ORIGINAL ARTICLE

Negative correlation among vitamin B12 levels, obesity severity and metabolic syndrome in obese children: A case control study

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Abstract

Objective: To determine the relationship among vitamin B12 status, obesity severity, and metabolic syndrome and its components in obese children.

Methods: This case-control study was conducted at the School of Medicine, Gaziosmanpasa University, Tokat, Turkey, from January 2012 and October 2014, and comprised cases of obese and healthy children. The obese children were divided into three groups according to body mass index-standard deviation score quartiles. Group 1 included the first quartile, group 2 included the second and third quartiles, and group 3 included the fourth quartile. Patients with a body mass index of ≥95th percentile, according to reference curves for Turkish children and adolescents, were considered obese.Patients with a body mass index between15th and 85th percentile were considered to have normal weight. The World Health Organisation's modified metabolic syndrome criteria for children were used to diagnose metabolic syndrome.SPSS 19 was used for data analysis.

Results: Of the 256 participants, 153(59.8%) were obese and 103(40.2%) were healthy controls. The mean age of the obese children was 12.69±2.29 years and that of healthy controls was 13.05±2.48 years. Mean vitamin B12 levels were significantly lower among obese children than healthy volunteers ($p<0.001$). Age and body mass index-standard deviation score were significantly associated with vitamin B12 status ($r= -0.175$, $p=0.030$; $r= -0.210$, $p=0.09$, respectively).

Conclusion: Increase in body mass index-standard deviation score was associated with a decrease in vitamin B12 levels.

Keywords: Vitamin B12, Obesity severity, Insulin resistance, Metabolic syndrome. (JPMA 67: 1648; 2017)

Introduction

Obesity among children and adolescents has emerged as a serious public health concern. The prevalence of childhood obesity has increased gradually worldwide over the past 30 years.[1,3] Genetic factors, sedentary lifestyle and dietary habits are causes of obesity, but the main cause is energy intake greater than the body's energy requirement.[4] Vitamin deficiencies have been reported in children with obesity. However, studies evaluating vitamin B12 status in obese children are rare. The dietary habits of obese children may comprise higher quantities of carbohydrates, fat and lower amounts of animal protein containing vitamin B12. Some investigators have suggested that obesity impairs absorption of vitamin B12.[5-7] Malabsorption of vitamin B12 is associated with metformin therapy, which is used to treat insulin resistance (IR).[8] Some studies have found that vitamin B12 deficiency is associated with obesity, whereas others have reported no association.[9-11] Elevated body mass index (BMI) is associated with elevated systemic markers of inflammation including C-reactive protein (CRP) and peripheral leukocyte counts.[12] There have been few clinical studies that have investigated paediatric obesity and inflammation using CRP and other inflammatory cytokines.[13] It has been suggested that vitamin B12 levels are significantly lower in adult Turkish patients with metabolic syndrome (MS) than in those without MS.[10] However, studies on the associations among vitamin B12 status, obesity severity, and MS in obese children and adolescents are rare. The current study was planned to investigate the relationships among vitamin B12 status, obesity severity, and MS and its components in obese children and adolescents.

Subject and Methods

This case-control study was conducted at School of Medicine of Gaziosmanpasa University, Tokat, Turkey, from January 2012 and October 2014, and comprised cases of obese and healthy children. Children aged between 10-17 years were included. Cases showing lack of data, sendromic obesity and metformin usage were excluded. Sample sizes for groups were enough according to power analysis for serum vitamin B12 which was 0.954. After obtaining approval from the institutional ethics committee, the subjects were diagnosed as obese

