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Serum 25-hydroxyvitamin D (25-OH-D) in obese adolescents

Stężenie 25-hydroksywitaminy D (25-OH-D) u otyłych nastolatków

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Abstract

Background: There is increasing evidence that vitamin D deficiency is common and has been associated with several non-bone related outcomes, including insulin resistance, type 2 diabetes and cardiovascular disease. The influences of gender, puberty, and adiposity on serum hydroxyvitamin D (25-OH-D) levels and the relationship between 25-OH-D and insulin resistance in obese children were studied.
Material and methods: Age, gender, pubertal stage, weight status (standard deviation score of body mass index: BMI-SDS, percentage body fat, waist circumference), 25-OH-D levels, and insulin resistance index calculated by homeostasis model assessment (HOMA-IR) were evaluated in 64 obese adolescents. Multivariable linear regression was used to determine factors associated with decreased serum 25-OH-D levels and to study the relationship between 25-OH-D and HOMA-IR.
Results: Median serum 25-OH-D level was 10.1 ng/mL (25.2 nmol/L). 14% of patients were vitamin D-sufficient (25-OH-D ≥ 20 ng/mL), 36% had intermediate values (11–19 ng/mL), and 50% were deficient (25-OH-D ≤ 10 ng/mL). In the multivariable model, older age, puberty, higher value of percentage of body fat, and the presence of acanthosis nigricans (AN) were all negatively associated with 25-OH-D. Lower 25-OH-D levels were also associated with higher blood glucose, insulin and HOMA-IR after adjustment for puberty and SDS-BMI. Summer positively correlated with 25-OH-D level.
Conclusion: Our study confirms that obesity is a risk factor for vitamin D deficiency. Hypovitaminosis D, common in obese adolescents at risk for type 2 diabetes (older age, puberty, acanthosis nigricans) is associated with worse insulin resistance.
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Key words: *vitamin D, obesity, adolescents, insulin resistance*

Streszczenie

Wstęp: Niedobór witaminy D jest zjawiskiem coraz bardziej powszechnym i związanym nie tylko z zaburzeniami metabolizmu kostnego, ale też z insulinoopornością, cukrzycą typu 2 i chorobami sercowo-naczyniowymi. Celem pracy było badanie wpływu płci, stadium pokwitania i otyłości na stężenie 25-OH-D w surowicy oraz zależności między witaminą D a insulinoopornością u otyłych dzieci.
Materiał i metody: U 64 otyłych nastolatków oceniano wiek, płeć, stadium pokwitania, stopień otyłości i wskaźnik insulinooporności (HOMA-IR). Do określenia czynników wpływających na obniżenie stężenia 25-OH-D w surowicy oraz do oceny zależności między 25-OH-D a HOMA-IR wykorzystano wielowymiarową analizę regresji.
Wyniki: Mediana stężenia 25-OH-D w surowicy wynosiła 10,1 ng/mL (25,2 mmol/L). Tylko u 14% pacjentów stężenie 25-OH-D w surowicy było wystarczające (≥ 20 ng/mL), u 36% wartości te wynosiły 11–19 ng/mL, u 50% stwierdzono znaczny niedobór 25-OH-D (≤ 10 ng/mL). W wielowymiarowej analizie regresji starszy wiek, bardziej zaawansowane stadium pokwitania, większy odsetek zawartości tłuszczu i obecność rogowacenia ciemnego korelowały negatywnie ze stężeniem witaminy D. Niższe stężenia 25-OH-D wiązały się z wyższym stężeniem glukozy, insuliny i HOMA-IR przy uwzględnieniu stadium pokwitania i SDS-BMI. Okres letni pozytywnie korelował ze stężeniem 25-OH-D.
Wnioski: Otyłość jest czynnikiem ryzyka niedoboru witaminy D. Niedobór witaminy D powszechny u otyłych nastolatków zagrożonych cukrzycą typu 2 wiąże się z większą insulinoopornością. **(Endokrynol Pol 2011; 62 (6): 506–511)**

Słowa kluczowe: *witamina D, otyłość, nastolatkowie, insulinooporność*

Introduction

Vitamin D is an important prohormone which regulates ~3% of the human genome [1], so it is only to be expected that its deficiency may have wide-ranging effects. The most frequent and immediate clinical presentations during childhood are skeletal complications such as *genu valgum* (bowed legs), fractures and radiographic bone features [2]. Non-specific musculoskeletal pain is another frequent feature, especially in adolescence [2]. Vitamin D deficiency in adolescent girls starting their reproductive life is of particular concern since a recent

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Finnish study showed that neonates born to mothers with low vitamin D status had significantly lower bone mineral content [1]. Moreover, this effect may continue into childhood [2].

