

HOMA-IR and serum vitamin D in obese children with metabolic syndrome.

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Abstract

Background: Vitamin D deficiency was a risk factor of metabolic syndrome and insulin resistance which causes premature morbidity and mortality. It was associated with the action of vitamin D through its various cell receptor.

Purpose: To examine the correlation between Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) and serum 25-hydroxyvitamin D (25-OH) D level in obese children with metabolic syndrome.

Methods: A cross sectional study on 6 to 18 years old students was conducted during June until August 2017. The samples consisted of 43 children with metabolic syndrome and 40 children without metabolic syndrome based on Indonesian Pediatric Association criteria. Serum level of 25 (OH) D was measured using Enzyme-Linked Immunosorbent Assay. HOMA-IR was used to calculate insulin resistance. Vitamin D deficiency was defined as serum 25 (OH) D <20 ng/mL. Data were analyzed using IBM SPSS version 21.

Results: Mean of vitamin D level in obese children with metabolic syndrome was 14.55 ng/mL, and without metabolic syndrome was 22.78 ng/mL. The frequency of metabolic syndrome was 70.6% in obese children with vitamin D deficiency, while in normal vitamin D status was 21.9% ($p < 0.001$; OR=8.571 (CI 95% 3.054-24.060). It was negative correlation between level of 25 (OH) D with fasting plasma insulin ($r = -0.587$; $p < 0.001$), as well as HOMA-IR ($r = -0.481$; $p < 0.001$) for all subjects.

Conclusion: Obese children with vitamin D deficiency were more risky to experience metabolic syndrome than obese children with normal vitamin D status. Level of 25 (OH) D was inverse correlation with fasting plasma insulin and HOMA-IR.

Keywords: Metabolic syndrome, HOMA-IR, Obese children, Vitamin D deficiency.

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Introduction

Increasing prevalence of obesity in children worldwide was considered as one of the most serious health challenges of the 21st century [1]. Vitamin D deficiency, as indicated by a serum concentration of 25 (OH) D level below 20 ng/mL (50 nmol/L), is commonly present in obesity, and has been implicated as a risk of metabolic syndrome. In Indonesia, there was a high prevalence of vitamin D insufficiency in healthy children aged 7-12 years. This result should increase the awareness regarding vitamin D status. Metabolic syndrome is associated with subsequent development of cerebrovascular disease and diabetes mellitus Type 2 (DMT2) [2,3].

Metabolic syndrome is a group of abdominal symptoms, dyslipidemia, hyperglycemia, and hypertension. This

syndrome is a condition commonly found in adults. The increased prevalence of metabolic syndrome in children and adolescents is in line with the increased prevalence of obesity. Metabolic syndrome criteria based on Indonesian Pediatric Association include abdominal obesity characterized by waist circumference \geq P80 according to Taylor et al. and added more or equal of two parameters including hypertension (by sex, age and height), HDL cholesterol \leq 40 mg/L, triglyceride levels \geq 110 mg/dL and fasting blood glucose \geq 100 mg / dL or diagnosed Diabetes Mellitus type 2 [4].

Vitamin D is very important in glucose homeostasis and insulin secretion by endocrine mechanism. In addition, adipose tissue plays a major role as an autocrine and paracrine organ. Insulin resistance is important in obesity; as the population of obesity begins at younger ages, the age

of onset type 2 diabetes mellitus would decrease [5,6].

Vitamin D is a fat soluble vitamin, a prohormone that has the main function of regulating the body's calcium balance. The action of 1,25 (OH) 2D₃ is mediated through the Vitamin D Receptor (VDR), a member of the nuclear receptor super family, which regulates the transcription of many target genes. VDR has been identified in most human tissues, including those which do not typically associated with calcium homeostasis and bone metabolism. Some of these include osteoblasts, skin keratinocytes, macrophages, smooth muscle, pancreatic β -cells, epithelial cells, and various cells of the immune system. The ubiquitous expression of VDR may underlie the diverse effects of vitamin D and provide a mechanistic basis for the link between vitamin D deficiency and a number of disorders, including certain types of cancer, cerebrovascular diseases, diabetes (type 1 and type 2), and metabolic syndrome [6,7]. Clinically, vitamin D status is normally assessed by measurement of the serum level of 25 (OH) D₃, the major form of vitamin D in the circulation, with a half life of between 15 and 50 day [8]. Vitamin D status was classified as normal when levels of 25 (OH) D₃ is range from 20-100 ng/mL, severe deficiency (serum of 25 (OH) D \leq 5 ng/mL), deficiency (serum of 25 (OH) D $<$ 15 ng/mL, and insufficiency (serum of 25 (OH) D levels 15-20 ng/mL [9].