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according to BMI, considering the sex-specific growth curves and cut-off levels proposed by Neyzi et al.[14] The subjects' demographic and clinical data, basic demographic information (age and sex) and physical data were collected from hospital records, including body height, body weight, BMI, and systolic and diastolic blood pressure (BP). Laboratory data was derived from fasting blood samples obtained from each participant. The laboratory tests performed included vitamin B12 and fasting glucose levels, as well as lipid profiles. Healthy control group was conducted retrospectively. Children who had no anaemia and any chronic disease and who were admitted to hospital only for health control were included in control group. Parents of obese children were questioned about the latter's dietary habits, including fast-food eating, eating meat weekly, amount of consumed foods, frequency of eating, skipping a meal and drinking sugared beverages. It was seen that obese children were under malnutrition. They were not eating healthy food. Children with endocrinologic, genetic and syndromic obesity, history of parenteral nutrition (PN), hepatic viral infection, alcohol consumption, type 1 or type 2 diabetes mellitus, Cushing's syndrome, overt hypothyroidism and use of drug as metformin were also excluded.

Weights were measured using a digital scale (SecaCorp., Chino, California, United States) while the patient was barefoot and wearing light clothing. Height was measured using a portable stadiometer (Seca) together with weight. If the BMI was more than the 95th percentile, the patient was considered obese. The participants were divided into three groups according to BMI-standard deviation score (SDS) quartiles. Group 1 included the first quartile, group 2 included the second and third quartiles, and group 3 included the fourth quartile. BP was measured using a standard digital sphygmomanometer (Omron705IT; Omron Electronics, Ltd., Hoffman Estates, Illinois, United States) and an appropriate collar according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, considering sex, age, and the height percentile as follows: normal BP (systolic and diastolic BP $<$ 90th percentile) and hypertensive (BP $\geq$ 95th percentile).

Biochemical data was obtained retrospectively from tests conducted at a biochemistry laboratory. All samples were obtained after a 10- to 12-hour fast. Serum fasting glucose, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) levels were estimated using reagent kits from Roche Diagnostics adapted to the COBAS 6000 Autoanalyser (Roche Diagnostics, Indianapolis, Indiana, United States). Abnormal glucose homeostasis was determined based on the presence of fasting hyperinsulinaemia, impaired fasting glucose, or impaired glucose tolerance. The homeostatic model assessment-insulin resistance (HOMA-IR) was considered positive if the value was over 2.67 (sensitivity 88.2%, specificity 65.5%) in boys and 2.22 (sensitivity 100%, specificity 42.3%) in girls in the prepubertal period, and 5.22 (sensitivity 56%, specificity 93.3%) in boys and 3.82 (sensitivity 77.1%, specificity 71.4%) in girls in the pubertal period.[15] MS was defined based on the modified World Health Organisation's (WHO) criteria adapted for children. The subjects were diagnosed with MS if they met three of the following four WHO criteria: (1) obesity, (2) abnormal glucose homoeostasis (fasting hyperinsulinaemia, impaired fasting glucose, or impaired glucose tolerance), (3) hypertension, and (4) dyslipidaemia (TGs >105 mg/dL in children $<$ 10 years of age and $>$ 136 mg/dL in children $\geq$ 10 years) was used in the study. HDL-C $<$ 35 mg/dL, or TC $>$ 95th percentile was used as cutoff values.[16]

Serum vitamin B12 concentrations were measured using a chemiluminescence immunoassay (COBASC-501 & E-601 Roche Diagnostics) and accepted normal at over 221 pmol/L.[17]

Shapiro-Wilk test was used to assess normality of the data. Data was expressed as means ± standard deviation (SD). Independent sample t-test or one-way analysis of variance (ANOVA) was used to compare continuous normal data among groups. Post-hoc comparisons between the pair-wise groups were made using Tukey's honest significant difference (HSD) test. Chi-square test was used to compare the categorical data between groups. Categorical variables were presented as counts and percentages. Pearson's correlation coefficient analysis was used to assess the relationships between variables. Scatter plot of variables was used for bivariate correlation. $P<0.05$ was considered significant. SPSS 19 was used for data analysis.

