Relationship between vitamin B12 levels and insulin resistance in postmenopausal women from Colombia Caribbean

Relação entre níveis de vitamina B12 e resistência à insulina em mulheres na pós-menopausa da Colômbia Caribe

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ABSTRACT

Introduction: The high prevalence of low vitamin B12 serum levels has been recognized as a public health problem in Latin America; however, the current magnitude of this deficiency in Colombia is uncertain. Low levels of vitamin B12 can induce clinical and subclinical hematological and neurological disorders. Epidemiological studies have demonstrated a relationship between vitamin B12 deficiency and cardiovascular diseases (CVDs). However, the role of vitamin B12 in insulin resistance has been poorly studied. **Objective:** This study aimed to evaluate the relationship between vitamin B12 serum levels and biochemical and anthropometric markers related to CVDs and insulin resistance in postmenopausal women from Colombia Caribbean. **Methods:** Correlational, descriptive study. By convenience sampling, 182 postmenopausal women from the medical consultation service of a health institution were linked. Serum vitamin B12 levels, anthropometric variables (body mass index, abdominal perimeter), and biochemical variables (glycemia, insulin, lipid profile, HOMA IR) were evaluated. **Results:** The average value of the vitamin B12 serum level was 312.5 ± 122.5 pg/mL (230.6 ± 90.4 pmol/L); 46.7% of the women had less than adequate levels of 300 pg/mL (> 221 pmol/L), and 9. 9% were deficient, with levels of less than 200 pg/mL (148 pmol/L). The women with metabolic syndrome were 63.7%, and according to HOMA IR, 52.7 % had insulin resistance. A significant inverse relationship was shown between serum vitamin B12 levels with basal glycemic (P =0.002) and HOMA-IR (P =0.040). **Conclusions:** A significant inverse relationship between vitamin B12 levels and basal glycemia and HOMA-IR was observed. These findings highlight vitamin B12 deficiency in postmenopausal women and suggest nutritional supplementation.

Keywords: Vitamin B12, Insulin resistance, Diet, Postmenopause, Cardiovascular diseases.

RESUMO

Introdução: A alta prevalência de baixos níveis séricos de vitamina B12 foi reconhecida como um problema de saúde pública na América Latina, mas a magnitude atual dessa deficiência na Colômbia é incerta. Baixos níveis de vitamina B12 podem induzir distúrbios hematológicos e neurológicos clínicos e subclínicos. Na verdade, estudos epidemiológicos demonstram uma relação entre deficiência de vitamina B12 e doenças cardiovasculares (DCVs). No entanto, o papel da vitamina B12 na resistência à insulina tem sido pouco estudado. **Objetivo:** O objetivo deste estudo foi avaliar a relação entre os níveis séricos de vitamina B12 e marcadores bioquímicos e antropométricos relacionados com doenças cardiovasculares e resistência à insulina em mulheres pós-menopáusicas da Colômbia Caribe. **Métodos:** Estudo correlacional, descritivo. Por amostragem de conveniência, foram vinculadas 182 mulheres na pós-menopausa do serviço de consulta médica de uma instituição de saúde. Níveis séricos de vitamina B12, variáveis antropométricas (índice de massa corporal, perímetro abdominal) e variáveis bioquímicas (glicemia, insulina, perfil lipídico, HOMA IR) foram avaliadas. **Resultados:** O valor médio do nível sérico de vitamina B12 foi de 312,5 ± 122,5 pg/mL (230,6 ± 90,4 pmol/L); 46,7% das mulheres tinham níveis abaixo do adequado de 300 pg/mL (> 221 pmol/L), e 9,9% eram deficientes, com níveis abaixo de 200 pg/mL (148 pmol/L). As mulheres com síndrome metabólica foram 63,7% e, segundo o HOMA IR, 52,7% apresentavam resistência à insulina. Uma relação inversa significativa entre os níveis séricos de vitamina B12 com glicemia basal (P = 0,002) e HOMA-IR (P = 0,040) foi mostrada. **Conclusões:** Foi observada uma relação inversa significativa entre os níveis de vitamina B12 e glicemia basal e HOMA-IR. Esses achados destacam a deficiência de vitamina B12 em mulheres na pós-menopausa e sugerem suplementação nutricional.

