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Original Article

Evaluation of vitamin B12 level in middle-aged obese women with metabolic and nonmetabolic syndrome: case-control study

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Aim: To investigate the correlation between vitamin B12 and body mass index (BMI) along with insulin resistance (IR) in middle-aged obese women.

Materials and methods: The study was designed as a case-control study. The study group included middle-aged obese women and the control group included aged-matched lean women. Weight, height, and hip and waist circumferences were measured. Biochemical parameters such as fasting and postprandial glucose, vitamin B12 and folic acid levels, and lipid profiles were assayed.

Results: Enrolled in the study were 116 middle-aged obese and 103 aged-matched healthy lean women. The vitamin B12 level of the obese women was significantly lower than that of the lean women (244.1 ± 131.5 pg/mL vs. 336.2 ± 163.1 pg/mL, P = 0.002). However, there was no significant difference in folic acid levels between the groups (P > 0.05). The vitamin B12 level was similar in the obese women with metabolic syndrome and those without (245.1 ± 145.3 pg/mL vs. 241.2 ± 96.5 pg/mL, P > 0.05), but the level in the control group was significantly higher than that of patients with obesity and metabolic syndrome (P = 0.010 and P = 0.020, respectively). Vitamin B12 levels correlated with BMI (r = –0.259, P = 0.003) but not with IR (r = –0.053, P > 0.05).

Conclusion: The vitamin B12 concentration was low in obese patients and this level negatively correlated with BMI, but not with homeostasis model assessment-estimated IR (HOMA-IR).

Key words: Obesity, vitamin B12, insulin resistance, body mass index

Introduction

Obesity and vitamin B12 deficiency are common health problems encountered in primary care settings. Obesity is associated with many diseases. People with obesity are at great risk for some diseases such as diabetes mellitus and cardiovascular diseases. In patients with obesity who also have metabolic syndrome (MetS) and those without, the metabolic state is changed and many inflammatory cytokines, such as interleukins, tumor necrosis factors, and C-reactive proteins, are increased (1-3). A number of diseases not classically considered to be caused by vitamin B12 deficiency are epidemiologically associated with it, raising questions of whether vitamin B12 status is an independent risk factor or a partial causal agent in these states. None of these causal links have been proven and all are under active investigation (4,5).

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The total amount of vitamin B12 stored in the body is about 2-5 mg in adults. Approximately 50% of this is stored in the liver (6,7). Vitamin B12 deficiency is usually due to pernicious anemia and an inadequate intake of nutrition enriched with vitamin B12, especially among vegetarian people. Various cutoff values for vitamin B12 have been propounded. Currently, there is no certain agreement on the clinical use of cutoff levels for vitamin deficiency. A recent widely used clinical cutoff level for vitamin B12 deficiency was 148 pmol/L (200 pg/mL) (8).

In the literature, some studies investigated vitamin B12 levels in obese patients, with MetS or without, and tried to find a relation between vitamin B12 deficiency and obesity. They reported different results. While vitamin B12 levels were normal in some, levels were low in others. Uehara and Rosa (9) reported that cobalamin levels were normal in their study. Guven et al. (10) also found that vitamin B12 levels were normal. However, Karatela et al. (11) conducted a study on vitamin B12 and homocysteine levels in hypertensive patients who were obese and overweight compared to normal-weight hypertensive patients, reporting a high homocysteine level and reduced vitamin B level. Moreover, Pinhas-Hamiel et al. (12) conducted a study on vitamin B12 levels and obesity in children and adolescents and found that obesity was associated with vitamin B12 deficiency. The purpose of the present study was to investigate the association between vitamin B12 and obesity, the correlation between vitamin B12 deficiency and anthropometric measurements, and insulin resistance (IR) in middle-aged obese women with and without MetS.

Materials and methods

The study design and patients

The case-control study was conducted at the outpatient clinic of the Family Medicine Department at Düzce University, between June and December 2010, in Düzce, Turkey. Women who met the study obesity criteria were included. Age-matched, lean, healthy women were enrolled in the control group. Exclusion criteria included being a strict vegetarian, being male, being over 50 years of age, current use of corticosteroids or vitamin supplementations, long-term use of proton pump inhibitors (PPIs; 3 months or longer) and metformin, and diabetes mellitus. Informed consent was obtained. Ethical approval was given by the ethics committee of our institute.

