Vitamin D Status, Insulin Resistance, Leptin-To-Adiponectin Ratio in Adolescents: Results of a 1-Year Lifestyle Intervention

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Abstract

AIM: We aimed to study the relationships between circulating 25-hydroxyvitamin D [25(OH)D], insulin resistance and leptin-to-adiponectin (L/A) ratio in Guadeloupean children and adolescents and to analyse the changes in 25(OH)D levels after a 1-year lifestyle intervention program.

METHODS: 25(OH)D concentrations were measured via a chemiluminescence assay. Cardiometabolic risk factors, homoeostasis model assessment of insulin resistance (HOMA-IR), and adipokines were measured. The lifestyle intervention included dietary counselling, regular physical activity.

RESULTS: Among 117 girls and boys (11–15 years old, 31.6% obese), 40% had vitamin D deficiency (25(OH)D levels < 20 ng/mL). With linear regression models where 25(OH)D and HOMA-IR acted as independent variables and age, sex, BMI, L/A ratio as covariates, 25(OH)D was significantly associated with HOMA-IR alone (P = 0.036). HOMA-IR was also associated with BMI z-score ≥ 2, L/A ratio and an interaction term BMI z-score ≥ 2*L/A ratio (P < 0.001 for all). After one year, in 78 children/adolescent, mean serum 25(OH)D increased significantly from 21.4 ± 4.9 ng/mL at baseline to 23.2 ± 6.0 after 1 year; P = 0.003 whereas BMI z-score, HOMA-IR and L/A ratio decreased significantly (P = 0.003, P < 0.001 and P = 0.012; respectively).

CONCLUSION: The association between 25(OH)D and HOMA-IR, independently of obesity and the high prevalence of vitamin D deficiency should be considered in order to prevent the later incidence of T2DM. A healthy lifestyle including non-sedentary and outdoor activities could be a way for improving vitamin D status.

Introduction

Vitamin D deficiency, a public health concern, define as serum 25-hydroxyvitamin D [25(OH)D] lower than 20 ng/mL (50 nmol/L) [1], is frequent in adolescents worldwide and particularly in presence of obesity. Vitamin D is mainly synthesised from 7-dehydrocholesterol by the skin's exposure to ultraviolet B (UVB) radiation. Circulating 25(OH)D is obtained from both UVB action and dietary intake,

provides an indication of vitamin D stores. Any barrier to the penetration of UVB radiation into the skin may result in a decrease in circulating 25(OH)D. Melanin pigment may absorb the ultraviolet B photons responsible for the photolysis of 7-dehydrocholesterol to vitamin D3. Vitamin D deficiency has negative consequences on indices of insulin resistance (IR) and metabolic parameters [2].

In a previous study conducted in Guadeloupean school children and adolescents

(children/adolescents), we found that obesity was associated with an adverse metabolic profile including a high frequency of insulin resistance (89%) [3].

This should also be a concern in the island of Guadeloupe (FWI), in which the prevalence of diabetes is high and estimated at 8.1% [4].

Vitamin D deficiency may be a major contributor to the obesity-associated complications with potential interactions between 25(OH)D, weight status, IR and leptin and adiponectin cytokines. These adipocytokines have opposite effects on BMI and IR. However, the leptin-to-adiponectin (L/A) ratio has been proposed as a potential clinical tool for the assessment of IR [5]. Few studies on vitamin D status and IR in adolescents measured circulating leptin and adiponectin concentrations and still less in black adolescents or in those living in sun-rich climates [6-9].

Thus, we aimed to evaluate the association of serum 25(OH)D levels with measures of obesity, insulin resistance and leptin-to-adiponectin ratio and to analyse the potential changes in 25(OH)D levels after a 1-year lifestyle intervention combining enhanced physical activity and diet counselling for the Guadeloupean children/adolescents.

Subjects and Methods

Study design and population

The present study concerned a sample of 117 children and adolescent, aged 11 to 15 years, from a previous study on overweight conducted in Guadeloupe Island (FWI) in 2013 [3]. In this study, volunteer healthy children from a middle school were enrolled to assess 1) their basal metabolic profiles according to weight status and 2) changes in these profiles after 1-year lifestyle intervention program.

The current study targeted vitamin D status in conjunction with obesity and insulin resistance.