Vitamin D deficiency may also be associated with several non-bone unfavourable outcomes. Other extraskeletal manifestations of hypovitaminosis D may include malignancy [3], autoimmune diseases [4], multiple sclerosis and schizophrenia [5]. Additionally, the role of vitamin D in the pathogenesis of type 2 diabetes has recently been reviewed [6]. An association has been found between low vitamin D status and insulin resistance. In some studies, vitamin D supplementation improved insulin secretion and glucose tolerance [6, 7].

The associations between serum concentration of vitamin D and insulin resistance, potentially leading to type 2 diabetes and cardiovascular diseases, have not been fully explored in children. In two studies, no relationship between low vitamin D status and insulin resistance in obese children was found [8, 9]; but there were several limitations to these studies. On the other hand, the study by Reis et al. [10] showed that low serum vitamin D in adolescents was strongly associated with increased risk for fasting hyperglycaemia, hypertension, and metabolic syndrome, independently of adiposity.

As data concerning the vitamin D status in obese children and its relation to insulin sensitivity is controversial, we studied serum 25-OH-D levels in obese adolescents and its relationship to selected parameters of carbohydrates and lipids' metabolism. Given the lack of consensus regarding the definition of optimal vitamin D status in children, it is vital to identify functional outcomes by which to define vitamin D status. One such outcome is insulin sensitivity. Thus, our study examined the prevalence of vitamin D deficiency, as well as the relationship of vitamin D and insulin resistance in obese adolescents based on the hypothesis that low vitamin D status is associated with worse insulin resistance, even after adjusting for such important mediators of insulin resistance as obesity, age and puberty.

Material and methods

Study group

The study group consisted of 64 obese adolescents (33 boys and 31 girls), aged 10–18 years, attending the Outpatients Clinic for Children with Metabolic Disorders. Obesity was recognised on the basis of a body mass index (BMI) above the 97th percentile for age and sex on the BMI percentile charts for Warsaw population of children and adolescents [11]. Children with acute or chronic infections, as well as children with significant medical conditions such as genetic syndromes, cancers, autoimmunologic diseases, hepatic or renal dysfunction, hormonal abnormalities or diabetes, were excluded. All patients were non-smokers without any regular medication.

The protocol of the study was approved by the Ethical Committee of the Pomeranian Medical University.

Anthropometric and clinical measurements

Anthropometric measurements (body height and weight, waist circumference) were performed by trained personnel, with the patients wearing only light underwear. Standard, electronic scale and Harpender's stadiometer were used to determine body weight and height. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square metres (kg/m^2). Since BMI changes with age, the BMI-SD score (BMI-SDS) was also calculated. The minimal abdominal circumference between the xiphoid process and iliac crest was measured to determine the waist circumference. Because waist circumference changes with age, the waist-SDS was also calculated for both genders. Percentage body fat (% FAT) and fat mass (in kg) were measured using the bioimpedance method (Bioelectrical Impedance Analyzer Tanita 131, Japan) with an applied current of 0.8 mA at a fixed frequency of 50 kHz.

Physical examination was performed to check the general health status, as well as for any evidence of *acanthosis nigricans*, commonly known to be a clinical marker of insulin resistance in obese patients. Pubertal status was ascertained during physical examination and classified according to Marshall and Tanner. All participants were pubertal, defined as Tanner stage 2 or greater. In girls, breast stage was used if there was a discrepancy between breast and pubic hair development. In boys, pubic hair was used if there was a discrepancy between genitalia and pubic hair staging.

Ambulatory blood pressure monitoring (ABPM) was performed using a Mobil-O-Graph device, which uses the oscillometric method. Systolic (SBP) and diastolic blood pressure (DBP) were measured hourly between 11 p.m. and 7 a.m., and half-hourly between 7 a.m. and 11 p.m.