There are several prospective studies of adults showing a link between vitamin D deficiency and the risk of developing metabolic syndrome. Similar research on children and adolescents is very small, and has not been conducted in Indonesia. This study aims to determine the relationship between HOMA-IR and serum vitamin D in metabolic syndrome obese children.

Material and Methods

Study design and population

This is an analytical research study with cross sectional design. This study was conducted from January to June 2017, in elementary, junior, and high school students in Makassar, Indonesia. This study was conducted in 83 children with obesity (6-18 years old).

Anthropometric measurements

A questionnaire was administered to the parents of all children and was considered as consent for their children's participation in the study. Anthropometric measures comprised height, weight, and waist circumference. Height was measured to the nearest 0.1 cm by using microtoice, obtained without shoes, back straight with buttocks, shoulders touching a wall, and head forward. Weight was measured to the nearest 0.1 kg using digital floor scale. The children were measured in light clothes (no shoes or heavy outer garments). Waist circumference was measured at the midpoint between the lower border of the ribcage and the iliac crest using non elastic tape measure. Body mass index was calculated by dividing

weight by height (kg/m^2). Obesity was defined as Body Mass Index (BMI) higher than 95th percentile for age and gender.

Blood pressure was measured twice on the right arm using a mercury sphygmomanometer while the participant was resting in a seated position. The children were considered hypertensive if they were on 95 percentile for both systolic and diastolic blood pressures based on her height, age, and sex.

Laboratory measurements

All blood analyses were performed on 8 h fasting samples from both the study and control groups. Blood analysis for Triglyceride, LDL-C, HDL-C level were measured with Homogenous method, Roche Diagnostics. Analysis of Fasting blood glucose was measured using hexokinase method, COBAS Roche. The serum 25 (OH) D levels were determined using ELISA (Bioassay Technology, China). Vitamin D deficiency was defined as a serum 25 (OH) D level $<$ 20 mg/mL. Insulin levels were analyzed using ELISA (Bioassay Technology, China). Insulin resistance was estimated from the fasting plasma measurements using homeostatic model assessment (HOMA-IR) [(insulin (mU/L) x glucose (mmol/L))/22.5].

Inclusion and exclusion criteria

Inclusion criteria were children diagnosed with obesity without underlying disease. Children with chronic liver and renal disease, hypo or hyperthyroidism, and those who were under corticosteroid or cytostatics therapy were excluded from the study.

Data analyses

Statistical analyses were performed using IBM SPSS version 21.0 software. A paired *t*-test was used to calculate the difference of two parameters in groups. Pearson correlation was used to assess association between continuous variable. Categorical data were evaluated using Chi-square test. $P < 0.05$ was accepted as statistically significant. The study was approved by Ethic Committee of Hasanuddin University's Faculty of Medicine.

Results

In total of 83 children, 43 children (51.8%) had metabolic syndrome. The mean age was 12.97 ± 1.89 years in the metabolic syndrome group and 12.49 ± 2.53 in the non metabolic syndrome group. No statistically significant difference was observed between age, gender, and puberty state ($p > 0.005$). Mean concentration of 25 (OH) D was 14.55 ± 6.55 ng/mL in metabolic syndrome group, and 22.78 ± 6.51 ng/mL in metabolic syndrome ($p < 0.01$). Characteristics of the participants are shown in Table 1.

The average fasting insulin level (17.03 ± 4.99 vs 12.81 ± 5.23 ; $p < 0.001$), HOMA-IR 1.79 ± 0.81 vs 1.19 ± 0.69 ; $p < 0.001$) were significantly higher in obese children with metabolic syndrome (Table 1).