Exclusion criteria included seizure disorders, diabetes, cardiovascular disease, pregnancy, and use of calcium or vitamin D replacement therapy.

The study was approved by the Ethic Committee (South West - Overseas III, France). Written informed consent, to participate in this study, was obtained from all children and parents. Clinical and biological examinations were performed at baseline and one year later.

The study protocol has been described in more details elsewhere [3]. Briefly, the 1-year lifestyle intervention program included 1) a nutritional information, focusing on overweight prevention and explaining healthy eating (with an increase in the consumption of fruits and vegetables and a decrease in the consumption of high-fat and high sugar meals) 2) Information on health risks for diseases related to lack of exercise and overweight 3) Encouragement for reduction of sedentary behaviors 4) advice to achieve five hours per week of school physical education and/or physical activity outside of school and 5) Participation of parents.

The school usually provided three hours per week of physical education, supervised by physical education teachers. These activities are outdoors except in bad weather.

Phone calls were made to maintain adherence to the program.

Survey data. Participants were interviewed and examined at baseline and 1 year after.

Physical examination. Height in centimetres (cm) and weight in kilogrammes (kg) was measured with participants standing without shoes and lightly clothed. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). The standard deviation score of body mass index (BMI z-score) was also used [10] and a BMI z-score $\geq$ 2 was considered as obesity. Waist circumference (WC) in centimetres (cm) was measured and the waist- to height ratio (WHtR) was calculated. Pubertal stage was assessed according to Tanner [11]. Tanner stages 3, 4 and 5 defined pubertal/postpubertal development.

Laboratory assessments. Blood glucose level (mmol/L) was assessed using the glucose oxidase method. Serum lipid levels (mmol/L) were measured enzymatically. Serum insulin levels (µIU/mL) were measured using the COBAS electrochemiluminescence immune assay test (Roche Diagnostics, Basel, Switzerland). The homeostasis model assessment to determine insulin resistance (HOMA-IR) was calculated: [fasting insulin (µIU/mL) x fasting glucose (mmol/L) / 22.5] [12].

Plasma samples were frozen at -80 °C until measurements of leptin, adiponectin and 25(OH) vitamin D. Leptin ng/mL and total adiponectin (µg/mL) were measured with ELISA kits Biovendor® (RD191001100) and Alpco® (47-ADPHUE-01) respectively. Plasma concentrations of 25(OH)D was measured via a chemiluminescence assay (DiaSorin SA, Antony, France), which includes 25(OH)D2 and 25(OH)D3.

These measurements were made concomitantly for the samples collected at baseline and one year after (end of the study).

Definition of factors

Weight status: The children were classified according to the definition of overweight and obesity by the International Obesity Task Force (IOTF) with

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three categories: normal weight (BMI<IOTF-25 kg/m^2), overweight with (BMI≥IOTF-25 kg/m^2 and BMI<IOTF-30 kg/m^2) and obese (BMI≥IOTF-30 kg/m^2) [13, 14]. _Abdominal obesity_ in children was defined as WHtR greater or equal to 0.5 [15]. _Insulin resistance_ was defined by a HOMA-IR > 3.16 [16]. _Vitamin D status_ was classified into the following three categories for 25(OH)D: deficiency (<20 ng/mL [<50 nmol/L]), insufficiency (≥ 20 ng/mL [≥ 50 nmol/L] and < 30 ng/mL [<75 nmol/L]) and sufficiency (≥ 30 ng/mL [≥75 nmol/L]) [17].

Statistical analysis

Data are presented as numbers (percentages) for categorical variables and as means ± standard deviations (SD) or median [inter quartile range] for continuous variables. Variables with a skewed distribution were log-transformed to approach a normal distribution. The chi-squared test and ANCOVA with adjustment for age, sex were used to test percentage and mean differences between groups according to the presence or absence of vitamin D deficiency and of insulin resistance. Non-parametric tests were used for comparison between data at baseline and at 1 year.

The Pearson correlation test was used to study the relationships between serum 25(OH)D levels, HOMA-IR and L/A ratio with other continuous variables. We also used the multivariate linear regressions in the overall study population to assess the associations of 25(OH)D concentrations and HOMA-IR index as dependent variables with age, sex, BMI z-score and L/A ratio as covariates. In addition, serum 25(OH)D concentrations or HOMA-IR were included in the models, as covariates, according to the dependent variable.

