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Relationship between deficiency of vitamin D and exponents of metabolic syndrome

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Abstract. – OBJECTIVE: Widespread hypovitaminosis D and an increased incidence of metabolic syndrome (MetS) represent significant problems of contemporary medicine but link between them remain unresolved. We aimed to define relationship between vitamin D serum concentration and exponents of MetS.

PATIENTS AND METHODS: The studies were conducted on 70 individuals (51 with and 19 without MetS). Concentrations of 25(OH)D (25-hydroxyergocalciferol and 25-hydroxycholecalciferol), calcium, cholesterol, HDL, cholesterol LDL, triglycerides, fasting glucose, blood pressure and anthropometric parameters were measured.

RESULTS: Median concentration of vitamin D in the research population amounted to 41.46 nmol/L. Concentration of 25(OH)D in MetS group was lower than in remainder participants (38.45 nmol/L vs. 58.50 nmol/L, $p = 0.0104$). An inverse correlation was demonstrated between 25(OH)D level on one hand and body weight, waist and hips circumference, adipose body weight, Body Mass Index, Waist to Height Ratio (WHtR), glycaemia and number of MetS components on the other in persons free of MetS. No such relationships could be documented in MetS group. In the entire population values of Waist to Hip Ratio (WHpR) and WHtR indices manifested correlation with hyperglycaemia, hypertriglyceridaemia, low HDL concentrations.

CONCLUSIONS: In persons without MetS a relationship was detected between vitamin D concentration and exponents of metabolic syndrome, although further studies on this problem are required.

Key Words:
Metabolic syndrome, Vitamin D, Vitamin D deficiency.

Introduction

Widespread deficiency of vitamin D in increased incidence of metabolic syndrome (MetS) represent significant problems of contemporary medicine. Epidemiological data conducted on groups of heterogeneous age document decreased blood concentrations of vitamin D both in young and in old individuals. It is estimated that around 40% of general population may suffer from deficiency of vitamin D although the proportion varies depending of geographic location. Above 35° of geographic width (on both hemispheres) intensity of sun light is insufficient for optimum dermal biosynthesis of the vitamin, in particular in obese individuals, in whom excess of visceral adipose tissue represents an additional factor which promotes deficiency of vitamin D[1-4]. In recent years readers' attention is increasingly drawn to pleiotropic effects of vitamin D. Its active form, both at the level of transcription and through membrane receptors is involved in control of expression of several genes, linked mainly to calcium-phosphate, carbohydrate and lipid metabolism, immune response and anti-neoplastic activities[5-7].

The metabolic syndrome encompasses such disturbances as visceral obesity, diminished tolerance of glucose, insulin resistance and/or hyperinsulinaemia, dyslipidaemia or arterial hypertension, which increase the risk of cardiovascular disturbances with arteriosclerotic background[4]. Pathogenesis of the syndrome remains to be fully clarified. Several factors predisposing to MetS manifestation used to be quoted, including genetic conditioning, involving i.a. polymorphisms and mutations in genes which code for vitamin D receptors (VDR) or environmental factors, such as high caloric, atherogenic diet or low physical activity. The dominating traits of metabolic syndrome involve excessive amounts of visceral adipose tissue in abdominal cavity and insulin resistance[8].

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It still remains unresolved whether exponents of metabolic syndrome manifest links to deficiency of vitamin D. Some data suggested that low serum concentration of 25(OH)D predisposes to development of metabolic disturbances[9,10]. On the other hand, other investigators failed to confirm such a relationship[11-13]. Moreover, it still remains to be established whether MetS represents the cause or the effect of vitamin D deficiency[14,15].

Therefore, the principal aim of the study involves definition of the relationship between serum vitamin D concentration and exponents of the metabolic syndrome. The exponents of MetS were accepted to include waist circumference, fasting blood glycemia (FGB), arterial systolic and diastolic blood pressure (SBP, DPB), triglyceridemia (TG) and level of HDL cholesterol. The aim could be implemented due to: (1) estimations of vitamin D, calcium concentrations, parameters of lipid metabolism, glycaemia and arterial blood pressure in patients with metabolic syndrome or free of this syndrome; (2) verification of usefulness manifested by selected anthropometric parameters in identification of MetS exponents; (3) analysis of correlation between concentration of vitamin D and number/type of metabolic syndrome exponents.

Patients and Methods

The protocol of analyses received consent of the local Bioethical Commission (consent No. 491/12).