Biochemical measurements

All blood samples were obtained between 8 a.m. and 11 a.m. after an overnight fast. Serum 25-OH-D was measured using Nichols radioimmunoassay (Nichols Institute, San Clemente, CA, USA) with intraassay and interassay CVs of 4.6% to 11.5% and 8.4% to 14.0%, respectively. Glucose was measured with the glucose oxidase technique (Glucose HK Analyzer, Olympus). Free insulin concentration was determined by RIA (Pharmacia RIA kit). HbA_{1c} was measured by the immunoturbimetric method. Total cholesterol (T-chol), HDL cholesterol (HDL-chol) and triacylglycerol (TG) levels were measured in serum by automated enzymatic procedures (Olympus). LDL cholesterol (LDL-chol) was

determined after separating LDL fraction from fresh serum by sequential ultracentrifugation, using an Olympus commercial kit. The homeostasis model was used for assessing insulin resistance (HOMA-IR), according to the following formula: HOMA-IR = fasting blood glucose (mmol/L) × fasting insulin (μU/mL)/ 22.5 [12].

Vitamin D status

Vitamin D status was classified as: severe deficiency (serum 25-OH-D: ≤ 10 ng/mL); insufficiency (serum 25-OH-D: > 10 to < 20 ng/mL); or sufficiency (serum 25-OH-D: 20–30 ng/mL) [13].

For the purposes of analysis, we defined seasons by months: winter (December–May) and summer (June–November).

Statistical analysis

Statistical analysis was performed using the STATA 11 software package. Means and standard deviations were used to summarise continuous variables that were normally distributed. Kolmogorov-Smirnov test was used to check for normality of distribution; $p < 0.05$ was considered evidence of non-normality. Medians, minima and maxima were used to present continuous variables that were not normally distributed. Statistically significant differences were tested for quantitative items by the Student's t-test, and for qualitative items by χ^2 test. 25-OH-D levels were correlated to degree of obesity (BMI-SDS, percentage of body fat), waist circumference, glucose, insulin, HOMA-IR as well as lipid profile and blood pressure by Pearson's correlation. Multivariable linear regression analysis was conducted for the dependent variable 25-OH-D concentration, including season of the study, age, pubertal stage, obesity status and HOMA-IR as independent variables.

Table I. *Clinical and biochemical characteristics of study group (n = 64)*

Tabela I. *Kliniczna i biochemiczna charakterystyka badanej grupy (n = 64)*

Age, years (mean ± SD)	14.6 ± 2.1
Studied in summer, n (%)	38 (59)
Male/female, n (%)	33 (52)/31 (48)
Tanner stage (2, 3, 4, 5)	13, 11, 6, 34
Body mass [kg] (mean ± SD)	82.6 ± 19.3
BMI-SDS, median (min, max)	3.3 (2.1, 9.2)
Percentage of fat (mean ± SD)	34.3 ± 5.0
Waist-SDS (mean ± SD)	4.0 ± 1.7
Acanthosis nigricans, n (%)	33 (52)
SBP [mm Hg] (mean ± SD)	122.9 ± 10.5
DBP [mm Hg] (mean ± SD)	78.9 ± 10.8
25-OH-D [ng/mL] (mean ± SD)	11.9 ± 6.4
Glucose [mmol/L] (mean ± SD)	5.2 ± 0.4
Insulin [μU/mL] median (min, max)	17.8 (6.0, 56.4)
HOMA-IR median (min, max)	4.2 (1.1, 12.9)
HbA_{1c} (%) (mean ± SD)	5.5 ± 0.3
T-chol [mg/dL] (mean ± SD)	174.6 ± 26.3
HDL-chol [mg/dL] (mean ± SD)	47.2 ± 10.9
LDL-chol [mg/dL] (mean ± SD)	103.3 ± 30,4
TG, mg/dL [mg/mL] (mean ± SD)	124.9 ± 41.8

Results

A total of 64 adolescents were recruited; 39 (60%) were tested in summer, and 25 in winter.

Clinical and biochemical characteristics of the study group are set out in Table I.

Serum 25-OH-D concentration was negatively correlated with most of the demographic and biochemical variables, and positively with HDL-cholesterol level. Summer was positively associated with 25-OH-D (Table II).