The effects of the covariates were assessed by the values of the regression coefficients corresponding to the non-standardized regression coefficients (nSRC). IBM SPSS Statistics, version 21 (SPSS, Chicago, IL) were used for data analyses. A _P value_ < 0.05 was considered significant.

Results

Characteristics of the study population at baseline

A total of 117 children/adolescents of both sexes, with a mean age of 12.5 ± 0.1 years, were concerned by the present study. Among them, 59.8% were girls. Most adolescents (98%) were Afro-Caribbean (with high skin pigmentation). There were: 31.6% obese, 32.5% with overweight and 35.9% of normal weight. The frequency of children eating at school canteen was higher in normal weight (53%) than in overweight (28%) and obese (30%) children; (P = 0.027), (data not shown). School canteens follow the recommendations designed to lower fat and sugar and increase vegetables and fruit in meals. Most children/adolescents (92.3%) were at pubertal/postpubertal stage (Tanner stage ≥ 3) and none was receiving vitamin D supplement therapy. Means of serum 25(OH)D concentrations was 21.2 ± 5.1 ng/mL. Seventy-eight (66.7%) children were insulin resistant. Regarding the vitamin D status, 40% had a vitamin D deficiency, 54% a vitamin D insufficiency, and 6% had sufficient vitamin levels. The frequencies of vitamin D deficiency in obese, overweight and normal-weight were 51%, 37% and 33%, respectively; P = 0.233. Considering those who were obese, mean 25(OH)D levels were significantly lower than in the rest of the study sample (19.6 ng/mL _v_ 21.9 ng/mL, respectively; P = 0.023).

Characteristics of the children and adolescents in presence/absence of vitamin D deficiency and of insulin resistance

Distribution of parameters according to presence/absence of vitamin D deficiency and of insulin resistance are summarised in Table 1.

Table 1: Characteristics of school-children 11 to 15 years according to Vitamin D and Insulin resistance status

	All adolescents	Vitamin D deficiency			Insulin resistance		
		No	Yes	P	No	Yes	P
	n =117	n =70	n =47		n =39	n =78	
Age (y)	12.0 ± 1.0	11.9 ± 1.1	12.0 ± 1.0	_0.979_	11.8 ± 1.0	12.0 ± 1.0	_0.237_
Sex (Girls)	59.8%	54.3%	45.7%	_0.136_	25.7%	74.3%	**_0.033_**
Tanner stage ≥ 3	92.3%	94.3%	89.4%	_0.327_	92.3%	92.3%	_1_
BMI (Kg/m^2)	24.2 ± 6.2	23.2 ± 5.22	25.72 ± 7.12	**_0.021_**	21.2 ± 4.7	25.8 ± 6.28	**_<0.001_**
BMI z-score	1.09 ± 1.19	0.94 ± 1.23	1.32 ± 1.10	_0.079_	0.58 ± 1.11	1.35 ± 1.15	**_0.001_**
Obesity (IOTF)	31.6%	25.7%	40.4%	_0.094_	10.3%	42.3%	**_<0.001_**
Abdominal Obesity	32.5%	15.4%	41.0%	**_0.002_**	27.1%	40.4%	_0.158_
Fasting blood glucose (mmol/L)	4.83 ± 0.43	4.74 ± 0.38	4.95 ± 0.46	**_0.011_**	4.55 ± 0.36	4.96 ± 0.39	_<0.001_
Leptin (ng/mL)	23.39 ± 20.44	20.54 ± 16.62	27.45 ± 24.52	_0.266_	13.42 ± 13.96	28.37 ± 21.39	**_<0.001_**
Adiponectin (μg/mL)	5.41 ± 2.61	5.86 ± 2.70	4.76 ± 2.35	**_0.010_**	6.56 ± 2.82	4.83 ± 2.30	**_0.001_**
Leptin to adiponectin ratio	5.94 ± 6.53	4.80 ± 5.05	7.55 ± 7.98	**_0.026_**	2.69 ± 3.50	7.56 ± 7.09	**_<0.001_**
HOMA-IR index	4.70 ± 3.01	4.04 ± 2.32	5.69 ± 3.63	**_0.003_**	--	--	--
HOMA-IR index>3.16	66.7%	28.2%	46.2%	_0.062_	--	--	--
25(OH)D (ng/mL)	21.17 ± 5.05	--	--	--	22.85 ± 4.72	20.33 ± 5.03	**_0.012_**
25(OH)D (ng/mL) <20	40.2%	--	--	--	28.2%	46.2%	_0.062_