Results

Of the 856 obese children, 153(17.9%) were included. Besides, there were 103 healthy controls. The mean age of the obese children was 12.69±2.29 years and that of healthy controls was 13.05±2.48 years. Moreover, 94(61.4%) of the participants were females and 59(38.6%) were males in the obese group, whereas there were 67(53.7%) females and 36(46.3%) males in the control group. The obese children were subdivided into three groups: there were 39(25.5%) children in group 1, 75(49%) in group 2 and 39(25.5%) in group 3. There was a

Table-1: Demographic and laboratory characteristics of obese and healthy children.

Variables	Control (n=103)	Group 1 (n=39)	Group 2 (n=75)	Group 3 (n=39)	p
Number (m/f)	36/67	4/35	32/43	23/16	<0.001
Age (year)	13.05±2.48	13.30±2.07	12.56±2.26	12.33±2.51	0.446
BMI-SDS	0.07±1.06a	2.07±0.28b	2.64±0.16c	3.28±0.29d	<0.001
Vitamin B12 (pmol/L)	351.15±149.61a	315.13±135.99ab	298.25±112.97b	250.79±43.18b	<0.001
Haemoglobin (g/dL)	13.93±1.60	13.79±1.91	13.33±1.42	13.59±1.27	0.084
Haematocrit (%)	41.07±3.61	41.16±6.77	40.49±4.53	41.31±3.61	0.758
MCV (fL)	80.08±6.41	81.39±4.49	79.56±6.73	79.69±7.32	0.527
BPs (mmHg)	111±11.33	113.75±10.28	112.57±14.31	119.85±16.99	0.052
BPd (mmHg)	70.34±9.27a	71.61±8.73a	72.36±9.67ab	77.53±13.52b	0.036
Total cholesterol (mg/dL)	-	161.26±28.83	161.18±34.75	167.58±26.22	0.556
Triglycerides (mg/dL)	-	102.13±44.59	113.68±49.55	116.53±49.22	0.371
LDL-cholesterol (mg/dL)	-	99.14±27.70	102.55±30.86	111.47±27.93	0.164
HDL-cholesterol (mg/dL)	-	47.95±11.54	45.69±11.54	47.45±11.87	0.562
Fasting glucose (mg/dL)	-	84.05±10.38	87.64±9.99	84.58±8.72	0.114
OGTT-Glucose (mg/dL)	-	95.61±20.64	105.56±22.02	106.36±27.21	0.066
Fasting insulin (µIU/mL)	-	16.5±9.30a	24.92±19.42b	22.85±14.21ab	0.031
HOMA-IR	-	3.35±2.10a	5.46±4.36b	4.52±2.99ab	0.012
ALT (U/L)	-	16.64±6.58a	26.28±26.5ab	33.97±26.04b	0.005
AST (U/L)	-	23.97±8.76a	25.69±7.88a	30.56±12.72b	0.007

BMI-SDS: Body mass index-standard deviation score
MCV: Mean corpuscular volume
BPs: Systolic blood pressure
BPd: Diastolic blood pressure
LDL: Low-density lipoprotein
HDL: High-density lipoprotein
ALT: Alanine amino transferase,
AST: Aspartate amino transferase
OGTT: Oral glucose tolerance test
HOMA-IR: Homeostatic model assessment-insulin resistance
Values are expressed as mean±SD or frequency. Different superscripts (a,b) in the same row (ANOVA) indicate statistical significant difference. Means of groups with at least one same superscript are the similar. Vitamin B12 level of control group is statistically lower than group2 and group3 but there is no difference between obesity groups.

Table-2: Relationship between vitamin B12 levels and metabolic syndrome and its components.

