS had significantly lower mean concentration of vitamin 25(OH)D₃. Vitamin D insufficiency was more prevalent in women with MS, compared with those who did not fulfill the criteria for this syndrome (63% vs 37%, respectively) as well as among women with metabolic syndrome mild deficiency occurred much more frequently than in without MS (58% vs 26%, respectively). When serum concentrations of 25(OH)D₃ were categorized in tertiles, there was a decreasing prevalence of MS in women with increasing concentrations of 25(OH)D₃.

The study findings suggest that insufficiency of vitamin 25(OH)D₃ is more common in women with excessive body weight and metabolic syndrome than in women with excessive body weight without metabolic syndrome.

INTRODUCTION

Intensive research on the role of vitamin D in the physiology and pathophysiology allowed to explore its involvement in the regulation of the human body mineral balance. It is one of a few vitamins that the human body can endogenously produce in sufficient quantities. Vitamin D is produced in the skin during sun exposure (UVB), through conversion of 7 - dehydrocholesterol (called provitamin D₃) into cholecalciferol (vitamin D₃) [1,2]. Dietary intake is also a minor source (10-20%) of 25(OH)D₃ which is delivered in the form of vitamin D₂ and D₃ [2,3]. Vitamin D, which is produced by a synthesis or dietary intake, is biologically inactive. It is metabolized to its biologically active form of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) in liver and then in kidneys [1,4]. 25-hydroxyvitamin D₃ (25(OH)D₃) is a generally accepted indicator of vitamin D status [5,6].

Vitamin D insufficiency, as determined by decreased concentrations of 25(OH)D₃ in the blood, is common and now considered a problem throughout the world [4]. According to the latest statistics, mean serum D₃ concentration worldwide is in the range of hypovitaminosis (50-75 nmol/L; 20-30 ng/mL), among Europeans is in the range of insufficiency (25-50 nmol/L; 10-20 ng/mL) [7]. As the optimal concentration of 25-hydroxyvitamin D₃ is considered to 75-100 nmol/L (30-40 ng/mL), although according to the latest reports, in order to obtain maximum health benefits from the action of vitamin D, its concentration should be in the range of 100-150 nmol/L (40-60 ng/mL) [8,11].

Concentration of vitamin 25(OH)D₃ is not only an indicator of bone health, but also constitutes an independent risk factor for cancer and other chronic diseases [9,10]. Data from the third National Health and Nutrition Examination Survey (3rd NHANES) not only has revealed that the prevalence of vitamin D deficiency and insufficiency is > 50% among children, teenagers, adults and elderly people, but also has made startling associations with increased risks for hypertension, type 2 diabetes, colorectal and breast cancers, myocardial infarction, stroke, peripheral vascular disease, and wheezing disorders [9,11,12]. In addition, vitamin D deficiency may be a risk factor for metabolic syndrome, whose incidence has increased in the recent years [13,14]. It is closely linked with the emergence of the obesity epidemic, one of the major health problems in the world [15].

The metabolic syndrome defined by the clustering of impaired glucose tolerance, hypertension, adiposity, and abnormal lipid profiles is especially important for identification of those at high risk for type 2 diabetes and coronary heart disease [13,15]. Linking the risk of metabolic syndrome with vitamin D deficiency is the result of a broad spectrum of its activities in the body, through the VDR receptors, which hold a majority of the cells and tissues involved in the pathogenesis of obesity and type 2 diabetes [1].

The investigation of the metabolic syndrome due to vitamin D insufficiency is becoming more common [13,14,16,17]. To provide additional information, in the present study, vitamin 25(OH)D₃ concentration and its relationship with the metabolic syndrome among young overweight and obese women were assessed.

SUBJECTS

The study group included 52 young women aged 20-40 yrs with abnormal body weight, recruited from patients of Department of Internal Diseases, E. Warminski City Hospital in Bydgoszcz. In the study group we defined two subgroups : women without metabolic syndrome (n=25) and with metabolic syndrome (MS) (n=27). The diagnosis of metabolic syndrome was based on the definitions of the International Diabetes Federation (IDF 2005) for Europoid women. Subjects had to have 3 or more of the following 5 features to be classified as having MS: central obesity measured by waist circumference (≥ 80 cm), elevated fasting triglyceride concentration ≥ 150 mg/dL, low HDL-C concentration < 50 mg/dl, high blood pressure (systolic blood pressure SBP ≥ 130 mm Hg, diastolic blood pressure DBP ≥ 85 mm Hg), elevated fasting glucose concentration ≥ 100 mg/dl. Women included into the study had not taken any contraceptives, anti-inflammatory or other medicines known to affect lipid or carbohydrate metabolism. The written informed consent from each participant was obtained and the study was approved by the Bioethics Committee at Nicolaus Copernicus University in Toruń Ludwik Rydygier Collegium Medicum in Bydgoszcz.