Research Group

Basing on criteria of IDF (International Diabetes Federation) and AHA/NHLBI (American Heart Association/National Heart, Lung, and Blood Institute) from 2009[16], the studies were conducted on 70 persons of Caucasian race, including 51 patients with MetS (MetS+) and 19 persons free of the MetS (MetS-), 30 to 60 years of age (Table I). In the studies harmonized definition of metabolic syndrome was taken into account. MetS was diagnosed on the basis of at least three of five exponents of the syndrome, including waist circumference (above 94 cm in men and 80 cm in women, in line with IDF recommendations for European inhabitants), elevated blood triglycerides concentration (> 1.7 mmol/L), decreased level of HDL cholesterol (< 1.0 mmol/L for men and < 1.3 mmol/L for women), elevated arterial blood pressure (> 130 mmHg for systolic blood pressure and > 85 mmHg for diastolic blood pressure) and elevated level of fasting glycaemia (> 5.6 mmol/L), with possible corrections of the values due to modifying effects of hypotensive, hypoglycaemic treatments and/or dyslipidaemia therapy[16]. In the group of MetS- 42.1% population exhausted two (most frequently waist circumference and arterial hypertension) and 31.6% exhausted one (most frequently arterial hypertension) of five criteria used to include the patient to victims of metabolic syndrome.

Inclusion Criteria

In qualification of patients to the studies the following inclusion criteria were accepted: a negative anamnesis linked to manifestation of neoplastic and autoimmune diseases, absence of clinical signs of hepatic, renal, adrenal, thyroid diseases, no signs of alcohol disease or acute infection in three months preceding analyses. None of study participants was administered vitamin D or calcium supplements in 6 months preceding the analyses or manifested physical restrictions or other conditions which might influence synthesis of vitamin D (e.g. immobilization, frequent hospital stays, current or past steroid therapy). All the participants obtained oral and written information on the studies and expressed their informed consent to the participation.

Examined Parameters

Anthropometric measurements, involving evaluation of body height and weight, were conducted using a stadiometer and a legalized electronic balance. Waist circumference was measured at half a distance between lower margin of costal arch and iliac crest while hips circumference was measured at the height of trochanter major. The obtained results were used to calculate BMI (Body Mass Index), WHpR (Waist to Hip Ratio) and WHtR (Waist to Height Ratio). In addition in both groups (MetS+ and MetS-) relative and absolute contents of adipose tissue, lean body mass and body content of water were estimated using electric bioimpedance (Bodystat 1500 apparatus). The analyses were conducted on fasting individuals, wearing only underwear. Arterial blood pressure was estimated on three occasions, in sitting position, after at least 10 min rest, using mercury sphygmomanometer.

Laboratory Measurements

Blood samples were accumulated for 12 months, beginning at February, 2013. Venous blood samples for biochemical assays were sampled from all participants (from cubital vein, sampled at 7:00-8:00 a.m., 12 hours after the last meal). The samples were saved and frozen at the temperature of –20ºC. Concentrations of total cholesterol (TC), its HDL and LDL fractions, triglycerides and glucose were determined using enzymatic techniques and standardized commercial tests. Concentrations of 25(OH)D (25-hydroxyergocalciferol and 25-hydroxycholecalciferol) were determined using electroluminescence in a Cobas E immunoanalyser (Roche Diagnostic, Mannheim, Germany) while total calcium (Ca) level was estimated by a complexometric technique with application of Cobas E Roche/Hitachi system (Roche Diagnostic, Mannheim, Germany).

Statistical Analysis

Results of the studies were subjected to statistical analysis, encompassing descriptive statistics and statistical procedures of extrapolated results of studies, including analyses of correlation and regression of studied variables and analysis of variance. Statistical processing of the results took advantage of STATISTICA 10.0 software (StatSoft Inc.). Normal distribution of data was examined using the test of Shapiro-Wilk. Parametric values were presented as means (± SEM), while non-parametric ones in the form of median values, 25% and 75% quartile. Two-tailed significance (Mann-Whitney, Student's t, Chi^2) tests and Spearman correlation matrix were used. The level of $p < 0.05$ was accepted as indicate significance of differences.