Data in this table are mean ± SD and column percentage BMI, body mass index; HOMA-IR, homoeostasis model assessment-insulin resistance; 25(OH)D, 25-hydroxyvitamin D. All p-values are in italic and significant p-value are in bold italic.

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BMI, WC, fasting blood glucose, triglycerides, insulin levels, HOMA IR index and L/A ratio were significantly higher whereas adiponectin levels were significantly lower in children with vitamin D deficiency or with insulin resistance than in the others. The leptin levels were significantly higher only in the presence of insulin resistance. There was no significant difference between groups for Tanner stages.

Correlation between serum 25(OH)D levels, HOMA-IR index, leptin-to-adiponectin ratio and other clinical and biological parameters

Negative correlations were noted between 25(OH)D levels and BMI FBG HOMA-IR index, leptin levels and L/A ratio. Positive correlations were noted for HOMA-IR index and L/A ratio with BMI, BMI z-score, FBG. HOMA-IR index was also positively correlated with L/A ratio, Table 2.

Table 2: Correlations between 25(OH)D, HOMA- IR index, leptin-to-adiponectin ratio and anthropometric and metabolic parameters

Variables	25(OH)D (ng/mL)		HOMA-IR index		Leptin-to-adiponectin ratio	
	r	P	r	P	r	P
Age (years)	- 0.03	0.749	0.18	0.051	0.31	0.001
BMI (kg/m²)	-0.220	0.019	0.50	<0.001	0.80	<0.001
BMI z-score	-0.13	0.178	0.39	<0.001	0.60	<0.001
FBG (mmol/L)	-0.24	0.010	0.46	<0.001	0.33	<0.001
HOMA-IR index	-0.29	0.001	--	--	0.58	<0.001
25(OH)D (ng/mL)	--	--	-0.29	0.001	-0.24	0.011
Leptin (ng/mL)	-0.25	0.008	0.52	<0.001	--	--
Adiponectin (µg/mL)	0.17	0.079	-0.38	<0.001	--	--
leptin-to-adiponectin ratio	-0.24	0.011	0.58	<0.001	--	--

FBG: fasting blood glucose.

Linear regression for 25(OH)D levels and of HOMA-IR index

Table 3 presents the results of the multivariate linear regression exploring the association between 25(OH)D levels and HOMA-IR with age, sex, BMI z-score ≥ 2, and L/A ratio as independent variables.

In model 1, for 25(OH)D levels, no significant association was noted with age, gender, BMI z-score ≥ 2, L/A ratio and an interaction term BMI z-score ≥ 2*L/A. However, a significant negative association with HOMA-IR was found (P = 0.036). The model accounted for 14% (r^2 = 0.14) of the variability in 25(OH)D levels.

In model 2, for HOMA-IR index, no significant association was noted with age and gender. HOMA-IR was negatively associated with 25(OH)D and the interaction term BMI z-score ≥ 2*L/A (P = 0.036; P < 0.001 respectively) and positively associated with BMI z-score ≥ 2 and L/A ratio (P < 0.001 for both). The model accounted for 50% (r^2 = 0.50) of the variability in HOMA-IR index.

Table 3: Multivariate linear regression for Vitamin D level and HOMA IR index in 117 adolescents

Variables	Model 1: 25(OH)D levels (ng/mL) R^2 = 0.14		Model 2: HOMA IR Index R^2 = 0.50	
	nSRC (SE)	P	nSRC (SE)	P
Age (Years)	0.39 (0.47)	0.507	0.06 (0.23)	0.250
Gender (girl)	-1.85 (0.98)	0.125	-0.21 (0.49)	0.379
BMI z-score ≥2	-1.09 (1.94)	0.956	3.21 (0.91)	<0.001
25(OH)D (ng/mL)	--	--	-0.08 (0.05)	0.036
HOMA IR index	-0.35 (0.20)	0.036	--	--
L/A ratio	0.04 (0.15)	0.761	0.34 (0.07)	<0.001
BMI z-score ≥2 * L/A ratio	-0.10 (0.18)	0.461	-0.24 (0.08)	<0.001

nSRC: non-standardized regression coefficient; SE: standard error.