METHODS

Fasting blood was drawn in the early morning (7.00-9.00 am). Serum was obtained within less than 1 hour to avoid proteolysis, and stored deep-frozen (-80°C) in small aliquots until assayed but not longer than 8 months. Serum was assayed for total cholesterol (TC), HDL-C (HDL-cholesterol), triglycerides (TGs), glucose (Architect ci8200, Abbott Diagnostics).

LDL-cholesterol (LDL-C) was calculated. Vitamin 25(OH)D₃ was assayed using an electrochemiluminescence immunoassay on the Cobas e411 Elecsys 2010 (Roche Diagnostics GmbH), assay measured range was 4-100 ng/mL/ (10-250 nmol/L). Concentration of 25(OH)D₃ < 30 ng/mL (< 75 nmol/L) has been accepted as insufficiency and 10-20 ng/mL (25-50 nmol/L) as mild deficiency. Serum insulin was measured with AxSYM[®] Insulin assay, reference range was 2,0 – 25,0 $\mu\text{U/mL}$. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated: fasting insulin (mU/L) x glucose (mmol/l)/22.5).

The height (cm), weight (kg), waist and hip circumferences (cm) were measured using standard methods. Waist circumference was measured in a horizontal plane midway in the distance of the superior iliac crest and the lower margin of the last rib. Hip circumference was taken around the pelvis at the point of maximal protrusion of the buttocks. The systolic and diastolic blood pressure (BP) was measured according to the standard procedures by trained personnel.

STATISTICAL METHODS

All data were presented as mean \pm standard deviation (Gaussian distribution of results) or median and the 25th and 75th percentile (non-Gaussian distribution). The student t-test and U-Mann-Whitney test were used to compare differences. Comparison of mean values between groups were done by ANOVA or Kruskal-Wallis test. Spearman correlation test was performed. $P < 0,05$ was considered statistically significant. Statistical analysis was performed using Statistica 8.0 for Windows (Stat Soft).

RESULTS

Out of 52 women with excessive body mass metabolic syndrome was recognized in 27 (52%). Women with MS had significantly lower mean concentration of vitamin 25(OH)D₃ (Table 1). Another characteristic features of metabolic syndrome in our study group were twofold higher HOMA-IR value, abnormal blood pressure and decreased HDL-C. Median concentrations of TC, LDL-C, TG and mean glucose were within the widely accepted reference range. Correlation analysis in women with metabolic syndrome showed a trend to increased HOMA-IR with decreasing vitamin 25(OH)D₃ concentration ($r = -0.37$; $p < 0.06$), whereas in women with excessive body weight a significant negative relation between vitamin D and all parameters of glucose metabolism (glucose $r = -0.42$; $p < 0.02$; insulin $r = -0.39$; $p < 0.004$; HOMA $r = -0.43$; $p < 0.001$) were found.

In order to investigate further the association of metabolic syndrome with 25(OH)D₃, the prevalence of vitamin 25(OH)D₃ insufficiency (< 30 ng/mL) as well as mild deficiency (10-20 ng/mL) among women with and without MS was evaluated. Vitamin 25(OH)D₃ insufficiency was more prevalent in women with MS, compared with those who did not fulfill the criteria for this syndrome (63% vs 37%, respectively) (Fig.1). Among women with metabolic syndrome mild 25(OH)D₃ deficiency was found in 58%, while among women without MS mild deficiency was present in 26%. Concentration of 25(OH)D₃ was the lowest (17,7 ng/mL) if 4-5 features of MS were present. When serum concentrations of 25(OH)D₃ were categorized in tertiles, there was a decreasing prevalence of MS in women with increasing concentrations of 25(OH)D₃ (Tertile 1 25[OH]D₃ $< 17,8$ ng/mL – MS 52%; Tertile 3 25[OH]D₃ $\geq 26,8$ ng/mL – MS 21%).

