

# Cobalamin, Folate and Metabolic Syndrome Parameters in Pediatric Morbid Obesity and Metabolic Syndrome

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**Abstract**—Obesity is known to be associated with many clinically important diseases including metabolic syndrome (MetS). Vitamin B<sub>12</sub> plays essential roles in fat and protein metabolisms and its cooperation with vitamin B<sub>9</sub> is well-known. The aim of this study is to investigate the possible contributions as well as associations of these micronutrients upon obesity and MetS during childhood. A total of 128 children admitted to Namik Kemal University, Medical Faculty, Department of Pediatrics Outpatient Clinics were included into the scope of this study. The mean age $\pm$ SEM of 92 morbid obese (MO) children and 36 with MetS were 118.3 $\pm$ 3.8 months and 129.5 $\pm$ 6.4 months, respectively ( $p > 0.05$ ). The study was approved by Namik Kemal University, Medical Faculty Ethics Committee. Written informed consent forms were obtained from the parents. Demographic features and anthropometric measurements were recorded. WHO BMI-for age percentiles were used. The values above 99 percentile were defined as MO. Components of MetS [waist circumference (WC), fasting blood glucose (FBG), triacylglycerol (TRG), high density lipoprotein cholesterol (HDL-Chol), systolic pressure (SP), diastolic pressure (DP)] were determined. Routine laboratory tests were performed. Serum vitamin B<sub>12</sub> concentrations were measured using electrochemiluminescence immunoassay. Vitamin B<sub>9</sub> was analyzed by an immunoassay analyzer. Values for vitamin B<sub>12</sub> < 148 pmol/L, 148-221 pmol/L, > 221 pmol/L were accepted as low, borderline and normal, respectively. Vitamin B<sub>9</sub> levels  $\leq$  4 mcg/L defined deficiency state. Statistical evaluations were performed by SPSSx Version 16.0.  $p \leq 0.05$  was accepted as statistical significance level. Statistically higher body mass index (BMI), WC, hip circumference (C) and neck C were calculated in MetS group compared to children with MO. No difference was noted for head C. All MetS components differed between the groups (SP, DP  $p < 0.001$ ; WC, FBG, TRG  $p < 0.01$ ; HDL-Chol  $p < 0.05$ ). Significantly decreased vitamin B<sub>9</sub> and vitamin B<sub>12</sub> levels were detected ( $p < 0.05$ ) in children with MetS. In both groups percentage of folate deficiency was 5.5%. No cases were below < 148 pmol/L. However, in MO group 14.3% and in MetS group 22.2% of the cases were of borderline status. In MO group B<sub>12</sub> levels were negatively correlated with BMI, WC, hip C and head C, but not with neck C. WC, hip C, head C and neck C were all negatively correlated with HDL-Chol. None of these correlations were observed in the group of children with MetS. Strong positive correlation between FBG and insulin as well as strong negative correlation between TRG and HDL-Chol detected in MO children were lost in MetS group. Deficiency state end-products of both B<sub>9</sub> and B<sub>12</sub> may interfere with the expected profiles of MetS components. In this study, the alterations in MetS components affected vitamin B<sub>12</sub> metabolism and also its associations

with anthropometric body measurements. Further increases in vitamin B<sub>12</sub> and vitamin B<sub>9</sub> deficiency in MetS associated with the increased vitamin B<sub>12</sub> as well as vitamin B<sub>9</sub> deficiency metabolites may add to MetS parameters.

**Keywords**—Children, cobalamin, folate, metabolic syndrome, obesity.

## I. INTRODUCTION

CHILDHOOD obesity may lead to many severe chronic disease such as diabetes mellitus, MetS, cardiovascular diseases (CVDs) and even cancer in adulthood. Aside from genetic, socioeconomic, and cultural factors, nutritional factors are also important. When excessive intake of macronutrients is combined with micronutrient deficiencies, the principle of sufficient and balanced nutrition is impaired. Cobalamin (vitamin B<sub>12</sub>) and folic acid (vitamin B<sub>9</sub>) are closely interrelated micronutrients and essentially involved in the events related to genetic information. Besides, the deficiency of vitamin B<sub>12</sub> may lead to hematological, psychiatric and neurological problems, whereas enzymes of vitamin B<sub>9</sub> metabolism serve as targets during cancer chemotherapy.

