Obese Children and Adolescents

A Risk Group for Low Vitamin B\textsubscript{12} Concentration

Orit Pinhas-Hamiel, MD; Noa Doron-Panush, RD; Brian Reichman, MD; Dorit Nitzan-Kaluski, MD, MPH, RD; Shlomit Shalitin, MD; Liat Geva-Lerner, MD

**Objective:** To assess whether overweight children and adolescents are at an increased risk for vitamin B\textsubscript{12} deficiency.

**Design:** Prospective descriptive study.

**Setting:** Two pediatric endocrine centers in Israel.

**Participants:** Three hundred ninety-two children and adolescents were divided into 2 groups as follows: the normal-weight group had body mass indexes, calculated as weight in kilograms divided by height in meters squared, under the 95th percentile (<1.645 standard deviation scores; n=228); the obese group had body mass indexes equal to or above the 95th percentile (≥1.645 standard deviation scores; n=164).

**Intervention:** We measured vitamin B\textsubscript{12} concentrations. Low serum B\textsubscript{12} was defined as a B\textsubscript{12} concentration less than 246 pg/mL, and vitamin B\textsubscript{12} deficiency was defined as a concentration below 211 pg/mL.

**Main Outcome Measure:** Vitamin B\textsubscript{12} concentrations corrected for body mass index standard deviation scores, age, and sex.

**Results:** Median concentration of serum B\textsubscript{12} in normal-weight children was 530 pg/mL and in obese children, 400 pg/mL (P<.001). Low B\textsubscript{12} concentrations were noted in 10.4% of the obese children compared with only 2.2% of the normal weight group (P<.001). Vitamin B\textsubscript{12} deficiency was noted in 12 children, 8 (4.9%) of the obese subjects and 4 (1.8%) of the normal weight group (P=.08). After we adjusted for age and sex, obesity was associated with a 4.3-fold risk for low serum B\textsubscript{12}, and each unit increase in body mass index standard deviation score resulted in an increased risk of 1.24 (95% confidence interval, 0.99-1.56).

**Conclusions:** Obesity in children and adolescents was associated with an increased risk of low vitamin B\textsubscript{12} concentration. We recommend that dietary assessment of obese children should include an estimation of vitamin B\textsubscript{12} intake. The possibility of vitamin B\textsubscript{12} deficiency in addition to other micronutrient deficiencies should be considered in obese children.

Arch Pediatr Adolesc Med. 2006;160:933-936

---

In general, food habits of adolescents are characterized by an irregular meal pattern with skipped meals. In a national survey among youth in the United States, the percentage of youth meeting national dietary recommendations was approximately 30% for the fruit, grain, meat, and dairy pyramid groups. Sixteen percent of youth did not meet any recommendations, and only 1% met all dietary recommendations. Dietary intakes of several micronutrients were found to be inadequate among adolescents in several studies.

Although it is hard to conceive of a nutritional deficiency occurring in subjects with excessive dietary and caloric intake, obese children tend to consume foods rich in carbohydrates and fat and thus may be at increased risk of micronutrient deficiency. For example, obesity has been associated with poor dietary calcium intake both in adults and in children. We have reported that 38.8% of obese children had low iron levels compared with only 4.4% of normal-weight children. Iron levels showed a significant negative correlation with greater standard deviation scores (SDSs) of body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. Similarly, the National Health and Nutrition Examination Survey III (1988 through 1994), providing cross-sectional data on iron deficiency among children aged 2 to 16 years, showed that the prevalence of iron deficiency increased with increasing BMI and iron deficiency was particularly common among obese adolescents (9.1% compared with 3.5% in nonobese adolescents). Vitamin B\textsubscript{12}, also known as cobalamin, is a required nutrient; its main source...
is from foods of animal origin. Vitamin B₁₂ deficiency is associated with hematologic, neurologic, and psychiatric manifestations. Furthermore, vitamin B₁₂ deficiency results in hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease. This study aimed to assess whether obese children are at increased risk for vitamin B₁₂ deficiency.