Palavras-chave: Vitamina B12, Resistência à insulina, Dieta, Pós-menopausa, Doenças cardiovasculares.

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INTRODUCTION

Vitamin B12 (cobalamin) deficiency is a health problem, mainly associated with hematological, neurological, and psychiatric disorders, affecting different population groups. Low vitamin B12 serum levels have been identified as a public health issue in Latin America[1,2], but the current magnitude of this deficiency in Colombia is unknown.

Vitamin B12 deficiency is caused by inadequate intake, inadequate bioavailability, or malabsorption. Individuals following vegetarian diets, people with gastrointestinal diseases associated with poor adsorption, chronic carriers of *Helicobacter pylori*, long-term metformin users, and older adults are especially vulnerable[3,4]. In the older adult population, the presence of achlorhydria generates a loss in the intestinal absorption capacity of vitamin B12, and the prevalence of vitamin B12 deficiency could be around 12%, according to the Framingham study[5]. However, depending on the reference values used, the analytical methodology, and the population evaluated in different studies, the prevalence of vitamin B12 deficiency could be approximately 30 to 40% among hospitalized elderly populations[6].

Vitamin B12 functions as a cofactor for enzymes like the methionine synthase, which catalyzes the conversion of homocysteine to methionine, and L-methyl malonyl-CoA mutase, which converts L-methyl malonyl-CoA to succinyl-CoA in the degradation of propionate, an essential biochemical reaction in fat and protein metabolism[7]. Low levels of vitamin B12 are associated with cellular stress due to increased levels of homocysteine. Homocysteinylation of proteins could explain some mechanisms involved in vitamin B12 deficiency related to neurological deterioration and dysregulation of gene expression by influence on DNA methylation processes[8]. There are other causes of elevation of homocysteine unrelated to vitamin deficiency, such as different disorders of methionine metabolism[9]. High homocysteine levels have been associated with endothelial dysfunction and CVDs risk. However, the molecular mechanisms involved in this relationship are not completely elucidated, and the studies carried out are contradictory in establishing hyperhomocysteinemia as the single and main cause of pathology[10]. Moreover, independent of homocysteine, serum vitamin B12 values have been inversely related to levels of triglycerides and very low-density lipoprotein (VLDL), as well as with inflammatory markers associated with insulin resistance, such as C reactive protein and interleukin 6[11]. Vitamin B12 is implicated in the pathogenesis of glucose intolerance; levels of vitamin B12 decrease with increasing severity of glucose tolerance; vitamin B12 is essential for the maintenance of the enzyme system necessary for the utilization of carbohydrates and fats[12].

Menopause is a condition where a woman has not had a menstrual period in a year. Due to hormonal changes, such as decreased estrogen levels, postmenopausal is associated with various metabolic disorders, including metabolic syndrome, cardiovascular diseases, and type 2 diabetes[13]. In menopausal women, psychological and physiological changes have an impact on food intake. Older adults are at high risk of vitamin B12 malabsorption due to the lack of intrinsic factor production, and low vitamin B12 levels increase blood pressure, contributing to CVDs[14].

In Latin America, there are few studies that evaluate serum levels of vitamin B12 in the population. More research is needed to understand the relationships between vitamin B12 deficiency and CVDs, especially in vulnerable populations such as postmenopausal women. In this work, we evaluate serum vitamin B12 levels in a group of postmenopausal women from the Atlantic department in Colombia Caribbean, and establish their relationship with biochemical and anthropometric variables associated with CVDs risk and insulin resistance.