Table II. *Unadjusted Pearson's correlation coefficients of 25-OH-D and some demographic and biochemical variables**

Tabela II. *Ocena zależności pomiędzy 25-OH-D a wybranymi demograficznymi i biochemicznymi* zmiennymi w korelacji Pearsona*

Selected parameters	25-OH-D	
	r	p-value
Age	–0.30	**0.016**
Summer	0.32	**0.010**
Gender	–0.23	0.072
Puberty	–0.33	**0.008**
BMI-SDS	–0.33	**0.008**
Percentage of fat	–0.63	**0.000**
Waist-SDS	–0.52	**0.000**
Acanthosis nigricans	–0.54	**0.000**
SBP	–0.48	**0.000**
DBP	–0.55	**0.000**
Glucose	–0.22	0.084
Insulin	–0.53	**0.000**
HOMA-IR	–0.54	**0.000**
HbA_{1c}	–0.57	**0.000**
T-chol	–0.39	**0.001**
HDL-chol	0.47	**0.000**
LDL-chol	–0.40	**0.001**
TG	–0.39	**0.002**

*After adjustment for BMI-SDS and puberty

Table III. *Clinical and biochemical characteristics of subjects based on vitamin D status*
Tabela III. *Kliniczna i biochemiczna charakterystyka grupy badanej w zależności od stężenia witaminy D w surowicy*

	Sufficient ≥ 20 ng/mL	Insufficient < 20 ng/mL	Deficient ≤ 10 ng/ml	p value
n (%)	9 (14)	23 (36)	32 (50)	
Age, years (mean ± SD)	13.3 ± 2.5	14.8 ± 1.6	16.2 ± 2.3	**0.025**
Studied in winter, n (%)	1 (4)	9 (36)	16 (60)	0.078
Male/female, n (%)	7(21) / 2(7)	10(30) / 13(42)	16(49) /16(51)	0.450
Body mass, kg (mean ± SD)	67.5 ± 15.4	81.4 ± 15.6	87.8 ± 20.6	**0.017**
BMI-SDS (mean ± SD)	2.9 ± 0.6	3.5 ± 1.3	4.1 ± 1.7	0.086
Percentage of fat (mean ± SD)	29.3 ± 4.2	32.6 ± 4.3	36.9 ± 4.1	**0.000**
Waist-SDS [cm] (mean ± SD)	2.7 ± 1.0	3.4 ± 1.3	4.7 ± 1.7	**0.001**
Acanthosis nigricans, n (%)	1 (3)	5 (15)	27 (82)	**0.000**
SBP [mm Hg] (mean ± SD)	114.8 ± 8.2	119.4 ± 10.3	127.7 ± 8.9	**0.000**
DBP [mm Hg] (mean ± SD)	70.4 ± 8.3	74.4 ± 10.0	84.5 ± 8.9	**0.000**
25-OH-D [ng/mL] (mean ± SD)	24.1 ± 1.9	14.1 ± 2.9	6.8 ± 1.7	**0.000**
Glucose [mmol/L] (mean ± SD)	5.1 ± 0.2	5.3 ± 0.4	5.3 ± 0.4	0.286
Insulin [μU/mL] (mean ± SD)	13.5 ± 5.4	13.8 ± 5.5	25.7 ± 9.9	**0.000**
HOMA-IR median (min, max)	3.0 ± 1.3	3.1 ± 1.4	5.9 ± 2.2	**0.000**
HbA_{1c} (%) (mean ± SD)	5.3 ± 0.2	5.4 ± 0.3	5.7 ± 0.3	**0.000**
T-chol [mg/dL] (mean ± SD)	159.2 ± 38.5	168.7 ± 24.5	183.2 ± 21.0	**0.019**
HDL-chol [mg/dL] (mean ± SD)	50.8 ± 9.1	54.2 ± 9.2	41.2 ± 9.2	**0.000**
LDL-chol [mg/dL] (mean ± SD)	87.6 ± 37.2	95.7 ± 45.4	113.0 ± 27.2	**0.027**
TG, mg/dL [mg/mL] (mean ± SD)	71.4 ± 38.7	93.7 ± 45.4	162.4 ± 43.0	**0.003**

As mentioned above, serum 25-OH-D concentration was within intermediate values, although in the lower range (Table I). Only nine (14%) obese children were vitamin D-sufficient (25-OH-D ≥ 20 ng/mL); 23 (36%) were insufficient, and 32 (50%) had severe deficiency (Table III).