Results

Anthropometric studies evaluating, i.a. body mass, waist and hips circumferences, and body composition (Table I) demonstrated that in the group of patients with metabolic syndrome (n = 51) median value (quartiles of 25% and 75%) of body weight amounted to 104.3 (94.25; 127.25) kg, and in persons free of this syndrome (n = 19) it amounted to 71.6 (63.10; 85.95) kg. Median value (quartiles of 25% and 75%) of Body Mass Index in MetS+ group amounted to 36.1 (32.35; 42.90) kg/m^2, while in MetS- group it amounted to 25.2 (23.25; 26.95) kg/m^2. Adipose tissue accounted for 44.8% of body mass in patients with metabolic syndrome, i.e. it was much higher represented than in MetS- group ($p < 0.0001$), in which it comprised 25.0% of body mass.

Results of biochemical analyses showed that median value (25% and 75% quartiles) of vitamin D concentrations in sera of the entire examined population (n = 70) amounted to 41.46 (25.35; 58.74) nmol/L, and this value was lower in patients with metabolic syndrome than in persons free of this syndrome [38.45 (24.29; 54.65) nmol/L for MetS+ group and 58.50 (41.71; 66.20] nmol/L for MetS- group, respectively). Significant

Table I. Anthropometric characteristics of patients with metabolic syndrome and in participants free of the syndrome.

Characteristic	Total (n = 70)	MetS+ (n = 51)	MetS- (n = 19)	p
Age (years)	46.50 (40.25; 53.75)	50.00 (42.00; 54.00)	45.00 (38.00; 50.00)	0.0211*
Sex (W/M)	34/36	24/27	10/9	0.6782***
Body weight (kg)	96.35 (84.28; 119.85)	104.3 (94.25; 127.25)	71.60 (63.10; 85.95)	< 0.0001*
Height (cm)	170.73 ± 1.27	171.04 ± 1.48	169.90 ± 2.53	0.6915**
Waist circumference (cm)	110.13 ± 2.55	119.57 ± 2.22	84.79 ± 2.43	< 0.0001**
Hip circumference (cm)	111.00 (105.25; 125.00)	120.00 (110.00; 129.50)	102.00 (94.50; 106.50)	< 0.0001*
BMI (kg/m^2)	33.65 (28.15; 41.20)	36.10 (32.35; 42.90)	25.20 (23.25; 26.95)	< 0.0001*
WHpR	0.96 (0.87; 1.04)	1.00 (0.95; 1.06)	0.82 (0.80; 0.87)	< 0.0001*
WHtR	0.65 ± 0.01	0.70 ± 0.01	0.50 ± 0.01	< 0.0001**
Body fat mass (%)	39.85 (30.65; 47.43)	44.80 (38.20; 50.30)	25.00 (23.05; 28.85)	< 0.0001*
Body lean mass (%)	60.15 (52.56; 69.35)	55.20 (49.70; 61.80)	75.00 (71.15; 76.95)	< 0.0001*
Water content in the body (%)	43.73 ± 0.98	39.82 ± 0.72	54.22 ± 1.07	< 0.0001**

n: number of examined persons; MetS+: patients with metabolic syndrome; MetS-: participants free of metabolic syndrome; p: level of statistical significance; W: women; M: men; BMI: Body Mass Index; WHpR: Waist to Hip Ratio; WHtR: Waist to Height Ratio; *Level of statistical significance in the test of Mann-Whitney for groups of MetS+ vs. MetS-; **Level of statistical significance in Student's t test for groups of MetS+ vs. MetS-; ***Level of statistical significance in Chi^2 test for the groups of MetS+ vs. MetS-. Parametric values were presented in the form of means (± SEM), while non-parametric ones in the form of median values (25% and 75% quartile).

differences were disclosed between median vitamin D concentrations in sera of patients with metabolic syndrome and sera of participants free of the syndrome ($p = 0.0104$) (Figure 1).

In line with recommendations given by Endocrine Society in 2011, related to "Evaluation, Treatment, and Prevention of Vitamin D Deficiency"[17], in all participants of the studies, deficiency of vitamin D (serum concentrations below 50 nmol/L) was disclosed in 61.4% of the participants. Most of participants manifesting such concentrations of 25(OH)D belonged to the group of patients with metabolic syndrome (81.4% MetS+ vs. 18.6% MetS-). On the other hand, the recommended values of vitamin D concentration D (> 75 nmol/L) were disclosed in 5 participants (2 persons of the MetS+ group and 3 persons of the MetS- group).

Significant differences were disclosed between median (or mean) concentrations of MetS exponents (SBP, DBP, HDL, TG, FBG) in participants of MetS+ group as compared to participants free of the syndrome (Table II). In the case of serum concentration of total cholesterol a tendency was disclosed ($p = 0.0717$) for differences in the parameter between the analysed groups (MetS+ vs. MetS-). Moreover, differences were documented in total calcium concentrations in sera between MetS+ and MetS- participants ($p = 0.0222$). While both groups contained individuals with normal values of calcemia, patients with metabolic syndrome manifested lower values of this parameter.