Anthropometric measurements

The anthropometric values of the participants from the study and control groups were measured: fasting body weight, height, and waist and hip circumferences were measured in the morning, according to standard procedures. Weight and height were measured with the subjects wearing light clothing and without shoes. Height was recorded to the nearest 0.1 cm with a stadiometer. Weight was recorded to the nearest 0.1 kg using a balance-beam scale. Waist circumference was measured to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the top of the iliac crest, at the end of exhalation, using a waistline measurer employed with subjects standing without clothing covering the waist area. Hip circumference was measured to the nearest 0.1 cm using a tape applied with the subjects standing and without clothing except for light underwear covering the hip area around the point with the maximum circumference over the buttocks. Body mass index (BMI) was calculated using the following formula: kg / height (m^2).

Biochemical analysis

All of the blood and urinary samples were collected in the morning, after 8-12 h of overnight fasting. After blood was drawn, the tubes were gently shaken and then separated by centrifugation at 3200 rpm for 10-15 min. A blood sample for postprandial glucose level was drawn 2 h after eating. A blood sample for complete blood count test was drawn into a tube containing ethylenediaminetetraacetic acid (EDTA). Lipid profiles were assayed using the colorimetric method (Cobas 6000 C 501, Roche Diagnostics GmbH, Mannheim, Germany). Insulin, thyroid-stimulating hormone, vitamin B12, and folic acid levels were assayed using the solid-phase 2-site chemiluminescent immunometric assay, solid-phase competitive chemiluminescent enzyme immunoassay, solid-phase chemiluminescent immunometric assay, and competitive immunoassay, respectively (IMMULITE 2000, Siemens Healthcare Diagnostics, Flanders, NJ, USA). Low density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formulation. Homeostasis model assessment-estimated IR (HOMA-IR) was also calculated with the following formula: fasting serum glucose (mg/dL) × fasting plasma insulin level (μU/mL) / 405. HOMA-IR was accepted as positive if it was >2.5 (13).

Determination of obesity, metabolic syndrome, and vitamin B12 deficiency

Obesity was defined as a BMI value over 29.9 kg/m^2, as described by the World Health Organization (14). MetS was defined, using criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III, as 3 or more of the following variables and cutoff points: 1) fasting blood sugar of ≥110 mg/dL, 2) triglyceride level of ≥150 mg/dL, 3) high-density lipoprotein cholesterol (HDL-C) of <50 mg/dL in women, 4) waist circumference of >88 cm, and 5) blood pressure of ≥130/85 mmHg (13). In our study, we used 3 descriptive cutoff points for the status of vitamin B12, as suggested by Tucker et al. (15). Accordingly, the current clinical cutoff was 200 pg/mL (148 pmol/L), the intermediate point was 250 pg/mL (185 pmol/L), and a point at which individuals may be at risk of deficiency was 350 pg/mL (258 pmol/L), although further testing is then needed.

Statistical analysis

Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as means ± standard deviations, medians (interquartile range), or percentages (%). Student's t-test was used to compare statistical differences of normal variables among the different groups, but for skewed variables, a Mann-Whitney U test or Kruskal-Wallis H test was used. One-way ANOVA (Bonferroni test) was used to compare statistical differences for variables of more than 2 groups. Correlation between vitamin B12 levels and BMI and HOMA-IR was analyzed using Pearson's correlation analysis. A 2-tailed P-value of less than 0.05 was considered statistically significant.

Results

Sociodemographic and clinical features of the study subjects

A total of 116 middle-aged obese women (obesity with MetS: 81, obesity without MetS: 35) and 103 aged-matched healthy lean women were included in the study and control groups, respectively. Some sociodemographic features of the total participants are shown in Table 1.

Table 1. Distribution of sociodemographic features and findings of the study and control groups.

Parameters	Study group (n = 116) (%)	Control group (n = 103) (%)	P*
Age	37.7 ± 9.1	35.3 ± 8.2	0.236**
Status of smoking			
Smoker	18 (15.5%)	15 (14.6%)	0.620
Nonsmoker	98 (84.5%)	88 (85.4%)	
Status of occupation			
Working	19 (16.4%)	81 (78.6%)	<0.0001
Not working (housewife)	97 (83.6%)	22 (21.4%)	
Alcohol use			
Yes	2 (1.7%)	3 (2.9%)	0.730
No	114 (98.3%)	100 (97.1%)	
Total	116 (100%)	103 (100%)	

*Fischer's exact/chi-square tests were used to compare categorical variables between the study and control groups. P < 0.05 was accepted as statistically significant.
**Independent Student's t-test was used for comparison of the mean age between the study and control groups. There was no significant difference observed (P = 0.236).