Table 1. Characteristics of the studied groups

No.	Characteristic Sample	Metabolic Syndrome (n= 43)	Without Metabolic Syndrome (n= 40)	p Value
1	Sex Male (%) Female (%)	24 (52.2%) 19 (51.3%)	22 (47.8%) 18 (48.7%)	0.129*
2	Age (years) Mean Median Minimum-maximum SD	12.97 13.58 6.67–17.08 1.89	12.49 12.46 7.75–17.25 2.53	0.941**
3	Body Mass Index (kg/m ²) Mean Median Minimum-maximum SD	28.79 28.62 19.24–35.06 3.06	26.09 25.32 19.63–33.91 3.62	
4	25 (OH)D level (ng/mL) Mean Median Minimum-maximum SD	14.55 12.50 8.30–33,30 6.55	22.78 23.25 8.37–35.75 6.51	0.00*
5	Puberty state Pre-puberty Puberty	3 (33.3%) 40 (54.1%)	6 (66.7%) 34 (45.9%)	0.24**
6	Fasting Insulin (IU/mL) Mean Median Minimum-maximum SD	17.03 17.77 6.91–26.74 4.99	12.81 12.50 4.23–23.93 5.23	0.001*
7	HOMA-IR Mean Median Minimum-maximum SD	1.79 1.81 0.26–3.72 0.81	1.19 1.05 0.18–3.72 0.69	0.000*

*Mann-Whitney U test

**Chi Square test

In metabolic syndrome group, 36 students (70.6%) had vitamin D level <20 ng/mL (deficiency and insufficiency), higher than in the group of children with normal vitamin D status, 7 (21.9%) ($p < 0.000$). The odds ratio (OR) = 8.571 (95% CI 3.054–24.060), which means the risk of metabolic syndrome in obese children with vitamin D deficiency, compared with no deficiency

for a metabolic syndrome was 8.57 times more risky (Table 2).

Table 3 showed that in obese children with vitamin D deficiency group, metabolic syndrome frequency was 29 (82.9%), and in vitamin D insufficiency group, metabolic syndrome frequency were 7 (41.2%), while in normal vitamin D status group, frequency of metabolic syndrome

Table 2. Comparison between vitamin D deficiency and metabolic syndrome

Vitamin D Status	Metabolic Syndrome		Total
	Yes	No	
Deficiency+insufficiency	36 (70.6%)	15 (29.4%)	51 (100%)
Normally	7 (21.9%)	25 (78.1%)	32 (100%)
Total	43 (51.8%)	40 (48.2%)	83 (100%)

Chi-square test $p = 0.000$

OR = 8.571 (CI 95%; 3.054–24,060)

Table 3. Comparison between Vitamin D status and metabolic syndrome

Vitamin D Status	Metabolic Syndrome		Total
	Yes	No	
Deficiency	29 (82.9%)	6 (17.1%)	35 (100%)
Insufficiency	7 (41.2%)	10 (58.8%)	17 (100%)
Normally	7 (22.6%)	24 (77.4%)	31 (100%)
Total	43 (51.8%)	40 (48.2%)	83 (100%)

Chi-square test $p=0.000$

Table 4. Correlation between 25 (OH) D (25-hydroxy vitamin D) level with metabolic parameters for all study subjects

Correlation (N= 83)	25 (OH) D	
	r	p
HOMA-IR	-0.481	0.001
Fasting Plasma Insulin (mIU/L)	-0.587	0.001

was 7 (22.6%). The analyses presented in Table 3 confirm that lower vitamin D status had a higher metabolic syndrome frequency ($p<0.001$).

Table 4 presents a negative correlation between level of 25 (OH) D serum and fasting plasma insulin ($r=-0.587$; $p<0.001$) and HOMA-IR ($r=-0.481$; $p<0.001$).

Discussion

Many studies have been conducted to identify the correlation between level of vitamin D and metabolic risk in adult population and or diabetic population, but still rare in children. This study was performed on school age population. There was a significant difference mean level of vitamin D between obese children with metabolic syndrome and without metabolic syndrome in the present study which was compatible with the results reported by some other studies. Besides, it was also found negative correlation between level of 25 (OH) D and fasting plasma insulin and HOMA-IR in obese children with metabolic syndrome.

