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## Plasma vitamin D levels in obese children: relationship with selected anthropometric and metabolic parameters

### Ocena zależności między stężeniem witaminy D w surowicy krwi a wybranymi parametrami antropometrycznymi i metabolicznymi u dzieci z otyłością prostą

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#### Key words

obesity, children, vitamin D, glucose, cholesterol

#### Słowa kluczowe

otyłość, dzieci, witamina D, glukoza, cholesterol

#### Summary

**Introduction.** The prevalence of overweight and obesity is increasing worldwide, particularly among children and adolescents. Investigations report a correlation between serum 25(OH)D level and body mass. Plasma 25(OH)D concentration is lower in obese children than normal-weight children. Recent studies suggest that vitamin D deficiency is associated with higher risk of: impaired glucose tolerance, diabetes mellitus, dyslipidemia, metabolic syndrome, cardiovascular disease and hypertension.

**Aim.** The aim of the study was to investigate the correlation between serum 25(OH)D level in obese children and their anthropometric and metabolic parameters.

**Material and methods.** A retrospective analysis of obese patients diagnosed at the Department of Pediatrics and Endocrinology of the Medical University of Warsaw was performed. The study included a total number of 65 obese patients, aged 5-18 and involved the analysis of selected biochemical parameters such as Oral Glucose Tolerance Test (OGTT), fasting blood glucose, insulin, total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride (TG), 25(OH)D. Atherogenic index of plasma (AIP) and HOMA-IR index were calculated and anthropometric measurements were taken.

**Results.** Sixty five patients (33 female and 32 male) aged  $12.9 \pm 2.96$  were included in the analysis. In 51 (78.5%) of them serum 25(OH)D level was  $< 20$  ng/ml, BMI =  $30.89 \pm 5.28$ , SDS BMI =  $4.26 \pm 1.91$ . In 14 children (21.5%) serum 25(OH)D level was  $> 20$  ng/ml, BMI =  $27.87 \pm 4.20$ , SDS BMI =  $3.04 \pm 1.44$ . The relationship of serum 25(OH)D level to biochemical and anthropometric parameters were as follows: 25(OH)D levels were negatively correlated with SDS BMI, HOMA-IR and fasting insulin level.

**Conclusions.** For obese children we observe a negative correlation between BMI, HOMA-IR, fasting blood insulin and 25(OH)D serum concentrations.

#### Streszczenie

**Wstęp.** Otyłość i nadwaga stanowią narastający problem na całym świecie, szczególnie wśród dzieci i młodzieży. Wyniki badań wskazują na istnienie zależności pomiędzy stężeniem 25(OH)D w surowicy krwi a zawartością tkanki tłuszczowej. Stężenie 25(OH)D u dzieci otyłych jest niższe niż u dzieci z prawidłową masą ciała. Ostatnie badania sugerują istnienie zależności pomiędzy występowaniem niedoboru witaminy D a nieprawidłową tolerancją glukozy, cukrzycą, zaburzeniami gospodarki lipidowej, zespołem metabolicznym, ryzykiem wystąpienia chorób układu sercowo-naczyniowego i nadciśnieniem tętniczym.

**Cel pracy.** Celem badania była ocena zależności pomiędzy stężeniem 25(OH)D w surowicy krwi a wybranymi parametrami antropometrycznymi i metabolicznymi u dzieci z otyłością prostą.

**Material i metody.** Przeprowadzono retrospektywną analizę pacjentów z otyłością prostą, którzy byli diagnozowani w Klinice Pediatrii i Endokrynologii Warszawskiego Uniwersytetu Medycznego. Do badania włączono 65 pacjentów z otyłością prostą w wieku 5-18 lat. U wszystkich dzieci wykonano test OGTT z oceną stężenia insuliny, oceniono gospodarkę lipidową (stężenie cholesterolu całkowitego, LDL, HDL, trójglicerydów w surowicy krwi), stężenie 25(OH)D w surowicy, obliczono współczynnik aterogenności, HOMA-IR, wykonano pomiary antropometryczne.

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**Wyniki.** Przeanalizowano 65 pacjentów (33 dziewczynki i 32 chłopców) w wieku  $12,9 \pm 2,96$ . U 51 dzieci (78,5%) stężenie 25(OH)D w surowicy krwi wynosiło  $< 20$  ng/ml, BMI =  $30,89 \pm 5,28$ , SDS BMI =  $4,26 \pm 1,91$ . U 14 dzieci (21,5%) stężenie 25(OH)D w surowicy krwi wynosiło  $> 20$  ng/ml, BMI =  $27,87 \pm 4,20$ , SDS BMI =  $3,04 \pm 1,44$ . Oceniono korelację pomiędzy stężeniem 25(OH)D w stosunku do parametrów biochemicznych i antropometrycznych: stężenie 25(OH)D było odwrotnie proporcjonalne do SDS BMI, HOMA-IR oraz stężenia insuliny w surowicy krwi na czczo.