Changes in 25(OH)D levels, in obese children, at one year of follow-up

Overall, in 78 children/adolescents who accepted to undergo evaluation after one year, mean serum 25(OH)D increased from 21.4 ± 4.9 ng/mL at baseline to 23.2 ± 6.0 after 1 year; P = 0.003 whereas BMI z-score, HOMA-IR and L/A ratio decreased significantly (data not shown).

Focusing on the 27 obese children/adolescents (table 4), we observed significant decrease in the BMI z-score (P = 0.009) as well as in HOMA-IR (P = 0.011) and L/A ratio (P < 0.001) and, serum 25(OH)D increased significantly from 19.8 ± 4.5 ng/mL at baseline to 21.4 ± 5.0 after 1 year; P = 0.007.

Table 4: Clinical and biochemical parameters at baseline and after 1-year of a lifestyle intervention program in obese adolescents

	Obese adolescents N = 27		
	Baseline	One year after	P
BMI z-score	2.18 ± 0.27	2.08 ± 0.40	0.009
25(OH)D (ng/mL)	19.77 ± 4.50	21.42 ± 5.02	0.007
HOMA-IR index	6.32 ± 3.19	5.53 ± 3.95	0.011
Leptin-to-adiponectin ratio	11.24 ± 8.43	8.13 ± 7.52	< 0.001

Discussion

In the current study, we observed a high frequency of vitamin deficiency (40%) in our healthy children/adolescents who not taking vitamin D supplement therapy and, obese children/adolescents were found with significantly lower circulating 25(OH)D concentrations than the others. But, a linear regression model showed that serum 25(OH)D concentrations were related to insulin resistance and not significantly to obesity and L/A ratio.

After a 1-year lifestyle intervention including diet counselling and encouraging increased physical activity, 25(OH)D concentrations increased significantly after this intervention suggesting that healthy lifestyle may protect against vitamin D deficiency in children/adolescents.

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Vitamin D status in children/adolescents and relation with ethnicity and weight status

The island of Guadeloupe is localised between the equator and the tropic of cancer, with a continual sunniness. Nevertheless, in this island population, mostly of African ancestry (Afro-Caribbean), our healthy children/adolescents exhibited a 40% prevalence of vitamin D deficiency. Ethnic disparities in the prevalence of vitamin D deficiency have been documented with higher frequencies, in individuals having high skin pigmentation. Turer et al, in US children, documented vitamin D deficiency prevalence (< 20ng/mL) of 68%, 38% and 12% in African-Americans, Latinos and Whites, respectively [18]. In an Italian study, non-white adolescents had extremely reduced median 25(OH)D levels (11.3 ng/mL) and only 5.9% of them had vitamin D sufficiency [19]. It should be noted that the prevalence of vitamin D deficiency in our adolescents is still less than that of the US African-Americans adolescents [18].

Our obese adolescents had significantly lower mean 25(OH)D levels than in rest of the study sample. Several mechanisms could explain the relationship between VitD deficiency and obesity. One hypothesis is the dilution or deposition of the ingested or cutaneously synthesised VitD in the large body fat compartments reducing its bioavailability [20, 21]. Decreased exposure to solar UV radiation and decreased outdoor activity are also potential mechanisms by limiting cutaneous VitD synthesis [22].

But, controversial results have been reported for the relationships between serum 25(OH)D levels and anthropometric measures in adolescents. Whereas some studies described significant associations with BMI, global obesity or measures of abdominal obesity [18, 23], some others did not find these associations [24, 25], suggesting that adiposity might not be the main determinant of vitamin D status in adolescents.

The multivariate linear regression for serum 25(OH)D levels, in the current study, showed no significant association with obesity and similar results were found when abdominal obesity was used in the model (data not shown), suggesting, as for other authors, that other factors, uncontrolled in the study, could have a stronger effect than obesity to decrease serum vitamin D levels [2]. Sun exposure time, the degree of skin pigmentation might also contribute significantly to vitamin D status.