Puberty statuses that can influence the metabolic syndrome were analyzed. At puberty, there is a dynamic change in anthropometric children. Female’s waist circumference at puberty will be wider than pre pubertal. Also, serum lipid levels are one component of the metabolic syndrome that peaks at age 9-10 years before decreased. Serum total cholesterol levels decreased between the ages of 10-16 years in male and 9-14 years of age in female. Decreased levels of HDL cholesterol and LDL cholesterol were associated with increased testosterone in male and elevated estradiol in female. A positive correlation between testosterone and HDL cholesterol, and between testosterone and Apo A1 levels was found in adolescent male with their puberty status at higher stages according to Tanner [10,11].

In this study, there was no statistically significant difference in frequency of metabolic syndrome based on puberty status with $p=0.24$ ($p>0.05$). This result was

compatible with previous study by Khadgawat et al. [12] which found that no significant association was found between the pre-puberty and puberty groups against the metabolic syndrome component in 62 study subjects. Meanwhile, Sangun et al. [13], on a study of 614 children in Turkey aged 7 to 18 years, found a significant difference in the incidence of metabolic syndrome between the pre-puberty and puberty groups with $p=0.00$ ($p<0.05$).

This study showed that frequency of metabolic syndrome was higher in children with vitamin D deficiency. It also showed a trend of increasing frequency of metabolic syndrome with decreased of vitamin D levels. Vitamin D metabolites are associated with the increasing of blood pressure due to their role in the rennin angiotensin system. Some studies have shown vitamin D role as a rennin angiotensin system inhibitor due to VDR. VDR and enzyme 1 hydroxylase found in smooth muscle and endothelial cells indicate the role of vitamin D in the presence of hypertension, which is a component of the metabolic syndrome [14]. It is similar with the role of vitamin D receptors in pancreatic β cells, by activating 1 α hydroxylase in pancreatic β cells, So the condition of vitamin D deficiency can disrupt the release of insulin from the pancreas and reduce glucose tolerance and lead to conditions of hyperglycemia and insulin resistance which is also a component of metabolic syndrome [8,15].

The results of this study were conformable with a cross-sectional study conducted by Al-Dabhani et al. [16] which found that serum vitamin D was 8% lower in children with metabolic syndrome with $p=0.01$. Alfawaz et al. [3], in Saudi Arabia, found a negative correlation between vitamin D levels and components of the metabolic syndrome including fasting blood glucose, triglycerides and systolic and diastolic blood pressure, and a positive correlation between vitamin D levels and HDL levels [3]. Gagnon et al. [17], in the study of 4164 adults during 5 year monitoring, found the prevalence of metabolic syndrome of 12.7%. The risk of significant metabolic syndrome occurs at levels of 25 (OH) D <18 ng/mL with an odds ratio of 1.41 (95% CI: 1.02-1.95) [10]. Levels of vitamin D have a negative correlation to waist circumference, fasting blood sugar and triglycerides with $p<0.001$ [18-21].

Several studies have proposed an inverse relationship between vitamin D status and insulin resistance. Our results are in agreement with the results of others. We found significant inverse correlation between level vitamin

D and fasting insulin and also HOMA-IR. Most cross sectional and prospective studies of various populations have found inverse associations between 25 (OH) D and fasting insulin, as well as HOMA-IR. Sufficient vitamin D levels decrease insulin resistance by influencing the expression of insulin receptors, thereby prompting the influx of calcium to promote the insulin response. Wang et al. [22], in a cross sectional study of 278 children found significantly different between HOMA-IR and vitamin D statuses ($p < 0.001$), HOMA-IR negatively correlated with serum 25-OHD level. These results are in agreement with Roth et al. [6] on sample of German children and by Olson et al. [23] on a sample of American children. But Kandeel et al. [24] study of obese Egyptian children found no correlation between 25 (OH) D and insulin resistance. Sufficient vitamin D levels decrease insulin resistance by influencing the expression of insulin receptors, thereby prompting the influx of calcium to promote the insulin response.