**Wnioski.** U otyłych dzieci występuje negatywna korelacja pomiędzy BMI, HOMA-IR, stężeniem insuliny na czczo a stężeniem 25(OH)D w surowicy krwi.

## INTRODUCTION

The prevalence of overweight and obesity is growing worldwide, particularly among children and adolescents and is becoming a global health problem. Several investigators report a correlation between serum 25-hydroxyvitamin D – 25(OH)D – level and body mass. According to recent studies plasma 25(OH)D concentration in obese children is lower than in normal-weight individuals (1, 2). Obesity-associated low serum 25(OH)D concentration is most probably due to the decreased bioavailability of vitamin D which is deposited in adipose tissue (3). Another study demonstrates that seasonal variations of 25(OH)D serum levels are lower in obese children than normal-weight controls (1). This could also be explained by reduced sun exposure in obese individuals (1, 4) as well as unhealthy dietary habits: high-calory food intake poor in vitamins and minerals (1, 5). New guidelines for therapeutic doses of vitamin D (for children with 25(OH)D  $< 20$  ng/ml) are as follows (6):

- neonates ( $< 1$  month) recommended dose of 1000 IU/ day,
- children aged 1-12 months recommended dose of 1000-3000 IU/day,
- children aged 1-18 years recommended dose of 3000-5000 IU/day.

Duration of treatment – about 1-3 months.

Guidelines for daily vitamin D intake for obese children (BMI  $> 90$  percentile for age and gender, with 25(OH)D concentration  $> 20$  ng/ml) (6) – dose of 1200-2000 IU/day, depends on the degree of obesity, it is recommended in the September-April period or throughout the year if no sufficient skin synthesis of vitamin D is ensured during the summer.

## AIM

The aim of the study was to investigate the correlation between serum 25(OH)D level and anthropometric and metabolic parameters in obese children with the purpose of assessment whether supplementation of 25(OH)D reduces the risk factors for adult chronic diseases such as: diabetes mellitus, metabolic syndrome, cardiovascular diseases and hypertension.

## MATERIAL AND METHODS

A retrospective analysis involved 65 obese patients (BMI  $> 2$  SDS), 33 female and 32 male, aged 5-18 (mean age  $12,9 \pm 2,96$ ) diagnosed at the Department of Pediatrics and Endocrinology of the Medical

University of Warsaw. They were hospitalized for assessment of their metabolic and hormonal status. Anthropometric measurements included: height, weight, waist and hip circumference. Percentiles for weight and height were calculated. Fat mass percentage was obtained from bioimpedance analysis (BIA). BMI (body mass index) used to assess obesity was defined as weight divided by height squared [weight in kg/(height in meters)<sup>2</sup>]. WHR (waist-to-hip ratio) was defined as the ratio of waist circumference to the hip circumference (cm). WHtR (waist-to-height ratio) was defined as the ratio of waist circumference to height (cm). Both indices were used to assess distribution of body fat. Anthropometric data were standardized according to mean value and standard deviation (SD) for population of Warsaw children to obtain normalized values. Blood samples were collected after overnight fasting. The analysis included biochemical parameters such as 2-hour Oral Glucose Tolerance Test (OGTT) with 1.75 g/kg, max 75 g glucose, including fasting glucose, insulin, total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride (TG), 25(OH)D. The atherogenic index of plasma (AIP) was calculated as the ratio of triglyceridemia to high-density lipoprotein cholesterol (TG/HDL-cholesterol), total cholesterol to high-density lipoprotein cholesterol (TC/HDL-cholesterol), total cholesterol minus high-density lipoprotein cholesterol [(TC) - (HDL-cholesterol)]. Individual HOMA-IR index (homeostasis model assessment – insulin resistance) was calculated for every patient. Blood samples were analyzed in the Department of Laboratory Diagnosis and Clinical Immunology of the Developmental Age of the Medical University of Warsaw.