METHODS

This cross-sectional correlational descriptive study was undertaken in the Atlántico department of the Colombian Caribbean between September and October of 2018. A convenience sample included 182 postmenopausal female patients from the internal medicine consult at a health institution (PROMOCOSTA). The inclusion criteria were postmenopausal women (at least one year after the last menstrual period), aged 50–80 years old, who do not consume replacement hormonal therapy, nutritional supplements, or another vitamin B12 source in addition to the diet, and who do not consume hypolipidemic drugs. The health-stable status of the woman was determined by a medical assessment performed by an internal medicine resident under the supervision of an internist. The medical assessment included taking blood pressure. The control of pathologies such as hypertension and diabetes through medicaments was not an exclusion criterion.

The anthropometric evaluation included height in cm, weight in kg, and abdominal perimeter in cm (digital scale, stadiometer, and a tape measure, mark SECA) and was carried out according to the criteria established in resolution 2465 of 2016 of the Ministry of Health of Colombia[15], and the procedures established by the World Health Organization (WHO).

For biochemical analysis, the women were cited at the health institution in the morning hours after fasting for 12 hours for the extraction by the vacutainer method of a total blood sample. Without using an anticoagulant, two tubes of blood were collected, and the samples were immediately transported to the Foundation Hospital University Metropolitan (FHUM) clinical laboratory for analysis of glycemia, cholesterol, high-density lipoprotein (HDL), and triglycerides. The analytical procedures were performed according to the manufacturer's instructions. The values for low-density lipoproteins (LDL) were calculated with the Friedewald formula.[16] In the ANAMED clinical laboratory, serum Vitamin B12 (competitive enzymatic delayed immunoassay in the Chromate 4300 Microplate Reader using the AccuBind ELISA Kit 7625-300), and serum insulin (Chemiluminescence Immunoassay-LIAISON kit), were evaluated. The HOMA-IR index was calculated according to the formula (fasting insulin (μU/L) x fasting glycemia (mmol/L)/22.5) [17].

The study was carried out with the authorization of the ethics committee of Metropolitana University. The postmenopausal women signed the informed consent according to the ethical norms stipulated in the Colombian Decree 8430 of 1983 and the Helsinki Declaration. The published information does not contain sensitive data about the participants.

Statistical analysis

An exploratory, descriptive analysis of the results was carried out to determine the average value of serum vitamin B12 levels in the total population. A serum vitamin B12 above 300 pg/mL (> 221 pmol/L) is interpreted as normal. Patients with vitamin B12 levels between 200 and 300 pg/mL (148 and 221 pmol/L) are considered borderline, and patients with vitamin B12 levels below 200 pg/mL (<148 pmol/L) are considered deficient[18,19,20].

Reference values for biochemical and anthropometric variables associated with metabolic syndrome (MS) were defined based on a consensus on diagnostic criteria issued by several leading institutions. According to these, the presence of 3 to 5 of the following criteria constitutes a diagnosis of MS: abdominal adiposity defined as a waist circumference > 80 cm for women, fasting blood glucose with values above 100 mg/dL, high blood pressure (BP) (Systolic BP ≥130 mmHg and/or Diastolic BP ≥85 mmHg), triglycerides greater than 150 mg/dl, and HDL cholesterol less than 50 mg/dL for women[21]. Other lipid criteria as total cholesterol greater than 200 mg/dL; and LDL cholesterol greater than 100 mg/dL, were defined according to the criteria ATP III [22]. The cut-off value for HOMA-IR ≥2.5 was a criterion to indicate insulin resistance[17,23].

The relationship between vitamin B12 values and each variable was evaluated through an analysis of linear regression. The relationship between vitamin B12 status (deficiency, borderline levels, and normal value) and each one of the variables was established with the ANOVA test. The Statgraphics Plus statistical program was employed.