Table III displays differences in clinical characteristics and results of biochemical investigations by vitamin D status.

The risk of vitamin D deficiency/insufficiency was greater in winter (25/26) than in summer (30/38; p = 0.078). Sex was not associated with vitamin D status, although boys had higher mean serum 25-OH-D levels compared to girls (13.3 ± 7.2 *vs.* 10.4 ± 5.4 ng/mL; p = 0.07; data not shown). Pubertal stage (2–5 according to Tanner's scale) was not associated with vitamin D status (p = 0.126; data not shown).

Both vitamin D deficiency and insufficiency were associated with higher body mass, (but not with BMI-SDS), higher content of fat tissue, greater waist circumference (waist-SDS), and the presence of *acanthosis nigricans*, which was found in 97% of vitamin D deficient / insufficient patients. Adolescents with vitamin D deficiency and insufficiency also had higher mean systolic and diastolic blood pressure (Table II).

Similarly, both vitamin D deficiency and insufficiency were associated with higher fasting insulin, HbA_{1c}, total and LDL-cholesterol, triacylglycerol and higher HOMA-IR.

Clinical and biochemical parameters of subjects were used in multivariable models with low 25-OH-D (≤ 10 ng/mL) concentration as a dependent variable. Similar models were performed for HOMA-IR. Results are presented in Tables IV and V, respectively.

Age was not a predictor when puberty, a known modulator of insulin sensitivity, was included in the model.

Discussion

Several recent studies have indicated that there is an increased prevalence of vitamin D deficiency in industrialised countries [13, 14]. Low vitamin D status may be caused by a number of factors, including insufficient synthesis in the skin (due to limited sunlight exposure) and inadequate intake or absorp-

Table IV. *Results of multivariable linear regression for associations of patients' characteristics with serum 25-OH-D concentration*

Tabela IV. *Korelacje między wybranymi parametrami a stężeniem 25-OH-D w surowicy w wieloczynnikowej analizie regresji*

Variable	Partial β-coefficient	p value	R^2 for multivariable model
			0.42
Puberty	–0.37	0.003	
% Fat	–0.39	0.002	
Acanthosis nigricans	–0.39	0.002	
Summer	0.35	0.008	
HOMA-IR	–0.48	0.000	

Table V. *Results of multivariable linear regression for association of serum 25-OH-D concentration with HOMA-IR*

Tabela V. *Korelacja między stężeniem 25-OH-D w surowicy a HOMA-IR w wieloczynnikowej analizie regresji*

Variable	Partial β-coefficient	p value	R^2 for multivariable model
			0.33
Puberty	0.29	0.065	
BMI-SDS	0.32	0.046	
25-OH-D	–0.48	0.000	

tion of vitamin D. Moreover, people living at higher latitudes (> 35°) — as in our country — are especially at increased risk for vitamin D deficiency, because in winter most of the UVB radiation from sunlight, which is required for cutaneous synthesis of vitamin D, is absorbed by the atmosphere and does not reach the earth's surface [15].

The serum concentration of 25-hydroxyvitamin D, an indicator of vitamin D status, has been previously found to be low in obese adults [16]. In our study, 86% of subjects were identified with hypovitaminosis D, whereas vitamin D deficiency was observed in one half (50%) of obese adolescents; 36% met the definition of vitamin D insufficiency, whereas only 14% of the subjects were vitamin D-sufficient. Vitamin D-deficient patients were older and had higher body mass, SDS-BMI, percentage of body fat, and SDS-waist circumference. The low levels of 25-OH-D in obese adolescents in our study concur with most studies in children and adolescents [8, 10, 17]. The explanation for this association has been the sequestration of vitamin D in the subcutaneous fat tissue and its consequent reduced bioavailability [16]. Furthermore, the low levels of 25-OH-D may be attributed to several other factors such as sedentary lifestyles of obese individuals associated with less outdoor activities and reduced sunlight exposure, which may decrease endogenous vitamin D production and compromise vitamin D status. Vitamin D insufficiency associated with obesity is likely to be functionally significant, as compensatory hyperparathyroidism has been observed in obese children and adolescents [9, 17]. It has been found that parathyroid hormone levels were positively, and 25-OH-D concentrations were negatively, related to weight status in prepubertal children [9]. Since these alterations normalised after weight loss, the authors concluded that these changes were consequences rather than causes of overweight.