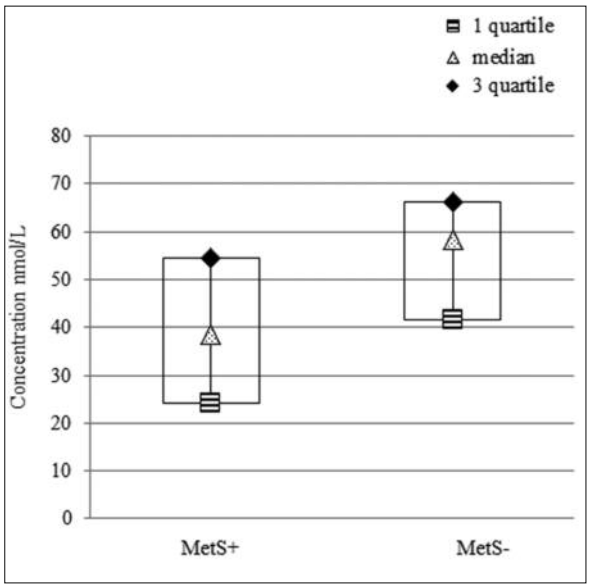

Figure 1. Median values of serum vitamin D concentration in patients with metabolic syndrome (MetS+) and in participants free of this syndrome (MetS-).

Among patients free of metabolic syndrome BMI and WHtR indices (Table I) manifested a negative relationship with HDL cholesterol concentration (BMI Spearman rank (Rs) = -0.53; $p < 0.02$ and WHtR Rs = -0.68; $p < 0.01$). Both in MetS+ group and in MetS- group WHtR manifested positive correlation with values of glycaemia (MetS+ Rs = 0.34; $p < 0.02$ and MetS- Rs = 0.46; $p < 0.05$). In the case of WHpR para-

Table II. Characteristics of arterial blood pressure and blood biochemical profile in participants with metabolic syndrome and those free of the syndrome.

Characteristic	Total (n = 70)	MetS+ (n = 51)	MetS- (n = 19)	p
SBP (mmHg)	140 (130; 150)	140 (140; 150)	125 (117; 144)	0.0030*
DBP (mmHg)	90 (80; 95)	90 (89.5; 100)	87 (77; 92)	0.0192*
TC (mmol/L)	5.58 ± 0.13	5.72 ± 0.15	5.20 ± 0.21	0.0717**
HDL (mmol/L)	1.22 (0.98; 1.56)	1.11 (0.93; 1.28)	1.45 (1.28; 1.89)	< 0.0001*
LDL (mmol/L)	3.44 (2.78; 4.03)	3.51 (2.82; 4.04)	3.31 (2.65; 3.87)	0.2698*
TG (mmol/L)	1.87 (1.30; 2.51)	2.28 (1.76; 2.87)	1.29 (0.94; 1.43)	< 0.0001*
FBG (mmol/)	5.61 (5.06; 6.09)	5.82 (5.32; 6.42)	4.72 (4.30; 5.52)	< 0.0001*
25(OH)D (nmol/L)	41.46 (25.35; 58.74)	38.45 (24.29; 54.65)	58.50 (41.71; 66.20)	0.0104*
Ca (mmol/L)	2.37 (2.29; 2.47)	2.35 (2.29; 2.45)	2.41 (2.37; 2.53)	0.0222*

n: number of examined persons; MetS+: patients with metabolic syndrome; MetS-: participants free of metabolic syndrome; *p*: level of statistical significance; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: concentration of total cholesterol; HDL: concentration of high density lipoprotein; LDL: concentration of low density lipoprotein; TG: concentration of triglycerides; FBG: concentration of fasting blood glucose; 25(OH)D: concentration of 25-hydroxyvitamin D; Ca: concentration of calcium; *Level of statistical significance in the test of Mann-Whitney for groups of MetS+ vs. MetS-; **Level of statistical significance in Student's *t* test for groups of MetS+ vs. MetS-. Parametric values were presented in the form of means (± SEM), whole non-parametric ones in the form of median values (25% and 75% quartile).

meter a positive correlation was detected with triglycerides level in the group of MetS+ (Rs = 0.38; $p < 0.03$), while in the group of MetS- the WHpR parameter showed positive correlation with glycemia (Rs = 0.38; $p < 0.01$) and a negative one with concentration of high density lipoproteins (Rs = -0.74; $p < 0.001$). All of those relationships were statistically significant.