DISCUSSION

In our study, serum concentration of 25(OH)D₃ was significantly lower in women with metabolic syndrome compared to women without MS. We have also observed that in women with metabolic syndrome mild deficiency occurred much more frequently than in women without MS.

These results are consistent with studies of Botella-Carretero et al., where the deficit of vitamin D was more prevalent (60.9%) in obese study participants with metabolic syndrome compared with patients without metabolic syndrome (33.3%) [4]. There are also suggestions that an increased concentration of parathyroid hormone, not vitamin D, indicates the occurrence of metabolic syndrome in obese subjects [19].

Negative association between serum concentrations of vitamin D and the presence of metabolic syndrome has been observed in several studies [4,17]. In a clinical study of 126 participants, those with hypovitaminosis D were nearly three times as likely to have the metabolic syndrome as participants with normal concentrations of vitamin D [18]. However, in an analysis of NHANES III, Ford et al. documented a strong negative association of 25(OH)D₃ level with metabolic syndrome [13].

The biological mechanism by which 25(OH)D₃ may influence metabolic syndrome has not been established.

It is considered likely that insulin resistance is the etiopathogenic link between obesity and type 2 diabetes, hypertension, hyperlipidemia and cardiovascular disease [20,21]. There is accumulating evidence from clinical and experimental studies that vitamin D may influence glucose homeostasis. [18,20].

Recent studies have shown that vitamin D is significantly associated with insulin resistance. In addition to the current vitamin D receptors on pancreatic β cells, it was also observed that vitamin 25(OH)D₃ insufficiency may predispose to glucose intolerance, impaired synthesis and secretion of insulin and an increased risk of type 2 diabetes [21,22].

The traditional indicator of insulin resistance is the HOMA-IR index [21]. In the present study significant, more than twofold value of HOMA was observed in women with metabolic syndrome. Also, concentration of glucose was significantly higher in these women. Furthermore, we have observed in women with metabolic syndrome a trend to higher HOMA-IR with decreasing 25(OH)D₃ concentration while results of correlation analysis in women with excessive body weight showed significant negative relation between vitamin D and all parameters of glucose metabolism (glucose $r = -0.42$; $p < 0.02$; insulin $r = -0.39$; $p < 0.004$; HOMA $r = -0.43$; $p < 0.001$).

Studies confirming a negative association between concentrations of vitamin D and insulin resistance provide a possible explanation for findings of a negative association between serum concentrations of vitamin D and the prevalence of the metabolic syndrome [18,23].

Accumulated data indicates that people with impaired glucose tolerance and diabetes have lower concentrations of vitamin D compared with those with normal glucose tolerance [14]. Chiu et al. underline the simple relation: the increase in concentrations of 25(OH)D₃ increases insulin sensitivity and improves the functioning of the pancreatic islet cells and vice versa: vitamin D deficiency reduces insulin sensitivity and impairs the proper functioning of β cells [18].

Recent data suggests a potential role of vitamin D in the development of atherosclerosis, vascular calcification process by macrophages producing 1,25(OH)₂D₃ (calcitriol) [7,16]. Experimental studies have shown that vitamin D concentration positively correlates with HDL-C and negatively with serum triglyceride levels [4,23]. We have found that in women with metabolic syndrome, total cholesterol, LDL-cholesterol, triglycerides and blood pressure were significantly higher, but HDL-cholesterol was significantly lower, when compared with women without metabolic syndrome. In addition, the analysis of the correlation between lipid parameters and the concentration of vitamin D in women with a BMI ≥ 25 kg/m² showed only a significant negative correlation between vitamin D and LDL-cholesterol.

Although the mechanistic role of vitamin D deficiency in the pathogenesis of dyslipidemia is not well known vitamin D supplementation was reported to attenuate the beneficial effect of hormone replacement therapy on serum lipid levels [24].

Numerous epidemiologic studies have suggested a negative association between serum concentrations of vitamin D and BMI [14,13,25] and also a negative correlation between plasma vitamin D levels and the occurrence of central-type obesity (abdominal obesity) [13,25].