Variables	Categories	n (%)	VitaminB12 Mean±SD	P
Hypertension	-	119 (77.7)	285.42±97.71	0.445
	+	34 (22.2)	301.83±114.76	
Dyslipidaemia	-	89 (58.2)	291.61±110.24	0.732
	+	64 (41.8)	285.49±105.66	
Abnormal glucose homeostasis	-	94 (60.4)	294.79±100.35	0.537
	+	59 (39.6)	283.56±122.23	
Metabolic syndrome	-	113 (73.9)	296.91±111.75	0.041
	+	40 (26.1)	252.23±100.14	
Insulin resistance (HOMA-IR)	-	65 (42.5)	297.03±105.44	0.523
	+	88 (57.5)	285.60±112.00	

-: Absent,+: Present
HOMA-IR: Homeostatic model assessment-insulin resistance. SD: Standard deviation.

significant difference among obese groups considering their BMI-SDS, systolic BP (mmHg), diastolic BP (mmHg), HDL-cholesterol, fasting insulin and HOMA-IR. The mean vitamin B12 level in the control group, group 1, group 2 and group 3 were 351.2 pmol/L, 315.1 pmol/L, 298.3 pmol/L and 250.8 pmol/L, respectively (p<0.001) (Table-1).

The distributions of the MS components among the participants were as follows: hypertension in 34(22.2%) patients, dyslipidemia in 64(41.8%), and abnormal

Table-3: Bivariate correlations of variables with Vitamin B12 in control and obese group.

Variables		Control (n=103)	Obese Group (n=153)
Age (year)	r	-0.109	-0.175
	p	0.275	0.030
Height (cm)	r	0.004	-0.187
	p	0.971	0.021
Weight (kg)	r	-0.082	-0.256
	p	0.410	0.001
BMI	r	-0.118	-0.290
	p	0.235	<0.001
BMI-SDS	r	-0.061	-0.210
	p	0.543	0.009
Haemoglobin (g/dL)	r	0.081	0.217
	p	0.416	0.008
Haematocrit (%)	r	0.131	0.147
	p	0.186	0.070
MCV (fL)	r	0.020	0.088
	p	0.845	0.279

BMI: Body mass index
SDS: Standard deviation score
MCV: Mean corpuscular volume.

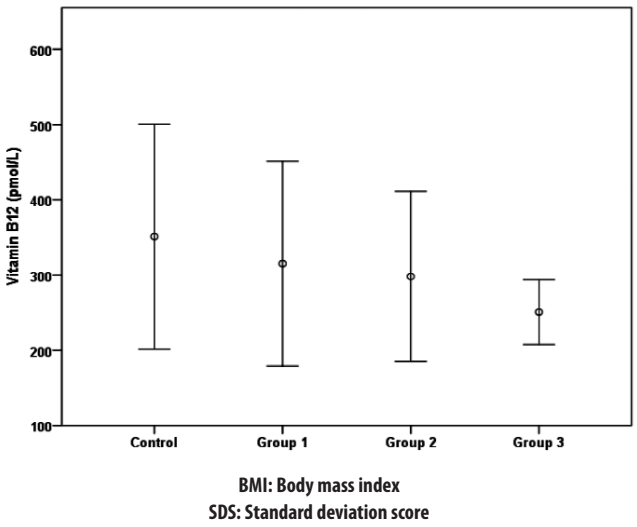

Figure-1: Vitamin B12 levels according to BMI-SDS.Error bar of Vitamin B12 for Mean±Standard Deviation.
The highest vitamin b12 level is seen in control group. Group2 and group3's results are statistically different from group 1 and control group.