In the group free of metabolic syndrome serum concentration of 25(OH)D manifested statistically significant negative correlation with anthropometric parameters, including body weight (Rs = -0.60; $p < 0.007$), waist circumference (Rs = -0.60; $p < 0.007$) and hips circumference (Rs = -0.67; $p < 0.002$), weight of adipose tissue in the body (Rs = -0.54; $p < 0.02$), BMI (Rs = -0.52; $p < 0.03$) and WHtR (Rs = -0.52; $p < 0.03$) while statistically significant positive correlation was detected between concentration of 25(OH)D and percentage of water content in the body (Rs = 0.54; $p < 0.02$). Moreover, concentration of vitamin D was found to manifest negative correlation with values of glycemia (Rs = -0.48; $p < 0.04$) and with the number of metabolic syndrome components (Rs = -0.60; $p < 0.007$). No such relationships could be detected in the participants of the MetS group. Neither in the investigated nor in the reference group correlations could be detected related to calcium concentration in serum.

Discussion

In the present studies serum concentration of vitamin D in most of participants has been lower than the reference value (< 75 nmol/L). The relatively frequent (68.6%) manifestation of deficiency of vitamin (< 50 nmol/L) among patients with metabolic syndrome deserves attention. Low concentrations of vitamin D in persons with MetS were detected also in other clinical studies[9,18]. Moreover, deficiency of vitamin D was found to accompany an excessive body weight due to marked content of adipose tissue[19]. In studies of Wortsman et al[20], exposure to UVB (at the dose of 27 mJ/cm^2) was found to be followed 24 hours later by an increase of serum vitamin D concentration, which was by 57% lower in persons with obesity (BMI > 30 kg/m^2) than in persons of an appropriate body weight. The difference in vitamin D concentrations among patients with an excessive body weight and persons with normal BMI may reflect existence of a natural barrier in form of adipose tissue, which manifests capacity to influence concentration of the compound. Among other, the tissue promotes sequestration of vitamin D, impedes its transport to circulation and disturbs metabolic processing of the compound[21].

In studies conducted in patients with MetS lower concentrations of calcium were detected in blood as compared to persons free of is this syndrome (even of normocalcemia was maintained in the entire analysed population). Calcium is thought to be capable of modulating the number of adipocytes. An increase in intracellular calcium concentration is suggested to provide a certain mediating agent, which augments apoptosis of adipocytes (with involvement of μ-calpain and caspase-12), pointing to its obesity-counteracting effect. It should be stressed that absorption of calcium in intestines and general calcium homeostasis are controlled by i.a. active form of vitamin D and dietary supply of this mineral component[22-25].

Individual anthropometric indices are thought to manifest a variable usefulness in identification of MetS exponents. In this study the index of Waist to Hip Ratio has been found to manifest correlation with incidence of metabolic disturbances, i.e. with higher than recommended serum concentrations of glucose and triglycerides and with lower concentrations of HDL cholesterol. Similar relationships have been obtained in the case of Waist to Height Ratio, while Body Mass Index has been found to be less applicable for the purpose. Similar results were obtained by Al-Odat et al[26] and Esmaillzadeh et al[27], who showed that WHpR manifested most pronounced correlation with exponents of MetS. In turn, in analyses conducted by Ashwell and Gibson[28] WHtR was found to be of a much greater use (as compared to BMI, waist circumference and WHpR) in evaluation of correlations between various risk factors of cardiovascular diseases. In contrast to results of the above quoted studies, Mooney et al[29] showed that no single principal predictor of MetS can be distinguished. Nevertheless, these authors stress high significance of anthropometric analyses in verification of cardiometabolic disturbances. Body measurements (including waist and hips circumferences) and calculation of anthropometric indexes (including BMI, WHpR, WHtR) are broadly used in evaluation of visceral obesity manifestation. Even if the analyses are easy to conduct, their usefulness for the pur-

pose used to be challenged because, i.a. they cannot directly measure body content of adipose tissue[30]. Despite of the above, simple anthropometric measurements used to accepted as equally valuable to direct analyses of body composition. Moreover, their execution poses no risk for the patients and provides highly valuable prognosis related to manifestation of MetS components[31].