Biochemical and anthropometric parameters of subjects in the study group

In Table 2, a comparison of the biochemical and anthropometric parameters in the study and control groups is shown. HOMA-IR value, HDL-C, triglycerides (TG), and anthropometric and blood pressure measurements in the study group were statistically different from those in the control group (P = 0.0001, P = 0.001, P = 0.0001, and P = 0.0001, respectively). However, total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), folic acid level, and complete blood counts [hemoglobin (Hb), hematocrit, and mean corpuscular volume (MCV)] were not significant between the 2 groups (P > 0.05). The vitamin B12 level in the obese group was significantly lower than in the control group (244.1 ± 131.5 pg/mL vs. 336.2 ± 163.1 pg/mL; P = 0.002). The study group was divided into subgroups, as obese with MetS and obese without. We compared the BMI, vitamin B12 level, folic acid level, HOMA-IR, lipid profile, measurement of blood pressure, and anthropometric measurements of the subgroup patients with those of the control group. The results are shown in Table 3. Accordingly, the mean BMI in the obese women with MetS and without was significantly higher than those in the control group (36.2 ± 6.6 kg/m^2 and 33.2 ± 4.3 kg/m^2 vs. 23.3 ± 2.4 kg/m^2; P < 0.0001). The average waist circumference measurement of the lean women was significantly lower than those of the obese women with MetS and without (84.2 ± 7.8 cm vs. 105.4 ± 12.1 cm and 98.6 ± 9.6 cm; P < 0.0001 and P < 0.0001). Furthermore, the mean waist circumference of patients with only obesity was significantly different from those of patients with obesity and MetS (P < 0.0001). The mean hip circumference measurement of the obese women with MetS and without was statistically higher than that of the control group (112.3 ± 15.1 cm and 104.9 ± 16.6 cm vs. 92.8 ± 18.6 cm; P < 0.0001). The mean HDL-C level was significantly lower in patients with MetS, compared to the lean and obese subjects (40.5 ± 9.2 mg/dL vs. 52.8 ± 13.8 mg/dL and 54.7 ± 13.3 mg/dL; P < 0.0001 and P > 0.05). The mean HOMA-IR in the participants (obese with MetS, obese without

Table 2. Comparisons of the anthropometric and biochemical parameters between the patients and the control group.

Parameters	Study group (n = 116)	Control group (n = 103)	P*
Anthropometric measurements			
BMI (kg/m^2)	36.7 ± 6.3	23.3 ± 2.4	<0.0001
Waist circumference (cm)	103.7 ± 12.1	84.2 ± 7.8	<0.0001
Hip circumference (cm)	110.6 ± 15.5	92.8 ± 18.4	<0.0001
Lipid profile (mg/dL)			
LDL-C (mg/dL)	107.1 ± 32.3	96.1 ± 26.6	0.046
HDL-C (mg/dL)	44.8 ± 12.3	52.8 ± 13.8	0.001
TG (mg/dL)	151.4 ± 87.4	95.7 ± 47.4	<0.0001
Total-C (mg/dL)	183.7 ± 37.1	174.7 ± 51.7	0.299
HOMA-IR	3.04 ± 2.26	1.32 ± 1.13	<0.0001
Blood pressure (mmHg)			
Systolic	129.6 ± 11.3	112.6 ± 6.3	<0.0001
Diastolic	84.3 ± 8.4	71.8 ± 4.8	<0.0001
B12 vitamin level (pg/mL)	244.1 ± 131.5	336.2 ± 163.1	0.002
Folic acid level (pg/mL)	8.9 ± 6.7	6.7 ± 3.2	0.058
Complete blood count			
Hb (g/dL)	12.3 ± 1.6	12.7 ± 1.1	0.083
MCV (μm^3)	81.2 ± 5.7	82.1 ± 5.7	0.421

*Student's t-test was used. P< 0.05 was accepted as statistically significant.

Table 3. Comparisons of anthropometric and biochemical parameters in women with obesity and MetS with lean healthy women.