**METHODS**

The study population comprised 392 children and adolescents aged 6 to 19 years of Sephardic and Ashkenazi Jewish origin. One hundred sixty-four were obese subjects referred to the obesity clinics of 2 endocrine centers in Israel. The study population comprised 392 children and adolescents aged 6 to 19 years of Sephardic and Ashkenazi Jewish origin. One hundred sixty-four were obese subjects referred to the obesity clinics of 2 endocrine centers in Israel. Two hundred eighty-two were normal weight children referred to the endocrine clinics because of familial short stature, precocious or delayed puberty, or hirsutism and in whom no endocrine disorder was subsequently detected. Celiac disease was excluded in 103 of 128 children with short stature. We excluded children who had chronic diseases, those using vitamin supplements, those who were declared vegetarians, and those treated with metformin.

Subjects were divided into 2 groups on the basis of BMI for age and sex according to the National Institutes of Health data as follows: the normal weight group had BMIs under the 95th percentile (≤1.645 SDSs) for age and sex, and the obese group had BMIs at or above the 95th percentile (≥1.645 SDSs) for age and sex.

The study protocol was approved by the human experimentation committees of Sheba and Schneider medical centers (Tel Hashomer and Petah Tikva, Israel, respectively). Written parental informed consent and child assent were obtained from obese participants. Serum B₁₂ concentrations were routinely taken from patients as part of initial blood test screening following an overnight fast. Serum B₁₂ concentration was measured using the ADVIA Centaur System, a competitive immunoassay using direct chemiluminescent technology (Bayer Diagnostics, Tarrytown, NY). Serum B₁₂ concentrations above 246 pg/mL were deemed normal, results between 211 and 246 pg/mL were considered low, and concentrations less than 211 pg/mL indicated a B₁₂ deficiency as recommended by the manufacturer.

Data were analyzed with SAS software version 8.0 (SAS Institute, Cary, NC). Variables were compared using a χ² test for discrete variables and t test or Wilcoxon rank sum test for continuous variables. All tests were 2-tailed and P values below .05 were considered statistically significant. Adjusted odds ratios and 95% confidence intervals were obtained from logistic regression models with low serum B₁₂ concentration (<246 pg/mL) as a dependent variable and age, sex, and obesity as predictors. Goodness-of-fit of the models was estimated by a Hosmer-Lemeshow test and c statistics.

**RESULTS**

Of 392 study participants, 228 were of normal weight, and 164 were obese. Age and sex distribution, BMI, and vitamin B₁₂ concentrations of each group are shown in Table 1. The median serum B₁₂ concentration of obese children was significantly lower than that of normal weight children; 400 vs 530 pg/mL, respectively (P = .001). This difference was especially marked in children aged 12 years and older.

Low vitamin B₁₂ concentrations (<246 pg/mL) were present in 22 subjects (5.6%), 17 (10.4%) of whom were obese and 5 (2.2%) of whom were normal-weight children (P = .08). Vitamin B₁₂ concentrations below 246 pg/mL were noted in 18 (9.7%) of 186 children older than 12 years of age compared with 4 (1.9%) of 206 children aged 6 to 11 years (P = .001). The percentages of boys (4.5%) and girls (6.4%) with B₁₂ concentrations below 246 pg/mL were not statistically different.

Vitamin B₁₂ deficiency (<211 pg/mL) occurred in 12 children, 8 of whom were aged 12 to 19 years. Vitamin B₁₂ deficiency was present in 8 (4.9%) of the obese subjects and in 4 (1.8%) of the normal weight group (P = .08).