Vitamin D, insulin resistance and leptin-to-adiponectin ratio

We found an inverse association between 25(OH)D levels and HOMA-IR, independently of obesity. Esteghamati et al also reported a linear inverse association between vitamin D and IR in non-diabetics that were independent of obesity [26]. In the linear regression analyses, while serum 25(OH)D was associated with HOMA-IR alone, HOMA-IR per se was associated with 25(OH)D levels, obesity and L/A ratio suggesting an indirect relationship between obesity and 25(OH)D concentrations.

Authors, in a paediatric study, have reported that low 25(OH)D concentrations are related to glucose intolerance and IR particularly in obese people [27]. Several mechanisms could explain the effect of vitamin D deficiency on insulin sensitivity and its role in promoting IR and glucose abnormalities: i) vitamin D receptors exist in pancreatic tissue and could be directly involved in the regulation of insulin [28], ii) Increased parathyroid hormone levels in the context of vitamin D deficiency could affect insulin sensitivity [29] iii) vitamin D deficiency would be associated with a high inflammatory response that predisposes to insulin resistance [30, 31].

The L/A ratio, a marker of IR [5], was inversely correlated with 25(OH)D concentrations but positively and more strongly correlated with BMI, BMI z-score, FBG and HOMA-IR (table 2). Leptin and adiponectin have opposite effects on inflammation and insulin resistance. High leptin levels increase the expression of pro-inflammatory and pro- angiogenic factors [32] and, in the same line, vitamin D deficiency predisposes to IR [30, 31]. In contrast, adiponectin induces the production of anti-inflammatory cytokines and improves peripheral insulin sensitivity [33]. The BMI independent positive correlation between 25(OH)D and adiponectin documented by some authors in T2DM, suggests a potential role for this adipocytokine as a link between 25(OH)D and IR [34].

Changes in 25(OH)D after 1-year lifestyle intervention

We have previously described the improvement in BMI z-score, leptin levels and HOMA-IR after the lifestyle intervention particularly in obese adolescents [3] while increasing in HOMA-IR would be expected after one year with increasing age or puberty [35]. The 25(OH)D concentrations increased significantly after the 1-year lifestyle intervention confirming that reduction of sedentary behaviours improves vitamin D status, in adolescents. High 25(OH)D levels have been positively associated with physical activity particularly when performed outdoors [36] and, adolescents who performed less than 3 hours/week of outdoor exercise were found with a higher prevalence of vitamin D insufficiency [19]. The nutrition counselling and the continual sunniness of our island may have exerted additive beneficial effects on serum 25(OH)D levels in the present study even in obese adolescents.

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Limitations and strengths of the study

The potential limitations of our study include i) its small sample size, ii) the lack of information on food intake affecting serum vitamin D levels such as milk products (although milk is not generally supplemented in our country), on time of exposure to solar UV radiation and on measure of outdoor activity at baseline . Nevertheless, the present study has a number of strengths: i) the children were healthy, not receiving vitamin D supplement therapy, comparable (between vitamin D status groups) for age, gender and Tanner stage distributions and presented no associated diseases that could influence the vitamin D status, ii) the continuously warm and sunny climate and an ethnic homogeneity of the study population and iii) the longitudinal design providing data on changes in serum 25(OH)D, HOMA-IR and L/A ratio at the end of the 1-year lifestyle intervention.

In conclusion, insulin resistance that showed a strong association with vitamin D deficiency is common among obese adolescents but, obesity is not the main factor explaining vitamin D deficiency in adolescents. The improvement in 25(OH)D level could be due to increasing outdoor physical activity and also to improvement in the nutritional status.

Patricians should encourage adolescents to have a healthier lifestyle with healthy eating, non-sedentary and outdoor activities that may protect against overweight and also improve vitamin D status. Since natural foods rarely contain enough vitamin D to compensate vitamin D deficiency, vitamin D supplementation may be considered and particularly in severely vitamin D deficiency and in very obese adolescents. But, further investigations are needed to better understand the role of vitamin D in the occurrence of insulin resistance.