According to guidelines the 25(OH)D serum level  $< 20$  ng/ml is defined as deficient, 20-30 ng/ml as insufficient and  $> 30$ -50 ng/ml as sufficient (6). The number of obese children with sufficient 25(OH)D serum concentration was rather small so for statistical purposes the patients were divided into two subgroups: one subgroup included children with 25(OH)D serum level  $< 20$  ng/ml, the second one included children with 25(OH)D serum level  $> 20$  ng/ml.

The differences between groups were analyzed using the Student's T-test and Mann-Whitney's U-test. Differences were considered statistically significant at  $p < 0.05$ .

## RESULTS

A total of 65 children and adolescents were enrolled in the study. For 51 children (78.5%), 27 girls and

24 boys the serum 25(OH)D level was < 20 ng/ml. The mean age for the group was  $13.15 \pm 2.98$ , BMI =  $30.89 \pm 5.28$ , SDS BMI =  $4.26 \pm 1.91$ . For 14 children (21.5%), 6 girls and 8 boys, the serum 25(OH)D level was > 20 ng/ml. The mean age for the group was  $11.96 \pm 2.80$ , BMI =  $27.87 \pm 4.20$ , SDS BMI =  $3.04 \pm 1.44$ . The mean 25(OH)D levels for these two groups together (< 20 ng/ml and > 20 ng/ml) were  $13.8 \pm 2.85$  ng/ml and  $23.8 \pm 3.08$  ng/ml, respectively. Differences ( $p < 0.05$ ) between the two groups of obese children (with 25(OH)D serum levels < 20 ng/ml and > 20 ng/ml) were statistically significant in: SDS BMI, level of fasting insulin and HOMA-IR. The relationship of 25(OH)D levels and biochemical and clinical parameters was as follows: 25(OH)D levels were negatively correlated with SDS BMI, HOMA-IR and fasting insulin level. The differences between percentage of fat mass, WHR, WHtR, atherogenic index of plasma (AIP) were statistically insignificant (tab. 1).

## DISCUSSION

We investigated the relationship of 25(OH)D serum level in obese children and their anthropometric and

metabolic parameters. Lower 25(OH)D levels in obese children and adolescents were found to be related to higher body mass index ( $p < 0.05$ ). Recent studies also suggest that the level of serum 25(OH)D is significantly lower in children with higher BMI and increased body fat mass. Olson et al. investigated a group of 411 obese children (aged 6-16 years, BMI  $\geq$  95 percentile for age, median BMI = 99.2 percentile) and 87 normal-weight children (aged 6-16 years, BMI  $\leq$  85 percentile for age, median BMI = 53.3 percentile) season/age/ethnicity-matched with the obese group (1). There was a wide difference in BMI percentile between the two groups. The study revealed a 25(OH)D serum level of < 30 ng/ml for 92% of obese patients and a < 20 ng/ml for 50%. For normal-weight children the 25(OH)D concentration levels were 68 and 22%, respectively. In a study of 127 obese children (aged 6.0-17.9 years) hypovitaminosis D was diagnosed in 74% of subjects (2). A study including 120 obese and 120 normal-weight children also confirmed a negative correlation between BMI and the level of serum 25(OH)D (7). According to the National Health and Nutrition Examination Survey (NHANES) 2001-2004 which involved children