So far, numerous studies have been performed to be able to detect the levels of vitamin B<sub>12</sub> as well as those of vitamin B<sub>9</sub>. Percent deficiencies have also been the matter of concern. Aside from healthy individuals, women of childbearing age, obese people, pregnant women, those with gestational diabetes have been the center of attraction for the investigations [1]-[4]. The deficiencies of vitamins B<sub>12</sub> and B<sub>9</sub> were also considered following some bariatric surgery techniques [5]. The profile of this couple was suggested to be examined also for fetal and maternal health in obese pregnancies [6]. However, most of these studies have been carried out on adults.

In very recent studies, vitamin B<sub>12</sub> and B<sub>9</sub> levels have been reported to be linked with some specific cancers. Low vitamin B<sub>12</sub> increases risk of gastric cancer [7]. Vitamin B<sub>9</sub> levels in erythrocytes are significantly lower in pancreatic cancer cases [8]. Levels of both vitamins were also investigated in childhood cancers [9].

Data on protective effects of vitamin B<sub>9</sub> obtained from both experimental and clinical studies are inconsistent [10]. There are also some ambiguities concerning the data on vitamin B<sub>12</sub>.

The aim of this study is to investigate the behavior of these micronutrients within the scope of childhood obesity and MetS.

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## II. PATIENTS AND METHODS

### A. Patients

128 children, who consulted to Pediatrics Outpatient Clinics of Namik Kemal University, Faculty of Medicine, were involved in the study. 92 MO children had the mean age $\pm$ SEM of 118.3 $\pm$ 3.8 months. The corresponding value for 36 children with MetS was 129.5 $\pm$ 6.4 months ( $p>0.05$ ). The ethical committee approved the study protocol. The families gave written permission to allow their children to be engaged in the research activity. Demographical characteristics were collected. Anthropometric measurements were taken.

### B. Obesity Classification

Children in MO group had the age and sex percentile values of BMI greater than 99 as recommended by WHO.

### C. MetS Criteria

For the evaluation of MetS components, WC of the children were measured, FBG, TRG, HDL-Chol analyses as well as SP, DP measurements were performed.

### D. Laboratory Analyses

Serum vitamin B<sub>12</sub> and vitamin B<sub>9</sub> concentrations were determined by immunoassay techniques. Values below 148 pmol/L were defined as low and 148-221 pmol/L as borderline. Concentrations above 221 pmol/L were accepted as normal. Vitamin B<sub>9</sub> levels lower than 4 mcg/L were considered as the deficiency state.

### E. Statistical Evaluations

Statistical evaluations were performed by SPSS Version 16.0.  $p$  values greater than 0.05 were accepted as statistically significant.

## III. RESULTS

In MetS group BMI, WC, hip C and neck C were higher than those of children with MO. Head C values did not differ between the groups.

MetS components were significantly increased in children with MetS (SP, DP  $p<0.001$ ; WC, FBG, TRG  $p<0.01$ ; HDL-Chol  $p<0.05$ ). On the other hand, vitamin B<sub>9</sub> and vitamin B<sub>12</sub> levels were lower ( $p<0.05$ ) in children with MetS than the other group (Figs. 1 (a) and (b)).

In both groups percentage of vitamin B<sub>9</sub> deficiency was 5.5%. In terms of vitamin B<sub>12</sub> levels of the study population, there were no cases below 148 pmol/L. However, in MO group 14.3% and in MetS group 22.2% of the cases were in borderline status (Fig. 2).