Acknowledgements

References

1. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-81. https://doi.org/10.1056/NEJMra070553 PMid:17634462

2. Lee DY, Kwon AR, Ahn JM, et al. Relationship between serum 25- hydroxyvitamin D concentration and risks of metabolic syndrome in children and adolescents from Korean National Health and Nutrition Examination survey 2008-2010. Ann Pediatr Endocrinol Metab. 2015;20:46-52. https://doi.org/10.6065/apem.2015.20.1.46 PMid:25883927 PMCid:PMC4397273

3. Rambhojan C, Bouaziz-Amar E, Larifla L, et al. Ghrelin, adipokines, metabolic factors in relation to weight status in school-children and results of a 1-year lifestyle intervention program. Nutr Metab (Lond). 2015;12:43. https://doi.org/10.1186/s12986-015-0039-9 PMid:26581745 PMCid:PMC4650925

4. Institut de Veille Sanitaire. Bulletin épidémiologique hebdomadaire. 2010:425-31.

5. Oda N, Imamura S, Fujita T, et al. The ratio of leptin to adiponectin can be used as an index of insulin resistance. Metabolism. 2008;57:268-73. https://doi.org/10.1016/j.metabol.2007.09.011 PMid:18191059

6. Kardas F, Kendirci M, Kurtoglu S. Cardiometabolic risk factors related to vitamin d and adiponectin in obese children and adolescents. Int J Endocrinol. 2013;2013:503270. https://doi.org/10.1155/2013/503270 PMid:23983686 PMCid:PMC3741940

7. Nunlee-Bland G, Gambhir K, Abrams C,et al. Vitamin D deficiency and insulin resistance in obese African-American adolescents. J Pediatr Endocrinol Metab. 2011;24:29-33. https://doi.org/10.1515/jpem.2011.107 PMid:21528812

8. Parikh S, Guo DH, Pollock NK, et al. Circulating 25-hydroxyvitamin D concentrations are correlated with cardiometabolic risk among American black and white adolescents living in a year-round sunny climate. Diabetes Care. 2012;35:1133-8. https://doi.org/10.2337/dc11-1944 PMid:22410810 PMCid:PMC3329810

9. Roth CL, Elfers C, Kratz M, Hoofnagle AN. Vitamin d deficiency in obese children and its relationship to insulin resistance and adipokines. J Obes. 2011;2011:495101. https://doi.org/10.1155/2011/495101 PMid:22254134 PMCid:PMC3255292

10. Cole TJ, Faith MS, Pietrobelli A, Heo M. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? Eur J Clin Nutr. 2005;59:419-25. https://doi.org/10.1038/sj.ejcn.1602090 PMid:15674315

11. Tanner JM. Growth and maturation during adolescence. Nutr Rev. 1981;39:43-55. https://doi.org/10.1111/j.1753-4887.1981.tb06734.x PMid:7010232

12. Cutfield WS, Jefferies CA, Jackson WE, Robinson EM, Hofman PL. Evaluation of HOMA and QUICKI as measures of insulin sensitivity in prepubertal children. Pediatr Diabetes. 2003;4:119-25. https://doi.org/10.1034/j.1399-5448.2003.t01-1-00022.x PMid:14655269

13. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. 2000;320:1240-3. https://doi.org/10.1136/bmj.320.7244.1240 PMid:10797032 PMCid:PMC27365

14. Keke LM, Samouda H, Jacobs J, et al. Body mass index and childhood obesity classification systems: A comparison of the French, International Obesity Task Force (IOTF) and World Health Organization (WHO) references. Rev Epidemiol Sante Publique. 2015;63:173-82. https://doi.org/10.1016/j.respe.2014.11.003 PMid:26002984

15. Varda NM, Gregoric A. Metabolic syndrome in the pediatric population: a short overview. Pediatr Rep. 2009;1:e1. https://doi.org/10.4081/pr.2009.e1 PMid:21589817 PMCid:PMC3096028

16. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and

___

adolescents. Pediatrics. 2005;115:e500-3. https://doi.org/10.1542/peds.2004-1921 PMid:15741351

17. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30. https://doi.org/10.1210/jc.2011-0385 PMid:21646368

18. Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics. 2013;131(1):e152-61. https://doi.org/10.1542/peds.2012-1711 PMid:23266927