It has become increasingly clear that vitamin D deficiency is an important risk factor for the development of type 2 diabetes mellitus (DM) [6, 18, 19]. Insulin resistance is a recognised precursor in the development of type 2 DM. It has been found that among adults without diabetes, vitamin D status was inversely associated with surrogate measures of insulin resistance [19, 20]. In our study, fasting insulin level and HOMA-IR were significantly correlated with low 25-OH-D concentration, even after adjustment for SDS-BMI and puberty. Moreover, in the multivariable model, pubertal stage, percentage of body fat, the presence of *acanthosis nigricans* and HOMA-IR were all negatively associated with 25-OH-D concentration. In another model, HOMA-IR positively correlated with puberty and SDS-BMI, and negatively correlated with serum 25-OH-D levels. Similar results have been obtained in most studies in children and adolescents [10, 17, 21]. The results of a cross-sectional study by Kelly et al. [21] showed that vitamin D deficiency is associated with worse insulin resistance in children, even after adjusting for obesity and puberty. Alemzadeh et al. [17] observed a positive relationship between vitamin D status and insulin sensitivity in children and adolescents. The hypovitaminosis D subjects had decreased insulin sensitivity compared to vitamin D-sufficient patients. Moreover, serum 25-OH-D levels were inversely correlated with HbA_{1c} independently of body adiposity, implying a higher risk for developing impaired glucose metabolism in children with vitamin D deficiency.

There are several possible mechanisms by which vitamin D deficiency may affect insulin sensitivity. Decreased vitamin D concentrations cause elevation of parathyroid hormone levels, which in turn affects insulin sensitivity by regulating the intracellular free calcium concentrations in target cells. Vitamin D may also play a role in insulin action by stimulating the expression of

insulin receptor and enhancing insulin responsiveness for the transport of glucose.

The mechanism of action of vitamin D in type 2 diabetes is suspected to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but also through a direct action on pancreatic β-cell secretory function [6]. Chiu et al. [19] showed that vitamin D levels were negatively correlated with both first- and second-phase insulin responses during the hyperglycaemic clamp and glucose levels during oral glucose tolerance test. They suggested that subjects with vitamin D deficiency not only displayed impaired β-cell function causing impaired glucose tolerance, but also were at increased risk of developing insulin resistance and metabolic syndrome compared to vitamin D-sufficient adults.

It is commonly accepted that insulin resistance potentially leads to several adverse clinical and biochemical outcomes known as metabolic syndrome [10, 19, 20]. In the current study, we observed significant trends for a lower body mass and lower waist circumference in adolescents with higher vitamin D levels. Mean blood pressure (systolic and diastolic), insulin, HbA_{1c} and triacylglycerol concentrations were also lower in those with higher levels of vitamin D. In contrast, subjects with lower HDL-cholesterol had also lower 25-OH-D levels.

Our results are consistent with previous studies that have suggested that hypovitaminosis D in adults may influence the risk of developing hypertension [22], diabetes [23] and cardiovascular disease [24]. Few other studies have examined the relationship between vitamin D deficiency and risk factors of cardiovascular disease in youth [10, 17]. Reis et al. [10], in a large, cross-sectional analysis including more than 3,000 adolescents, showed that low serum 25-OH-D was strongly associated with hypertension, hyperglycaemia, and metabolic syndrome, independently of body adiposity.

Further longitudinal studies are necessary to determine whether vitamin D deficiency during childhood significantly predicts the occurrence of cardiovascular disease and type 2 DM in adulthood.

Conclusion

Vitamin D deficiency and insufficiency are common among obese adolescents. Based upon current results, low vitamin D status is an independent predictor of insulin resistance, even after adjusting for SDS-BMI and puberty, which are known to be important mediators of insulin resistance. Moreover, we also found a significant association between vitamin D deficiency and some clinical and biochemical parameters of insulin resistance syndrome (metabolic syndrome). The possibility that low vitamin D status promotes insulin resistance holds the promise of a simple medical intervention that would decrease the risk of type 2 DM and cardiovascular disease.

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