Parameters	MetS (n = 81)	Obesity (n = 35)	Control (n = 103)	P*
Age (years)	39.8 ± 8.6	35.3 ± 7.2	35.1 ± 8.3	>0.05
Anthropometric measurements				
BMI (kg/m^2)	36.9 ± 6.2	33.2 ± 4.3	23.3 ± 2.4	<0.0001
Waist circumference (cm)	105.4 ± 12.1	98.6 ± 9.6	84.2 ± 7.8	<0.0001
Hip circumference (cm)	112.3 ± 15.1	104.9 ± 16.6	92.8 ± 18.4	<0.0001
HOMA-IR	3.5 ± 2.5	2.1 ± 2.5	1.3 ± 1.1	0.001, <0.001, >0.05
Blood pressure (mmHg)				
Systolic blood pressure	132.1 ± 10.3	123.7 ± 11.1	112.6 ± 6.3	<0.001
Diastolic blood pressure	86.3 ± 7.5	79.6 ± 8.7	71.8 ± 4.8	<0.001
Lipid profile				
LDL-C (mg/dL)	108.4 ± 32.5	104.5 ± 33.2	96.1 ± 26.6	>0.05
HDL-C (mg/dL)	40.5 ± 9.2	54.7 ± 13.3	52.8 ± 13.8	<0.001, >0.05
TG (mg/dL)	170.5 ± 98.2	108.5 ± 32.4	95.7 ± 47.4	<0.001, >0.05
Total-C (mg/dL)	183.7 ± 39.2	184.1 ± 33.5	174.7 ± 51.7	>0.05
B12 vitamin level (pg/mL)	245.1 ± 145.3	241.2 ± 96.5	336.2 ± 163.1	0.010, 0.002, >0.05
Folic acid level (pg/mL)	9.1 ± 7.8	8.4 ± 3.9	6.8 ± 3.3	>0.05

*ANOVA (Bonferroni test) was used. P < 0.001 was accepted as statistically significant.

MetS, and lean women) was 3.4 ± 2.5, 2.1 ± 2.5, and 1.3 ± 1.1, respectively. A statistically significant difference was found between the obese women with MetS and without (P = 0.001) and between the obese women with MetS and lean women (P < 0.001), but not between the obese women without MetS and the lean women (P > 0.05).

Vitamin B12 levels in the lean patients were significantly higher than in patients with obesity with and without MetS (336.2 ± 163.2 pg/mL vs. 245.1 ± 145.3 pg/mL and 241.1 ± 96.5 pg/mL; P = 0.010 and P = 0.020, respectively). However, a comparison of vitamin B12 levels between obesity with MetS and obesity without MetS was not significant (P > 0.05), although the mean B12 level in patients with MetS was slightly higher (Table 3).

Correlation of vitamin B12 and folic acid level with insulin resistance

In Table 4, vitamin B12 and folic acid levels in the obesity group were compared to the status of HOMA-IR. The vitamin B12 level in subjects with HOMA-IR (+) (n = 54) was lower than in those with HOMA-IR (–) (n = 62), but no significant difference was detected (278.2 ± 152.7 pg/mL vs. 249.6 ± 131.5 pg/mL, P > 0.05; 7.8 ± 3.5 pg/mL vs. 9.3 ± 9.1 pg/mL, P > 0.05). A negative correlation between vitamin B12 levels and both IR and BMI was observed, but it was only statistically significant with BMI (r = –0.237, P = 0.003; r = –0.058, P = 0.447, respectively).

Comparison of vitamin B12 levels in subjects according to different cutoff values

Table 5 shows the number of obese participants with and without MetS and the control group, and the comparison with the cutoff value of vitamin B12 levels. Here, there were significant differences in the number of subjects according to 3 vitamin B12 cutoff value classifications. The cutoff value classification was set as 200 pg/mL and the majority of the obese patients with MetS were under this cutoff value (n = 41, 50.6%), while only 20.3% of the control group individuals (n = 21) were under this value.

Table 4. Vitamin B12 concentration according to HOMA-IR status in women with obesity.

Parameters	HOMA-IR (–) (n = 62)	HOMA-IR (+) (n = 54)	P*
B12 vitamin level (pg/mL)	278.2 ± 152.7	249.6 ± 131.5	0.245
Folic acid level (pg/mL)	7.8 ± 3.5	9.3 ± 9.1	0.211

*Student's t-test was used. P < 0.05 was accepted as statistically significant.

Table 5. Correlation of vitamin B12 concentration with BMI and HOMA-IR.

	BMI (kg/m^2)		HOMA-IR	
	r	P*	r	P*
B12 vitamin level (pg/mL)	–0.237	0.003	–0.058	0.447

*Pearson's correlation analysis was used to analyze the correlation of vitamin B12, BMI, and IR. P < 0.05 was accepted as statistically significant.

Discussion

We found that middle-aged obese women had significantly lower vitamin B12 levels than normal lean women. We also detected that serum vitamin B12 levels were negatively correlated with BMI.