Negative correlations between B<sub>12</sub> levels and BMI, WC, hip C, head C were observed in MO group. Negative correlations were also detected between HDL-Chol and WC, hip C, head C, neck C. There was not such a correlation in children with MetS.

It was also interesting to note that strong positive correlation detected between FBG and insulin as well as strong negative correlation observed between TRG and HDL-Chol in MO children were lost in MetS group.

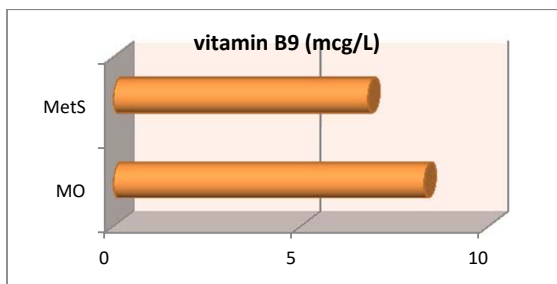


Fig. 1 (a) Vitamin B<sub>9</sub> status of the groups

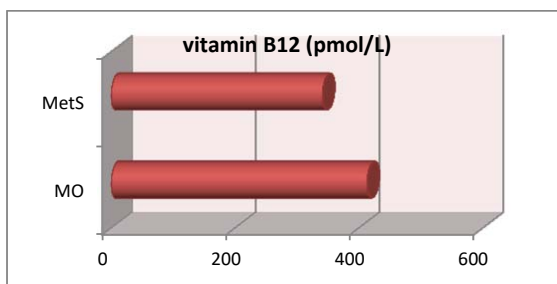


Fig. 1 (b) Vitamin B<sub>12</sub> status of the groups

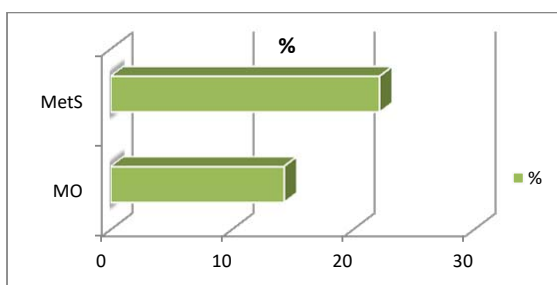


Fig. 2 Percentages of borderline cases based upon vitamin B<sub>12</sub> levels of the groups

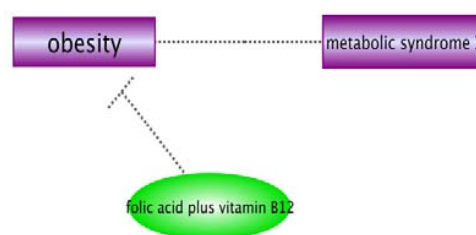


Fig. 3 The possible functional association among vitamin B<sub>12</sub>, vitamin B<sub>9</sub>, obesity, and MetS

## IV. DISCUSSION

An interesting functional association may exist among vitamin B<sub>12</sub>, B<sub>9</sub>, and obesity, which in turn gives rise to the development of MetS. Experimental studies have pointed out that supplementation with methyl donors such as vitamin B<sub>9</sub> and vitamin B<sub>12</sub> prevent transgenerational amplification of obesity suggesting that DNA methylation mechanisms are involved in this process [11] (Fig. 3).

The MetS, a significant consequence of obesity, is

characterized by extended WC, low HDL-C, high TRG, impaired FBG and elevated blood pressure. There are complex relations among these parameters. Within this context, the

possible involvement of vitamin B<sub>12</sub> as well as vitamin B<sub>9</sub> still keeps its enigma (Fig. 4).