We have documented negative correlations between vitamin D concentration and exponents of metabolic syndrome in persons free of this syndrome. In parallel, such relationships have not been presented in cases of MetS patients. The data do not contradict results of analyses in other investigative centres[32-34], which demonstrated an inverse relationship between concentration of vitamin D and manifestation of several metabolic syndrome components in population of persons free of traits typical of the syndrome as well as in the group of persons prone to develop the syndrome in future (i.e. burdened with a single or two risk factors of MetS). It was suggested that potential deficits of the compound may provide background for MetS development[35]. Low concentration of 25(OH)D in blood predisposes for manifestation of several disturbances, including higher values of glycemia, insulinemia, visceral obesity and dyslipidaemia[34,36,37]. Vitamin D manifests correlation with elevated level of apolipoprotein A-1 (linked to high density cholesterol), normalization of triglyceridemia and exerts effects on renin-angiotensin-aldosterone system and of pancreatic β-cells[4,38]. In meta-analysis evaluating relationships between serum concentration of vitamin D on one hand and risk of MetS, diabetes type 2 or insulin resistance on the other (in a group of over 210 thousand participants), high levels of this vitamin in blood were found to reduce frequency of such disturbances[39]. It should be added that in the treatment of morbid obesity, one of the effective methods of therapy is bariatric surgery. The meta-analysis of randomized controlled trials[40] assessing the efficacy of non-surgical treatment of obesity versus bariatric surgery have shown that this procedure leads not only to greater loss of body weight, but also to the remission of type 2 diabetes and reduction of the prevalence of metabolic syndrome among obese people. In addition, other studies[41] have shown that bariatric surgeries contribute to cardiovascular risk reduction among the obese, e.g. by lowering blood pressure and increasing HDL cholesterol level. Moreover, it is believed that the use of vitamin D supplementation in obese subjects and people with type 2 diabetes can improve their metabolic profile. Thus, an appropriate concentration of vitamin D in blood may represent a specific prevention against manifestation of MetS components.

However, studies of Rueda et al[13] failed to fully confirm the described relationships: a lowered blood concentration of vitamin D manifested no association with the occurrence of metabolic syndrome. Also other investigators[11,12] detected no relationships between vitamin D concentration and exponents of MetS in persons with an excessive body weight but on the other hand, an increased risk of metabolic disturbances was found to correlate with elevated parathormone levels. The study of Manco et al[42] conducted in a group of 116 obese women (BMI > 40 kg/m^2) undergoing malabsorptive bariatric surgery, proves there is no relationship between low serum of vitamin D level and the increased level of insulin resistance (one of most important components of MetS). Measurements of the concentrations of the 25(OH)D and parameters of insulin resistance before the surgery and, next, 5 and 10 years after this procedure showed the decrease in vitamin D levels in the serum of obese subjects (39.2 ± 22.3, 27.4 ± 16.4 and 25.1 ± 13.9 nmol/L, respectively) while their level of insulin sensitivity reverted to normal. In turn, the detected in presented studies absence of relationships between vitamin D concentration and exponents of MetS, including values of SBP, DBP, HDL, TG, might have resulted from metabolic activity of adipose tissue cells or the applied treatment (e.g. by pharmacotherapy of dyslipidaemia, hyperglycemia, hypertension).

It is worth noting that in meta-analysis of Vimaleswaran et al[43], encompassing 21 cohorts (over 42 thousand individuals), originating from Great Britain, Germany, Sweden, Finland, Canada and USA, a pronounced unidirectional relationship was documented between Body Mass Index and hypovitaminosis D in sera. The authors suggested that the excessive body weight represented the main cause of decreased concentration of vitamin D while deficiency of the compound may predispose to higher BMI values to a negligible extent only. Therefore, the presented equivocal results related to relationship between vitamin D concentration in blood and manifestation of metabolic disturbances argues for continuation of analyses in this investigative field.

Conclusions

Decreased concentrations of vitamin D were encountered both in patients with metabolic syndrome and in persons free of this syndrome.

Deficiency of vitamin D (with preserved normocalcemia) was more frequent in patients with metabolic syndrome than in persons free of this syndrome.

Significance of WHpR and WHtR anthropometric indices was confirmed as predictors helpful in identification of the metabolic syndrome risk.

Relationships between concentration of vitamin D on one hand, selected anthropometric traits (waist circumference, BMI) and selected biochemical parameters (glycemia) on the other were not seen in patients with metabolic syndrome but were observed in persons free of this syndrome.

Declaration of Founding Interests

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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