Vitamin B12 deficiency results from an inadequate intake of nutrition, abnormal nutrient absorption, and rare inborn errors of vitamin B12 metabolism. Vitamin B12 is mainly present in animal protein, particularly organ meats, bivalves, and, to a lesser extent, in seafood, milk, and milk products. However, prevalence of vitamin B12 deficiency is not rare, and it is especially common the elderly. Vitamin B12 deficiency does not only cause anemia and megaloblastic anemia, but also causes neurological symptoms. Recent studies have shown that long-term use of metformin decreases vitamin B12 levels in patients, especially diabetic patients (17,18). Therefore, we excluded the patients who had used metformin for a long period of time.

A correlation between obesity and vitamin B12 levels has been investigated in a few studies. Guven et al. (10) conducted a study on plasma homocysteine and lipoprotein levels in patients with MetS and found low levels of vitamin B12 compared to normal healthy individuals. We studied vitamin B12 and folic acid levels, but not homocysteine levels, and we also found that vitamin B12 levels were low but that folic acid levels were normal.

IR is a metabolic assault. It is associated with many undesired medical conditions. In diseases with IR (+), a proinflammatory state is activated. IR does not develop in every obese patient. The correlation between vitamin B12 levels and IR is not clear. Cemil et al. (19) conducted a study on the relation between IR and plasma vitamin B12 levels in women with polycystic ovary syndrome, and they found that vitamin B12 levels were lower in obese women with IR compared to those without IR. In the present study, there were 62 subjects with IR (–) and 54 subjects with IR (+) in the obese group. None of the women in the control group had IR [HOMA-IR (+)]. We compared the correlation between the obese women with IR (+) and IR (–), using HOMA-IR. We did not find any significant difference. We observed a negative correlation, but it was not significant. On the other hand, Tungtrongchitr et al. (20) studied serum homocysteine, vitamin B12, and folic acid levels in overweight and obese subjects and they found no statistically significant difference in the vitamin B12 levels compared with normal weight subjects. Reitman et al. (21) conducted a study on plasma antioxidants, vitamin B12, and homocysteine levels in patients with obesity and found no significant difference in vitamin B12 levels between the obese and lean subjects. In contrast, the present study indicated that vitamin B12 levels were significantly lower in the obese patients compared to the normal subjects, and we found no significant difference in folic acid levels between the obese and nonobese women.

In our study, we did not only compare vitamin B12 levels in obese and lean middle-aged women, but also in patients with MetS. We detected no significant difference between the obese women with and without MetS. However, we found that vitamin B12 levels in the control group were significantly different from those of both the obese women with MetS and those without. In our study, we used a classification for vitamin B12 levels that was suggested by Tucker et al (15), since it was widely used in clinical practice. According to this classification, the majority of patients with MetS and obesity were under the vitamin B12 level cutoff value. When we observed the 3 vitamin B12 level cutoff values, we detected a significant difference in the number of patients between the study and control groups (obesity and MetS). As a result, we declare only that obesity might be risk factor, but not that it is a causal factor because further community-based study is required.

A few studies have demonstrated that long-term use of PPIs caused vitamin B12 deficiency in patients with dyspeptic symptoms (22). In our study, the patients who had used PPIs for over 3 months were excluded. Chronic but intermittent (short-interval) use of PPI in the population is not rare. Van Oijen et al. (23) studied the association between BMI and prevalence of gastrointestinal symptoms and found that there was a small but not statistically significant increase in the prevalence of gastrointestinal diseases and related symptoms. We know that chronic but intermittent use of PPIs is common in the Turkish population in middle-aged women (24-26).

In the present study, BMI, HDL-C, TG, blood pressure, and anthropometric measurements were significantly different in patients with obesity and MetS compared to the control group. Moreover, another interesting result in our study was that the majority of women with obesity were not working or were housewives. This indicates that actively participating in social life and having a social role are important for sociopsychological impact (27).

There were some limitations in our study. First, homocysteine levels were not evaluated. In some studies, it was shown that there was a relation between homocysteine and vitamin B12 concentrations. Second, long-term use of PPIs in our patients was examined, but intermittent use of PPIs was not. Intermittent use of PPIs might be effective at lowering vitamin B12 levels. Third, it was shown that there was a relation between vitamin B12 deficiency and *H. pylori* manifestation in previous studies. We did not investigate the state of *H. pylori*.

In the present study, vitamin B12 levels were low in middle-aged obese women with and without MetS. The more the BMI increases, the lower the vitamin B12 level is in middle-aged women. We observed that vitamin B12 levels in obese women correlated with BMI but not with IR. The causes of obesity are multifactorial diseases and the intake of imbalanced nutrition, as well as a sedentary lifestyle. Obesity is an ill-balanced medical condition and carries many risk factors for metabolic and cardiovascular diseases. Therefore, we should advise the implementation of a well-balanced diet.

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