RESULTS

This cross-sectional correlational descriptive study included 182 post-menopausal women with an average age of 65.6±6.2 years (range 50-80 years). Table 1 shows the average values of the anthropometric and biochemical variables of the population, as well as the number and percentage of women who presented altered values for each variable according to the parameters described in the materials and methods. Anthropometric evaluation allowed us to classify the population analyzed according to BMI into eutrophic women with a normal BMI of between 18.5 and 24.9 (n=34) 18.6%; overweight women with a BMI of between 25 and 29.9 (n=75) 41.0% and obese women with a BMI greater than 30 (n= 74) 40.4%. The presence of MS was observed in 63.7% of the women, and the most frequent diagnostic criteria were increased abdominal circumference, triglycerides greater than 150 mg/dl, and low levels of HDL cholesterol. According to HOMA IR, 52.7 % of the women had insulin resistance.

Table 1
Average values of the anthropometric and biochemical variables of the population and the percentage of women who presented altered values for each variable.

Variable	Total population (n= 182)	Population with altered values	Reference criteria
	Average value ± DE	(n) %	
Body Mass Index (BMI)	29.9 ± 5.9	(148) 81.3 %	>25
Abdominal perimeter (cm)	101.1 ± 9.4	(180) 98.9 %	>80
Basal glycemic (mg/dL)	94.4 ± 33.5	(47) 25.8 %	>100
Total cholesterol (mg/dL)	183.5 ± 48.6	(62) 34.1 %	>200
Triglycerides (mg/dL)	182.6 ± 70.9	(117) 64.3 %	>150
HDL cholesterol (mg/dL)	51.6 ± 11.5	(88) 48.3 %	<50
LDL cholesterol (mg/dL)	95.4 ± 40.6	(72) 39.6 %	>100
Serum insulin (uUI/ml)	14.0 ± 9.0	(16) 8.8 %	> 25
HOMA-IR index	3.3 ± 2.6	(96) 52.7 %	≥ 2.5
Vitamin B12 (pg/mL)	312.5 ± 122.5	(85) 46.7 %	<300
BP systolic (mmHg)	125.7 ± 12.2	(71) 39.0 %	≥130
BP diastolic (mmHg)	78.1 ± 7.3	(22) 12.1 %	≥85
MS presence*		(116) 63.7 %	

BP stands for blood pressure. *Metabolic syndrome (MS) is defined based on the presence of 3 to 5 of the criteria previously described.

Regression analysis showed a statistically significant inverse relationship between the vitamin B12 values with the glycemia levels (R- squared =3.98%, p=0.006) and the HOMA-IR Index (R-squared =2.17%, p=0.047). Table 2 shows the relationships (ANOVA test) between the average values of the anthropometrics and biochemicals variables and the vitamin B12 status (deficiency, borderline, and adequate level). The average value of the vitamin B12 serum level was 312.5 ± 122.5 pg/mL (230.6 ± 90.4 pmol/L); 46.7% (n = 85) of the women had less than adequate levels of 300 pg/mL (> 221 pmol/L), and 9.9% were deficient (n=18), with levels less than 200 pg/mL (<148 pmol/L), and 36.8% had borderline values (n = 67). Analysis of the variance between groups according to vitamin B12 conditions showed a significant inverse relationship between serum vitamin B12 serum levels with basal glycemic (p = 0.002) and HOMA-IR (p = 0.040), but not with total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, or the anthropometric variables. Only 3.8% of the women evaluated were diagnosed, and in treatment for type 2 diabetes mellitus (n = 7), 76.5% were in treatment for high blood pressure (n = 140), and 19.2% had the two pathologies simultaneously (n = 35).

Table 2
Average values of anthropometric and biochemical variables concerning vitamin B12 status in the general population.