Similar research on children and adolescents is very small. Reis et al. [14] in a cross sectional study of 3577 adolescents who participated in the NHANES study from 2001 to 2004 concluded that there was an association between vitamin D deficiency with hypertension, hyperglycemia, and metabolic syndrome [13,14].

This is in contrast to a study by Samingan et al. [23], found no significant association between vitamin D deficiency and the incidence of metabolic syndrome. This is because the research is done on multiethnic, while the research we do on one ethnicity. The cause of this difference is related to the presence of vitamin D vitamin receptor polymorphisms that play a role in the incidence of metabolic syndrome. In this study showed that although there were 17.1% obese children with vitamin D deficiency, the group had not yet metabolic syndrome. Similarly, 22.6% of children with normal vitamin D status had metabolic syndrome. This is because the increase in blood pressure in obese children is also influenced by other factors outside the process that occur, among other factors such as diet, stress, smoking, race and genetics are not analyzed in this study. Similarly, lipid abnormalities that occur via the pathway of increased free fatty acids due to distortion of chronic adipocytes in obese children. Distortion of adipocytes makes release of highly complex inflammatory mediators. Increasing cytokine like TNF α , IL-6, leptin, and also decrease adiponectin level. This series make increasing free fatty acid. Increased long-term fatty acid levels in obese children can cause disruption to the β -cell response to glucose. Insulin inhibits lipolysis in fat tissue and triggers free fatty acid transfer from circulating lipoproteins to fat tissue. Therefore the condition of insulin resistance causes free fatty acid levels to increase in circulation due to uncontrolled lipolysis and decrease the clearance of free fatty acids in the periphery. Increased circulation of free fatty acids to the liver is more common in obese children causing increased secretion

of triglyceride-rich VLDL that clinically manifests as an increase in fasting triglyceride levels [20]. The mechanism is suspected as the cause of the incidence of metabolic syndrome in obese children with normal vitamin D status. Lipid abnormalities are also influenced by external factors such as physical activity, stress and diet patterns, as well as internal factors such as race/ethnicity, hormonal, and genetic (family history of dyslipidemia) [24].

But in groups of children with vitamin D deficiency and not yet metabolic syndrome, it is necessary to get attention and early intervention to prevent the incidence of metabolic syndrome later in life. A prospective study conducted by Gagnon et al., during 5-year monitoring, the incidence of metabolic syndrome was higher in the group with levels of 25 (OH) D < 18 ng/mL, then in the 25 (OH) D 18 -23 ng/mL (OH) OR=1.41 (95% CI: 1.02-1.95) and 1.74 (95% CI: 1.28-2.37) [10]. In our study, we didn't know how long the student got obesity and vitamin D deficiency. But this result make awareness for their parents, professional and government, that we have to early detection and intervention for children with obesity and vitamin D deficiency and risk of insulin resistance and also metabolic syndrome later.

The limitation of this study is the absence of diet analysis, given that the factor plays a role in the incidence of metabolic syndrome. The strength of this study on adherence to sampling procedures preceded by fasting for 8 h and analysis of puberty status was different from previous studies. The hormonal status during puberty especially in female adolescents might affect glucose metabolism, increase in growth hormone during puberty may contribute to insulin sensitivity. To the best our knowledge, this the first study in Indonesia.

Conclusion

The 25 (OH) D mean level in obese children with metabolic syndrome was lower than in obese children without metabolic syndrome. Obese children with vitamin D deficiency have a risk of 8.57 times to experience metabolic syndrome than obese children with normal vitamin D status. Level of 25 (OH) D was inversely related to fasting insulin and also HOMA-IR. Researchers suggest the need for further monitoring of obese children with vitamin D deficiency against the risk of insulin resistance and also metabolic syndrome by making prevention efforts and early interventions, among others, the policy of giving vitamin D in obese children to reduce premature morbidity and mortality. Further research is needed with a cohort design study and involve other factors that may affect the incidence of vitamin D deficiency and metabolic syndrome such as ethnic/genetic factors and nutrition.

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