**Table 1.** Clinical and biochemical comparison of obese children (mean  $\pm$  SD) based on hypovitaminosis D status.

Parameters	Group < 20 ng/ml 25(OH)D (n = 51)	Group > 20 ng/ml 25(OH)D (n = 14)	p values
25(OH)D (ng/ml)	$13.80 \pm 2.85$	$23.81 \pm 3.08$	$p < 0.00001^*$
Age (years)	$13.15 \pm 2.98$	$11.96 \pm 2.8$	NS
Body height (cm)	$162.59 \pm 17.16$	$157.05 \pm 12.3$	NS
Height (SDS)	$0.83 \pm 1.21$	$1.07 \pm 1.13$	NS
Body weight (kg)	$84.31 \pm 28.84$	$70.17 \pm 19.97$	NS
Body weight (SDS)	$3.88 \pm 2.16$	$2.73 \pm 1.89$	NS
BMI (kg/m <sup>2</sup> )	$30.89 \pm 5.28$	$27.87 \pm 4.20$	NS
BMI (SDS)	$4.26 \pm 1.91$	$3.04 \pm 1.44$	$p < 0.05^{*1}$
Waist circumference (cm)	$92.22 \pm 15.87$	$85.93 \pm 10.6$	NS
Hip circumference (cm)	$103.98 \pm 13.68$	$96.21 \pm 12.12$	NS
WHR	$0.88 \pm 0.08$	$0.89 \pm 0.05$	NS
WHtR	$0.57 \pm 0.06$	$0.55 \pm 0.04$	NS
Percent of Body Fat (BIA)	$39.12 \pm 6.62$	$37.66 \pm 5.92$	NS
Fasting Blood Glucose (mg/dl)	$74.22 \pm 7.12$	$77.93 \pm 11.03$	NS
Fasting Blood Insulin (uIU/ml)	$18.60 \pm 12.69$	$10.20 \pm 6.95$	$p < 0.05^{*1}$
HOMA-IR	$3.43 \pm 2.45$	$2.03 \pm 1.56$	$p < 0.05^{*1}$
Total Cholesterol (TC) (mg/dl)	$177.06 \pm 28.68$	$178.86 \pm 23.13$	NS
HDL-C (mg/dl)	$44.24 \pm 10.46$	$44.85 \pm 12.71$	NS
LDL-C (mg/dl)	$103.95 \pm 25.27$	$106.98 \pm 24.15$	NS
Triglyceride (mg/dl)	$142.43 \pm 55.4$	$141.93 \pm 65.58$	NS
TG/HDL-C	$3.53 \pm 1.98$	$3.75 \pm 2.32$	NS
TC/HDL-C	$4.19 \pm 0.97$	$4.32 \pm 1.19$	NS
(TC) - (HDL-C)	$132.81 \pm 26.5$	$136.54 \pm 24.43$	NS

\*statistically significant

Tests applied for statistical analysis:

data with normal distribution: Student's T-test,

<sup>1</sup>data with abnormal distribution: Mann-Whitney U-test.

aged 1-21 years, obese subjects were at a higher risk of 25(OH)D deficiency than normal-weight children (8). Lenders et al. also reported a negative correlation between 25(OH)D and BMI in obese adolescents (9).

In a study of obese children Reinehr et al. report an increase of serum 25(OH)D level after weight loss (10). Moreover, a study of adult women confirmed the relationship between weight loss and increase of 25(OH)D as well as improvement of insulin sensitivity (11). Wortsman et al. suggested that obesity-associated low serum 25(OH)D concentration is most probably due to the decreased bioavailability of vitamin D which is deposited in adipose tissue (3). In this study the 25(OH)D serum level was evaluated in obese and non-obese subjects 24 hours after UVB irradiation of the whole body. For obese patients the increase of 25(OH)D was 57% lower than for normal-weight subjects. Baseline values for 25(OH)D concentration were not significantly different, circulating vitamin D levels significantly increased 24 hours after sun exposure whereas the percentage conversion of provitamin D<sub>3</sub> (7-dehydrocholesterol) to vitamin D<sub>3</sub> in the skin was not significantly different. In conclusion: skin capacity to produce vitamin D<sub>3</sub> is not affected in obese individuals, obesity may however alter the release of 25(OH)D from the skin to the blood stream. It is suggested that due to fat-soluble properties of vitamin D it can be stored in subcutaneous fat. It is likely that it is sequestered in the fat mass of obese subjects and so contributes to its low levels in the serum. This study also suggests higher bioavailability of vitamin D following oral supplementation. Lower seasonal variations of 25(OH)D serum levels in obese children as compared to normal-weight children (1) may also be explained by reduced sun exposure in obese individuals who lead a more indoor lifestyle (1, 4) and have unhealthy eating habits (intake of high caloric food poor in vitamins and minerals) (1, 5).

A potential limitation to our study is that it was performed throughout the whole year including spring and summer. Moreover, the results come from only one hospitalization. We were therefore unable to analyze seasonal variations of 25(OH)D serum levels nor the relationship between 25(OH)D values before and after weight loss.

We observed a negative correlation between 25(OH)D and HOMA index and fasting serum insulin levels in children with serum 25(OH)D deficiency. It has been suggested that in obesity proinflammatory molecules, secreted by adipocytes and adipose tissue macrophages, are involved in development of insulin resistance (12, 13). Vitamin D inhibits cytokine production (14) and therefore vitamin D deficiency may contribute to insulin resistance (15). Another mechanism which might explain the beneficial effect of 25(OH)D in the decrease of insulin resistance and improvement of insulin sensitivity in obese subjects is the reduction of inflammation (16) or enhancement of peripheral/hepatic uptake of glucose through regulation of the level of insulin secreted from  $\beta$ -cells (17-19). The positive effect of 25(OH)D on insulin sensitivity was