Variables evaluated	Serum levels of B12 vitamin			
	Deficiency (<200 pg/mL) (n=18) 9.9%	Borderline (200-300 pg/mL) (n=67) 36.8 %	Adequate level (>300 pg/mL) (n=97) 53.2%	*P*
B12 vitamin (pg/mL)	102.3 ± 54.6	257.0 ± 28.9	389.8 ± 103.4	
Body Mass Index	29.4 ± 5.0	28.8 ± 4.2	30.7 ± 6.9	0.132
Ab. perimeter (cm)	99.3 ± 7.9	99.9 ± 9.8	102.3 ± 9.4	0.200
Basal glycemic (mg/dL)	112.5 ± 41.7[a]	96.8 ± 38.7[ab]	89.3 ± 26.4[b]	0.002
Cholesterol (mg/dL)	173.0 ± 39.0	189.6 ± 51.4	181.3 ± 48.2	0.407
Triglycerides (mg/dL)	184.6 ± 70.7	193.8 ± 79.1	174.4 ± 64.3	0.353
HDL Cholesterol (mg/dL)	54.4 ± 11.5	51.5 ± 12.0	51.1 ± 11.2	0.547
LDL Cholesterol (mg/dL)	81.7 ± 32.2	99.2 ± 42.5	95.4 ± 40.6	0.264
Serum insulin (uUI/mL)	17.0 ± 14.2	13.5 ± 8.3	13.7 ± 8.3	0.320
HOMA-IR index	4.7 ± 4.5[a]	3.2 ± 2.3[b]	3.1 ± 2.2[b]	0.040
BP systolic (mmHg)	129.8 ± 22.9	124.4 ± 11.3	125.9 ± 9.9	0.250
BP diastolic (mmHg)	79.6 ± 11.9	77.2 ± 6.4	78.4 ± 6.8	0.339

The table shows the average values ± standard deviation of the evaluated variables. *P*: the value of statistical significance of the comparison (ANOVA test) between Vitamin B12 conditions, which is representative if it is less than 0.05. The averages in the same row that do not share the same superscript letter are different. Blood pressure is abbreviated as BP.

The mean values of vitamin B12 for each condition were for the group with diabetic at 326.8 ± 70.7 pg/mL (241.2 ± 52.2 pmol/L), for the hypertensive groups at 314.6±123.5 pg/mL (232.2 ± 91.2 pmol/L) and for those with both pathologies at 300.8±128.1 pg/mL (222.0 ± 94.5 pmol/L), with no statistically significant differences between groups ($P > 0.005$). The average value of vitamin B12 in the total of the women with diabetes was 305.2 ± 120.1 pg/mL (225.23 ± 88.7 pmol/L) without significant differences with the only hypertension group.

Between the groups of women with MS and without MS, no significant differences were observed concerning the value of vitamin B12, the values of 311.7 ± 120.0 pg/mL (225.23 ± 88.7 pmol/L) and 313.7 ± 127.6 pg/mL (225.23 ± 88.7 pmol/L) for each group, respectively.

DISCUSSION

This work evaluated serum vitamin B12 levels in a group of postmenopausal women from the Atlantic department in Colombia Caribbean, and established their relationship with biochemical and anthropometric variables associated with CVD risk and insulin resistance.

Vitamin B12 is used in the body as a cofactor for enzymes involved in important physiological functions such as the synthesis and maintenance of DNA, the formation of fatty acids, and myelin, among others. Deficiency of this vitamin has been associated with metabolic abnormalities such as hyperhomocysteinemia, insulin resistance, and defective synthesis of neurotransmitters and fatty acids[24]. According to reports of different world studies, vitamin B12 insufficiency frequently occurs among elderly people [25,26]. In this study, 182 postmenopausal women were evaluated, and the results revealed that nearly half of the women had vitamin B12 values lower than normal, and one in ten had a deficiency. This result is consistent with the Framingham study, which reported a prevalence of vitamin B12 deficiency in the adult population of around 12% [5].

There is little data in Colombia about vitamin B12 deficiency in the population. Herran et al. evaluated a population of 9500 Colombians between under 18 and women of fertile age, finding a prevalence of 6.6% of vitamin B12 deficiency and 22.5 % of marginal deficiency [27]. Data that, together with those reported in this study, could suggest that in Colombia, the deficiency of this micronutrient affects the population from an early age and is accentuated in older adults.