On multivariate analysis (Table 2), obesity was associated with an excess risk for low vitamin B₁₂ levels (odds ratio, 4.33) after adjustment for age and sex. The Hosmer-Lemeshow goodness-of-fit test and c statistics showed that the model fitted well (P = .90, c = 0.77). A similar model was conducted with BMI SDSs and age as continuous vari-

**Table 1. Age, Sex, and Vitamin B₁₂ Levels According to Weight Status**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Weight (n = 228)</th>
<th>Obese (n = 164)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>11.4 ± 2.7</td>
<td>12.4 ± 3.3</td>
<td>.002</td>
</tr>
<tr>
<td>Age, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 y</td>
<td>137 (60.1)</td>
<td>69 (42.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥ 12 y</td>
<td>91 (39.9)</td>
<td>95 (57.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, median (interquartile range)*</td>
<td>16.8 (15.2-18.7)</td>
<td>31.5 (27.0-36.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>86 (37.7)</td>
<td>70 (42.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>142 (62.3)</td>
<td>94 (57.3)</td>
<td>.32</td>
</tr>
<tr>
<td>Vitamin B₁₂ concentration, median, pg/mL (interquartile range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>530 (410-663)</td>
<td>400 (304-518)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Boys</td>
<td>526 (384-695)</td>
<td>410 (304-520)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Girls</td>
<td>530 (420-635)</td>
<td>396 (304-504)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &lt; 12 y</td>
<td>541 (425-709)</td>
<td>490 (401-598)</td>
<td>.02</td>
</tr>
<tr>
<td>Age ≥ 12 y</td>
<td>504 (385-614)</td>
<td>337 (279-439)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Body mass index is calculated as weight in kilograms divided by height in meters squared.

**Table 2. Multivariate Analysis for Low Serum Vitamin B₁₂ Levels**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Low B₁₂, No. (%)</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI SDSs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>228</td>
<td>5 (2.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>164</td>
<td>17 (10.4)</td>
<td>4.33 (1.54-12.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 y</td>
<td>206</td>
<td>4 (1.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥ 12 y</td>
<td>186</td>
<td>18 (9.7)</td>
<td>4.46 (1.46-13.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156</td>
<td>7 (4.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>236</td>
<td>15 (6.4)</td>
<td>1.67 (0.46-4.31)</td>
<td>.29</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio; SDSs, standard deviation scores.

*Serum B₁₂ concentration was less than 246 pg/mL.
Our results show that obese children and adolescents had significantly lower B12 concentrations than normal-weight children and that 10% of obese children had low serum B12 concentrations. Obesity was associated with a greater than 4-fold risk for low vitamin B12 concentrations, and for each unit increase in BMI SDS, there was a 24% increase risk of low serum B12 concentrations. To the best of our knowledge, this is the first report of low B12 concentrations in obese children. Lower serum B12 concentrations were detected in overweight Brazilian adolescents compared with those of normal-weight adolescents; however, this difference did not reach statistical significance. Among Thai adults, no statistically significant difference in vitamin B12 concentrations was found in overweight and obese subjects compared with normal control subjects. Among adult Turkish patients with metabolic syndrome, serum B12 concentrations were significantly lower than those of healthy subjects.

Vitamin B12 deficiency results from decreased intake, abnormal nutrient absorption, and rare inborn errors of vitamin B12 metabolism. Abnormal absorption may be due to medications that decrease gastric acid secretion, pernicious anemia, infection with giardia lamblia, and any disruption of the ileal mucosa such as Crohn and celiac disease. Because obese children gain weight easily, there is no reason to suspect they have a problem with absorption. Although declared vegetarians were excluded from our study, dietary habits of obese children may be high in carbohydrate and fat and low in proteins from animal sources that contain vitamin B12. Indeed in a recent study, low-nutrient-density foods contributed more than 30% of daily energy intake, and intake of micronutrients related inversely to intake of low-nutrient-density foods. In the present study, although obese children were new to our clinic and had not yet been started on a weight-loss diet, it is possible that some of them had tried unbalanced diets prior to their referral to the clinic. Furthermore, it is possible that obese children have increased vitamin B12 needs compared with nonobese children because of their increased growth and body surface area. Finally, B12 concentrations noted reflect the status in Israeli children and may not be comparable with data from other countries. For example, in our cohort, the mean B12 concentration of normal-weight children aged 6 to 11 years was 541 pg/mL and in the 12- to 18-year-old group, 504 pg/mL, compared with 708 and 528 pg/mL in same age groups in the United States.