19. Vierucci F, Del Pistoia M, Fanos M, Erba P, Saggese G. Prevalence of hypovitaminosis D and predictors of vitamin D status in Italian healthy adolescents. Ital J Pediatr. 2014;40:54. https://doi.org/10.1186/1824-7288-40-54 PMid:24902694 PMCid:PMC4064504

20. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72:690-3. PMid:10966885

21. Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring). 2012;20:1444-8. https://doi.org/10.1038/oby.2011.404 PMid:22262154

22. Florez H, Martinez R, Chacra W, Strickman-Stein N, Levis S. Outdoor exercise reduces the risk of hypovitaminosis D in the obese. J Steroid Biochem Mol Biol. 2007;103:679-81. https://doi.org/10.1016/j.jsbmb.2006.12.032 PMid:17267209

23. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med. 2004;158:531-7. https://doi.org/10.1001/archpedi.158.6.531 PMid:15184215

24. Jari M, Qorbani M, Moafi M, et al. Association of 25-hydroxy Vitamin D levels with indexes of general and abdominal obesity in Iranian adolescents: The CASPIAN-III study. J Res Med Sci. 2015;20:122-6. PMid:25983762 PMCid:PMC4400704

25. Weng FL, Shults J, Leonard MB, Stallings VA, Zemel BS. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. Am J Clin Nutr. 2007;86:150-8. PMid:17616775

26. Esteghamati A, Aryan Z, Esteghamati A, Nakhjavani M. Vitamin D deficiency is associated with insulin resistance in nondiabetics and reduced insulin production in type 2 diabetics. Horm Metab Res. 2015;47:273-9. PMid:25230322

27. Olson ML, Maalouf NM, Oden JD, White PC, Hutchison MR. Vitamin D deficiency in obese children and its relationship to glucose homeostasis. J Clin Endocrinol Metab. 2012;97:279-85. https://doi.org/10.1210/jc.2011-1507 PMid:22072738 PMCid:PMC3251943

28. Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, et al. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. FASEB J. 2003;17:509-11. https://doi.org/10.1096/fj.02-0424fje

29. Chiu KC, Chuang LM, Lee NP et al. Insulin sensitivity is inversely correlated with plasma intact parathyroid hormone level. Metabolism. 2000;49:1501-5. https://doi.org/10.1053/meta.2000.17708 PMid:11092519

30. Bikle DD. Vitamin D: newly discovered actions require reconsideration of physiologic requirements. Trends Endocrinol Metab. 2010;21:375-84. https://doi.org/10.1016/j.tem.2010.01.003 PMid:20149679 PMCid:PMC2880203

31. Gao D, Trayhurn P, Bing C. 1,25-Dihydroxyvitamin D3 inhibits the cytokine- induced secretion of MCP-1 and reduces monocyte recruitment by human preadipocytes. Int J Obes (Lond). 2013;37:357-65. https://doi.org/10.1038/ijo.2012.53 PMid:22508334 PMCid:PMC3428854

32. Aleffi S, Petrai I, Bertolani C, et al. Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells. Hepatology. 2005;42:1339-48. https://doi.org/10.1002/hep.20965 PMid:16317688

33. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clin Chim Acta. 2007;380:24-30. https://doi.org/10.1016/j.cca.2007.01.026 PMid:17343838 PMCid:PMC2755046

34. Al-Daghri NM, Al-Attas OS, Alokail MS, et al. Hypovitaminosis D associations with adverse metabolic parameters are accentuated in patients with Type 2 diabetes mellitus: a body mass index-independent role of adiponectin? J Endocrinol Invest. 2013;36:1-6. PMid:22183134

35. Jeffery AN, Metcalf BS, Hosking J, et al. Age before stage: insulin resistance rises before the onset of puberty: a 9-year longitudinal study (EarlyBird 26). Diabetes Care. 2012;35:536-41. https://doi.org/10.2337/dc11-1281 PMid:22279034 PMCid:PMC3322712

36. Miettinen ME, Kinnunen L, Leiviska J, et al. Association of serum 25- hydroxyvitamin D with lifestyle factors and metabolic and cardiovascular disease markers: population-based cross-sectional study (FIN-D2D). PLoS One. 2014;9:e100235. https://doi.org/10.1371/journal.pone.0100235 PMid:25000408 PMCid:PMC4085035