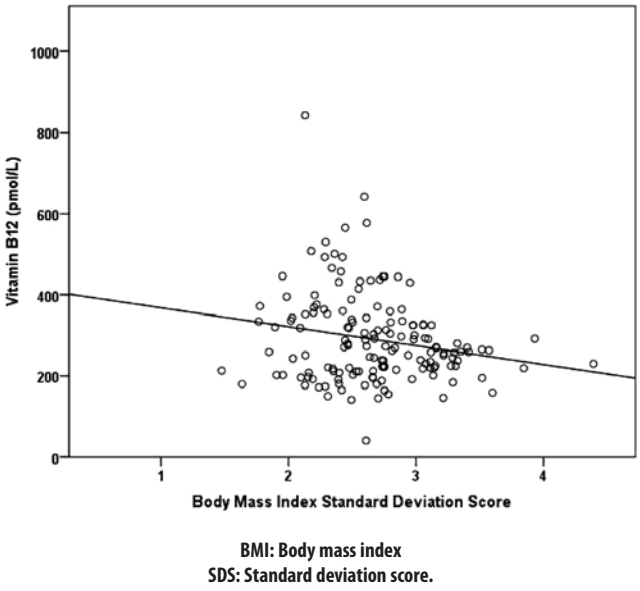

Figure-2: Scatter plot of Vitamin B12 and BMI-SDS in patient group.
BMI-SDS was in a negative correlation with vitamin B12 levels (r:-0.210; p:0.009). Values were mean and 95% confidence intervals. As obesity severity increases vitamin B12 levels decrease.

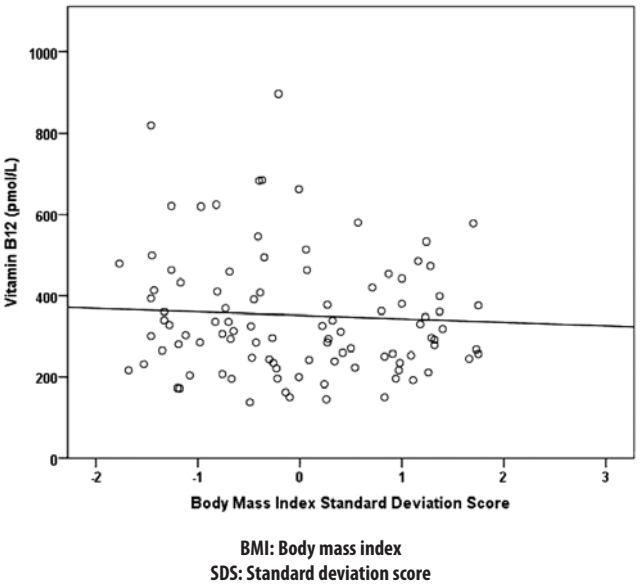

Figure-3: Scatter plot of Vitamin B12 and BMI-SDS in control group.

glucose balance in 59 (38.6%). IR (identified according to HOMA-IR) was present in 88(57.5%) patients. IR was the most common MS component. MS was presented in 40(26.1%) obese children (Table-2).

Bivariate correlations of variables with Vitamin B12 were as follows: age, r= -0.109 and p=0.275 among controls and r= -0.175 and p=0.030 among patients; height, r=0.004 and p=0.971 among controls and r= -0.187 and p=0.021 among patients; weight, r= -0.082 and p=0.410 among controls and r= -0.256 and p=0.001 among patients (Table-3).

Mean vitamin B12 levels were significantly different between the healthy and obese children (Figure-1). Although vitamin B12 levels of all groups were in normal range (>221pmol/L), BMI-SDS was in a negative correlation with vitamin B12 levels (r=-0.210; p=0.009). Values were mean and calculated at 95% confidence interval. BMI was in a close relationship with low vitamin B12 levels. As obesity severity increased vitamin B12 levels decreased (Figure-2, 3).