The clinical manifestations of vitamin B12 deficiency are highly variable. Some studies report older adults with low levels of serum vitamin B-12 but not classical clinical or metabolic signs of vitamin B12 deficiency; macrocytic anemia may not be present in patients with neuropsychiatric disorders associated with vitamin B12 deficiency [4,28]. Other symptoms like loss of appetite, diarrhea, fatigue, low blood pressure, and confusion can also be present. In this study, the apparent good health of women was evaluated through medical review.

The link between vitamin B12 deficiency and CVD risk could be explained by several mechanisms: Vitamin B12 deficiency causes macrocytosis, which is linked to circulatory problems, coronary disease, and infarction [29]. According to several studies, including the Framingham study, high homocysteine levels from nutritional vitamin B12 deficiencies cause adverse effects on the cardiovascular endothelium, such as alterations in arterial structure, endothelial dysfunction, hypercoagulation, and high blood pressure [30]. Low vitamin B12 has also been associated with visceral obesity and insulin resistance[31]. In this study, we did not find any relationships between low vitamin B12 serum levels and lipemic values, blood pressure alterations, or anthropometrical data, but we did show a significant inverse relationship between serum vitamin B12 deficiency and basal glycemic and HOMA-IR as an insulin resistance indicator. Low levels of serum vitamin B12 were linked to insulin resistance and metabolic syndrome in 278 obese French patients, according to Li et al.[32], and Ho et al. found that one-third of obese Australian adolescents with clinical insulin resistance had low or borderline serum vitamin B12 status [33].

The relationship between vitamin B12 deficiency and insulin resistance is possibly due to the insufficient synthesis of methionine, which increases stress in the endoplasmic reticulum by causing deficient oxidation of free fatty acids. In addition, the accumulation of methylmalonic acid due to the low conversion to succinylcholine causes lipogenesis and insulin resistance [30]. Women with vitamin B12 deficiency have a higher risk of developing gestational diabetes Mellitus compared with vitamin B12 sufficient women, but more studies are needed to clarify the possible pathogenic mechanisms of this relationship [24].

Long-term therapy with metformin in patients with type 2 diabetes is associated with a potential risk of vitamin B12 deficiency. According to recent research, the duration of treatment and the daily dose of metformin are significant factors in developing vitamin B12 deficiency. Kim et al. found that doses of metformin higher than 1500mg/d are related to the development of vitamin B12 deficiency [34]. However, this relationship is the subject of debate among various studies since the mechanisms by which metformin reduces serum levels of vitamin B12 have not been fully elucidated [35]. Some authors suggest that metformin antagonizes the calcium in the terminal ileum, interfering with the absorption of vitamin B12-intrinsic factor complex[36,37]. But more knowledge is needed about the effects of this oral hypoglycemic agent and its interaction with factors such as age, sex, diet, alcohol consumption, and multivitamin supplementation, among others. The results of this research show no relationship between the average values of vitamin B12 between patients with or without diagnosis and treatment for type 2 diabetes Mellitus. It is of great interest to propose new studies that, in the context of the Colombian Caribbean, allow us to know the relationship between the consumption of metformin and vitamin B12 deficiency, also looking for the mechanisms that influence this relationship.

There are different criteria for determining vitamin B12 deficiency and its reference values. Some authors consider that an efficient diagnosis of vitamin B12 deficiency should be based on its serum values and the determination of other biomarkers associated with metabolism such as serum folate, holotranscobalamin, methylmalonic acid, or homocysteine. It is necessary to unify concepts and carry out new studies that allow defining, according to the circumstances and diagnostic needs, which is the best marker to evaluate. However, the measurement of serum B12 levels is an acceptable and cost-effective method [38,39].

CONCLUSIONS

This study draws attention to vitamin B12 deficiency in postmenopausal women from the Colombian Caribbean, showing that almost half of the evaluated population had serum vitamin B12 values lower than adequate. There is a significant inverse relationship between vitamin B12 levels and basal glycemia and HOMA-IR. The results show the need to further evaluate the effects of this deficiency in postmenopausal women and suggest the need for nutritional supplementation in this population group. The study of the relationship between vitamin B12 and insulin resistance should be deepened.

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