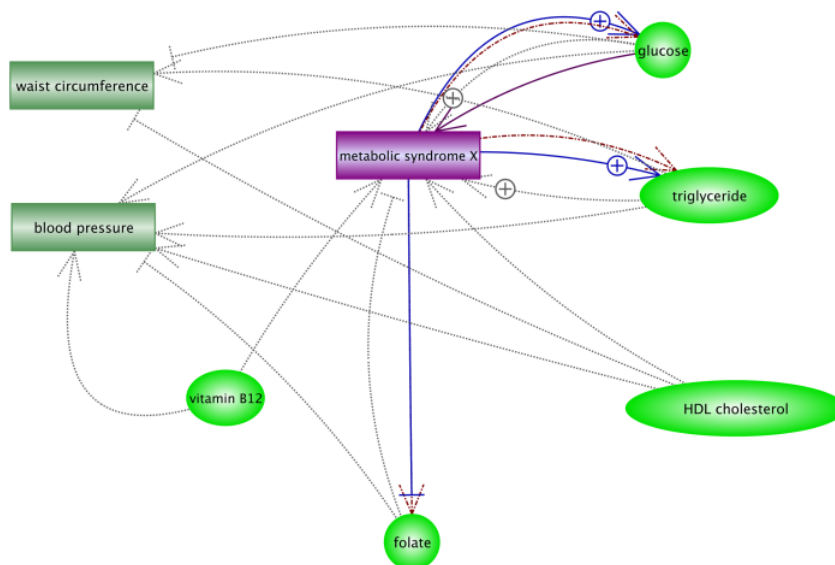


Fig. 4 Network among vitamin B<sub>12</sub>, vitamin B<sub>9</sub> and MetS parameters

There are many studies on vitamin B<sub>12</sub> as well as B<sub>9</sub> performed on adults with MetS [12]-[14]. However, to the best of authors' knowledge, not much attention has been paid to the roles of vitamin B<sub>12</sub> and B<sub>9</sub> within the network of obesity-MetS parameters particularly in children.

Lower vitamin B<sub>9</sub> levels were reported in subjects with MetS than those without MetS [12]. Indian patients with MetS exhibit strong associations with reduced levels of vitamin B<sub>12</sub> and B<sub>9</sub> [13]. Serum concentrations of both vitamins were found to be inversely associated with MetS in Turkish women [14].

In a study performed on children, an increase in BMI was reported to be associated with a decrease in vitamin B<sub>12</sub> levels [15]. In another study, about a third of obese adolescents had a low or borderline serum vitamin B<sub>12</sub> status. In the same study, vitamin B<sub>9</sub> levels did not differ among the groups with low, borderline and normal vitamin B<sub>12</sub> [16].

In our study, both vitamin B<sub>9</sub> and vitamin B<sub>12</sub> levels were decreased in children with MetS in comparison with MO children. However, vitamin B<sub>9</sub> deficiency percent detected for both groups were the same. Although, none with vitamin B<sub>12</sub> deficiency was detected in the study population, percentage of children with borderline vitamin B<sub>12</sub> status was greater in children with MetS than those in the other group.

Low vitamin B<sub>9</sub> intake is suggested as one of the predictors of MetS. It should be paid attention particularly during the primary care of patients [17]. In another report, this vitamin was introduced as a new biomarker of MetS, particularly suitable for screening purposes in general population [18].

Among all, people mostly wondered how blood pressure would be in relation to this complicated network. Considering

the fact that vitamin B<sub>12</sub> and vitamin B<sub>9</sub> work in a collaborative manner as coenzymes in the regeneration of methionine from homocystein, this couple may have synergistic effects on blood pressure or endothelial function [19], [20]. Increases in blood pressure have been shown to be reduced by vitamin B<sub>9</sub> and vitamin B<sub>12</sub> administration [21].

The metabolisms of vitamin B<sub>9</sub> and vitamin B<sub>12</sub> are impaired during their deficiency. The end products synthesized may affect and interact with MetS components. This study points out vitamin B<sub>12</sub> fluctuations possibly caused by the variations in MetS components. The associations between vitamin B<sub>12</sub> and anthropometric measurements are also altered. As a result of the increases in severity as well as percent of both vitamin B<sub>9</sub> and vitamin B<sub>12</sub> deficiency in MetS, the concentrations of deficiency metabolites will also increase. This may affect the status of MetS parameters.

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