Discussion

In this study, we demonstrated that BMI was in a negative correlation with vitamin B12 levels in obese children. The prevalence of obesity is steadily increasing worldwide.[1] Obesity brings with it many public health problems, such as vitamin B12 deficiency as we tried to show in this study. It is well known that obesity is closely associated with IR, dyslipidaemia, hypertension and MS.[1,3] The main source of vitamin B12 is red meat. Vitamin B12 deficiency results from decreased intake, a defect in nutrient absorption, or rare inborn errors of vitamin B12 metabolism.[2,18] Vitamin B12 plays important roles in deoxyribonucleic acid(DNA) synthesis, optimal haematopoiesis and neurological function. Vitamin B12 deficiency is associated with a spectrum of diseases from asymptomatic to serious haematological, neurological and psychiatric disorders, as well as a possible risk of irreversible neurological damage despite treatment.[19] Recent studies indicate that low vitamin B12 concentrations may be associated with childhood obesity. MacFarlane et al. found that vitamin B12 levels in obese Canadian children were significantly lower than those in healthy children. They suggested that the decrease was caused by poor diet, decreased use of vitamin B12 supplements or the physiological effects of obesity on nutrient absorption.[17] Pinhas et al. and Gunanti et al. claimed that a higher BMI was a risk for vitamin B12 deficiency and recommended that dietary assessments of obese children should include an estimate of vitamin B12 intake.[18,20] The present study demonstrated lower vitamin B12 levels in obese children with higher BMI-SDS. Low vitamin B12 levels in obese children and adolescents are thought to result from insufficient intake due to a nutrient-poor diet and increased nutrient requirements secondary to increased growth and body size.[21] Gammon et al. investigated the relationship between vitamin B12 and overweight and obesity in adults. They found no relationship between IR and vitamin B12 levels.[22] In our study, lower vitamin B12 levels were seen in obese children with MS than in those without MS. Additionally, lower vitamin B12 levels were detected in children with IR than in those without IR but the results were not statistically significant. Baltaci et al. reported that low vitamin B12 levels were associated with obesity and overweight, and that vitamin B12 level was not associated with IR; these findings were the same as our findings. They found that vitamin B12 level was negatively correlated with BMI, as in our study.[7] Guven et al. detected a negative correlation between homocysteine levels and vitamin B12 levels in Turkish adults with MS, and that a lower vitamin B12 level was associated with MS.[10] Setola et al. used vitamin B12 to treat IR. They reported that subjects who were administered vitamin B12 had lower IR after 2 months.[9] Chen et al. investigated the relationships among CRP, vitamin B12, the C677T polymorphism of the N-5,10-methylenetetrahydrofolatereductase (MTHFR) gene, IR, and risk factors for MS in a Chinese population. They suggested that the MTHFR C677T gene polymorphism was related to a high CRP level, as the vitamin B12 level decreased due to inflammation, which was in contrast to the results of Hernández-Guerrero et al.[23,24] The serum vitamin B12 level is a highly sensitive marker of vitamin B12 deficiency. Childhood obesity is associated with increased CRP and decreased adiponectin levels. Low-grade inflammation persisting in obese children may increase the risk of metabolic events in later life.[25]

A lower vitamin B12 level was found to be associated with the severity of obesity. This decrease in vitamin B12 may be caused by the increase in vitamin B12 required during weight gain. We speculate that causes may include poor dietary content, and increased requirements. Another cause of vitamin B12 deficiency in obese children is increasing inflammation by increase in BMI-SDS. Inflammatory markers and vitamin B12 levels may be compared in obese children to explain the relationship between vitamin B12 deficiency and inflammation in childhood obesity. Our results suggest that clinicians should evaluate vitamin B12 status in children with obesity. Although these results point a relationship between BMI-SDS and vitamin B12, further studies should be conducted to determine the association between BMI-SDS and vitamin B12.

The current study was not without its limitations. Measuring serum vitamin B12 levels using holotranscobolamin, methylmalonic acid and homocysteine is more sensitive. We did not measure these parameters, which was a limitation of our study. Some investigators suggested that obesity severity is in a close relationship with inflammatory markers such as CRP and cytokines. We did not measure the CRP or any cytokines levels. Moreover, the sample size was small, therefore, the findings of this study cannot be

generalised.

Conclusion

Vitamin B12 levels were negatively correlated with BMI-SD. At the same time, vitamin B12 levels were lower in obese children with MS than in those without MS.

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