demonstrated by Maestro et al. (20). Administration of 1,25(OH)<sub>2</sub>D<sub>3</sub> was observed to increase the level of insulin receptor mRNA and insulin stimulated glucose transport in U-937 promonocytic cells, probably through the up-regulation of phosphatidylinositol 3-kinase activity (20). A study by Belenchia et al. confirmed significant improvement in HOMA-IR and QUICKY – the two markers of insulin resistance and sensitivity – in obese adolescents who received vitamin D (4000 IU/day) for 6 months (21). A study by Roth et al. reported a significant relationship of higher insulin concentration and insulin resistance HOMA-IR in obese subjects with lower level of 25(OH)D (15). The correlation between 25(OH)D and insulin resistance persisted even after adjustment for body mass. It is therefore likely that 25(OH)D deficiency is directly related to insulin resistance irrespective of body fat mass (15). Data from another study also reveal a negative correlation between 25(OH)D level and insulin resistance (HOMA-IR) (1). In a study by Kardas et al. the authors compared 63 obese subjects (mean age 13.5  $\pm$  1.7) and 51 normal-weight individuals (mean age 13.4  $\pm$  1.6) and reported a negative correlation between serum 25(OH)D level, HOMA index and fasting glucose (22). The study suggested that obesity is a risk factor for lower vitamin D levels, and therefore it increases insulin resistance. On the other hand, a study by Torun et al. demonstrates significantly higher insulin concentrations and higher insulin resistance in children with higher BMI, independent of 25(OH)D levels (23).

Vitamin D deficiency is considered a risk factor for impaired glucose tolerance in obese children (1). A study by Olson et al. related a negative correlation between 25(OH)D level and glucose levels (OGTT) in obese children. Poor glycemic control in 25(OH)D deficient subjects may result not only from insulin resistance but also from  $\beta$ -cell dysfunction (15). Chiu et al. also confirmed that 25(OH)D deficient subjects display impaired  $\beta$ -cell function responsible for impaired glucose homeostasis and are at higher risk of developing insulin resistance (24). A negative relationship was observed between 25(OH)D levels and first- and second-phase insulin responses during a hyperglycemic clamp and glucose levels during oral glucose tolerance test (OGTT). Vitamin D treatment was observed to improve  $\beta$ -cell function (24) and higher serum 25(OH)D levels predict better function of these cells and lower levels of glycemia (25). Recent studies also suggest a negative correlation between vitamin D levels and diabetes type 1 in children and adolescents (26). 25(OH)D deficiency was observed to increase the risk of diabetes mellitus type 1 by 200% (27).

In our study we also examined the relationship of 25(OH)D and the lipid profile. The results were not statistically significant. Recent studies report a likely involvement of vitamin D in lipid metabolism in adipose tissue. In a study by Querfeld et al. a significant increase in lipoprotein lipase activity in 3T3-L1 adipocytes was attributed to 1,25(OH)<sub>2</sub>D<sub>3</sub> (28). Another

study related that fatty acid synthase (catalyses adipocyte lipogenesis) is down regulated by  $1,25(\text{OH})_2\text{D}_3$  in 3T3-L1 cells (29). It is suggested that VDR (vitamin D receptor) inhibits lipid metabolism. It was observed that mice which lacked VDR, were resistant to high-fat diet-induced obesity. This was most likely caused by increased fatty acid  $\beta$ -oxidation in white adipose tissue, the expression of uncoupling proteins in brown fat and overall energy expenditure (30). Studies report a negative correlation between serum 25(OH)D and LDL-C, triglyceride (7, 22) and total cholesterol (22) and positive correlation with HDL-C (7, 22). In a study of 217 obese children Smotkin-Tangorra et al. confirmed a positive correlation between 25(OH)D and HDL-C (31). According to Botella-Carretero et al. this relationship is probably caused by vitamin D which maintains adequate levels of apolipoprotein A-1, the major component of

HDL cholesterol (32). It was observed that low HDL cholesterol levels in childhood are a risk factor for adult cardiovascular diseases (33). Another study confirmed that patients with cardiovascular diseases usually have lower 25(OH)D levels than healthy subjects (34).

The crucial role of 25(OH)D in prevention of metabolic disorders and future adult chronic disease draws attention to the significance of healthy dietary habits and treatment of vitamin D deficiency in obese children.

## CONCLUSIONS

In obese children a negative correlation is observed between BMI, HOMA-IR, fasting blood insulin and 25(OH)D serum concentrations. The results of the study show that treatment of vitamin D deficiency could be beneficial particularly in obese children and could protect them against adult chronic diseases.

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