Since the excessive weight is a major component of the metabolic syndrome, it can significantly contribute to lowering the levels of vitamin D in women characterized by metabolic syndrome.

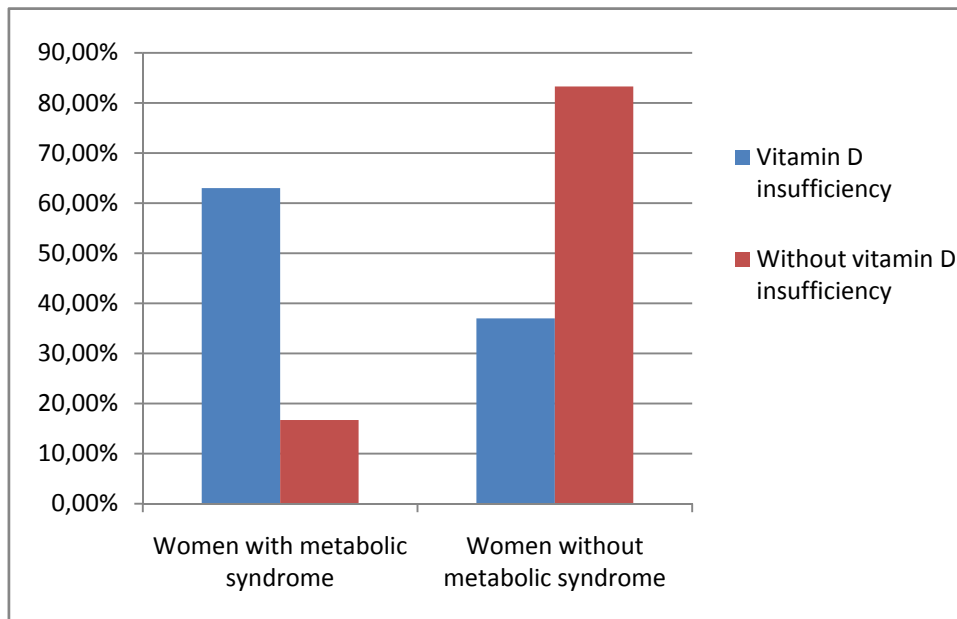
The high prevalence of vitamin D insufficiency in obesity has been hypothesized to result from the sequestering effect of a high quantity of subcutaneous fat on circulating vitamin D. However, the studies of Reis et al. deny that the link between vitamin D levels and the metabolic syndrome is dependent on BMI [17].

In conclusion, the study findings suggest that insufficiency of vitamin 25(OH)D₃ is more common in women with excessive body weight and metabolic syndrome than in women with excessive body weight without metabolic syndrome. Further studies are necessary to confirm these findings, including prospective research to determine whether vitamin 25(OH)D₃ insufficiency is a cause or a consequence of metabolic syndrome.

Table 1. Clinical and biochemical characteristics of women with and without metabolic syndrome.

Parameters	Women with metabolic syndrome (n=27)	Women without metabolic syndrome (n=25)	p
Body mass index (kg/m ²)	36.1 ± 6.2	29.0 ± 3.6	0.00002
Waist circumference (cm)	108 (100 – 120)	89 (84.5 – 95.5)	0.000006
Systolic blood pressure (mmHg)	140 (130 – 150)	120 (115.5 – 127)	0.0000009
Diastolic blood pressure (mmHg)	93 (85 – 101)	75 (70 – 83.5)	0.000002
Fasting glucose (mg/dL)	95 ± 14	86 ± 7.4	0.009
HOMA-IR	2.9 (1.9 – 4.4)	1.2 (0.9 – 2)	0.00003
Total cholesterol (mg/dL)	192 (165 – 244)	156.5 (132 – 186.5)	0.004
HDL-cholesterol (mg/dL)	45 (39 – 50)	53.5 (42 – 60.5)	0.03
LDL-cholesterol (mg/dL)	116 (96 – 140)	92.5 (69.5 – 107.5)	0.002
Triglycerides (mg/dL)	115 (90 – 148)	72.5 (55.5 – 89)	0.0001
Vitamin 25(OH)D ₃ [ng/mL]	19.9 ± 9.5	27.3 ± 11.4	0.02

Mean ± SD or median (Q1 - Q3)

Figure 1. Prevalence of vitamin D insufficiency among women with and without metabolic syndrome.

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