Vitamin B12 is a cofactor in the synthesis of methionine from homocysteine; therefore, deficiency in vitamin B12 leads to hyperhomocystinemia. Longitudinal cohort studies have established that even mild hyperhomocysteinemia both predicts and precedes the development of cardiovascular morbidity and mortality. Hyperhomocysteinemia correlated with insulin resistance in obese prepubertal children. Among adults with the metabolic syndrome, levels of homocysteine were significantly higher and levels of vitamin B12 were significantly lower compared with those of healthy subjects. Homocysteine-lowering treatments have resulted in improvement of cardiovascular reactivity and coagulation factors. It is thus possible that vitamin B12 deficiency may further contribute to the high risk of developing cardiovascular disease among obese children. Folate and vitamin B12 treatment improved insulin resistance and endothelial dysfunction, along with decreasing homocysteine levels, in patients with metabolic syndrome.

In assessing the results of this study, a number of limitations should be considered. First, although measurement of serum vitamin B12 concentration has been widely used as the standard screening test for deficiency, the test has poor positive and negative predictive values. A "normal" concentration does not reliably exclude deficiency and low serum vitamin B12 concentration does not necessarily indicate deficiency. Other assays are expensive, such as those for methylmalonic acid and homocysteine, which seem to provide greater sensitivity and specificity, and concerns about the use of these assays and the interpretation of their results are emerging. Second, in the absence of an Israeli population-based reference, we used the manufacturer reference for definitions of low and deficient. Vitamin B12 concentrations in serum vary with the analytical method used and the laboratory conducting the analysis. Data from the National Health Examination Survey in the United States (1988-1994) defined B12 deficiency as levels lower than the fifth percentile for age, which in the US population aged 4 years and older corresponded to 233 pg/mL. The fifth percentile for children aged 6 to 11 years was 380 pg/mL and for those aged 12 to 19 years was 289 pg/mL. These values are higher than our cutoff levels. A detailed dietary questionnaire was not obtained from the children, so we could not correlate B12 levels with intake.

Third, vitamin B12 levels reflect results in Israeli children and may not be comparable with data from other countries. Lower B12 levels have been reported in a population of young adult men in Israel compared with those of the United States. Unfortunately, B12 levels of healthy children in Israel have not been reported. Finally, although low vitamin B12 levels were significantly more prevalent among obese children, B12 deficiency was more prevalent only with borderline significance, maybe because of the relatively small sample size. These results are therefore preliminary observations and need further investigation.

In summary, our findings show that obese children are at high risk for low serum vitamin B12 levels. We speculate that causes may include poor dietary content, repeated short-term restrictive diets, and increased requirements. We recommend that dietary assessment of obese children should include an estimation of vitamin B12 and other micronutrient intakes.
Accepted for Publication: March 24, 2006.

Author Affiliations: Pediatric Endocrinology and Diabetes Unit, Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Tel Hashomer, Israel (Dr Pinhas-Hamiel, Ms Doron-Panush, and Dr Reichman); Pediatric Endocrinology and Metabolism Unit, Schneider Children’s Medical Center, Petah Tikva, Israel (Ms Doron-Panush and Dr Shalitin); Women and Children’s Health Research Unit, Gertner Institute, Tel Hashomer (Drs Reichman and Geva-Lerner); Food and Nutrition Administration and Department of Epidemiology and Preventive Medicine, Ministry of Health, Jerusalem, Israel (Dr Nitzan-Kaluski); and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel (Dr Pinhas-Hamiel, Ms Doron-Panush, and Drs Reichman, Nitzan-Kaluski, Shalitin, and Geva-Lerner).

Correspondence: Orit Pinhas-Hamiel, MD, Pediatric Endocrinology and Diabetes Unit, Sheba Medical Center, Ramat-Gan, 52621, Israel (orithami@sheba.health.gov.il).


REFERENCES