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Research Article

Evaluation of whole blood, mean platelet volume (MPV) and neutrophil-lymphocyte ratios (NLR) in people with B12 vitamin deficiency

B12 vitamin eksikliği olan kişilerin tam kan, ortalama trombosit hacmi (MPV) ve nötrofil-lenfosit oranlarının (NLR) değerlendirilmesi

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Abstract

Introduction: It was aimed to investigate the effects of vitamin B12 deficiency on blood tests, mean platelet volume (MPV), and neutrophil-lymphocyte ratio (NLR), which is one of the inflammation markers.

Methods: Our study is a case-control study of 375 patients. 170 patients with low B12 (<130 pg/dL) were accepted as the experimental group, and 205 individuals with normal B12 levels were accepted as the control group. Between these two groups, white blood cells (WBC), platelet count (Plt), hemoglobin (Hgb), mean erythrocyte volume (Mean Corpuscular Volume-MCV), mean platelet volume (Mean Platelet Volume-MPV), neutrophil, lymphocyte counts, and neutrophil -lymphocyte ratios (NLR) were examined.

Results: The mean age was 48.45 ±17.497 years in the B12 deficient group and 51.93 ±16.175 years in the control group. The mean of vitamin B12 in the deficient group was 101.41 ± 20.50 pg/mL (min-max 37-130), while it was 257.24 ± 88.13 pg/mL (131–498) in the control group. It was observed that there was no statistically significant difference between WBC, Hgb, Plt, neutrophil, lymphocyte, MVC, MPV and NLR values.

Conclusion: In our study, we could not find a significant relationship between B12 deficiency and blood tests. In previous studies, there has been information that MPV values are affected by B12 deficiency. In our study, we found that there was no significant relationship between B12 deficiency and MPV or NLR ($p > 0.05$). There is a need for new studies on how B12 deficiency will change as the degree and duration of B12 deficiency increases, especially its effect on atherogenic events.

Keywords: Vitamin B12 deficiency, mean platelet volume, neutrophils, lymphocytes

Öz

Giriş: B12 vitamin eksikliğinin; kan tetkiklerine, ortalama trombosit hacmine (MPV) ve inflamasyon markerlarından nötrofil-lenfosit oranına (NLR) etkilerinin araştırılması amaçlanmıştır.

Yöntem: Çalışmamız 375 hasta üzerinde yapılmıştır. B12'si düşük (<130 pg/dL) saptanan 170 hasta deney grubu olarak, B12 düzeyleri normal olan 205 kişide kontrol grubu olarak kabul edilmiştir. Bu iki grup arasında beyaz kan hücreleri (WBC), trombosit sayısı (Plt), hemoglobin (Hgb), ortalama eritrosit hacmi (MCV), MPV, nötrofil, lenfosit sayıları ve nötrofil-lenfosit oranları (NLR) incelenmiştir.

Bulgular: Yaş ortalaması B12 eksik grupta 48.45 ±17.497 yıl, kontrol grubunda ise 51.93 ±16.175 yıl idi. Eksik grupta B12vitamini ortalaması 101,41 ± 20,50 pg/mL (min-max; 37-130), kontrol grubunda ise 257,24 ± 88,13 pg/mL (min-max; 131-498) idi. WBC, Hgb, Plt, nötrofil, lenfosit, MVC, MPV ve NLR arasında istatiksel açıdan anlamlı bir fark olmadığı gözlendi.

Sonuç: Çalışmamızda B12 eksikliği ile kan tetkikleri arasında anlamlı bir ilişki bulamadık. Önceki çalışmalarda B12 eksikliğinde MPV değerlerinin etkilendiğine dair bilgiler bulunmaktadır. Yaptığımız çalışmada da B12 eksikliği ile MPV ve NLR arasında anlamlı bir ilişkinin olmadığını saptadık ($p>0,05$). B12 eksikliğinin, düzeyi ve süresi uzadıkça nasıl değişiklikler gözlenebileceği ve özellikle de bu vitamin eksikliğinin aterojenik olaylara olan etkileri hakkında yapılacak yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: B12 vitamini eksikliği, ortalama trombosit hacmi, nötrofil, lenfosit

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Key Points

1. In cases with B12 deficiency, immediate macrocytosis should not be expected.
2. In B12 deficiency, changes in whole blood tests, MPV and NLR rates do not occur contrary to what is known.
3. New research is needed on NLR and B12 deficiency, which are new inflammatory markers.
4. MPV is more significant in cases such as inflammatory events, malignancies, and new platelet synthesis.

Introduction

Vitamin B12 (cobalamin) is a vitamin that is found in foods of animal origin, especially red meat, cannot be synthesized in our body, is water-soluble and has vital importance. It is separated from food proteins by acid and pepsin in the stomach, and it binds to haptocorrin in saliva and gastric secretions. The formed haptocorrin-cobalamin is released by pancreatic proteases and binds to intrinsic factor secreted from the stomach in the proximal ileum. It is then taken into the cell by CUBAM (cubilin+amnionles) receptors in the ileum. Entering the portal circulation, it is transported by transcobalamin. It plays a role in chemical reactions in our body by transforming into adenosylcobalamin and methylcobalamin [1]. Vitamin B12 plays a role as a cofactor during the conversion of homocysteine to methionine in the folate and methionine cycles in purine synthesis. Homocysteine levels increase in vitamin B12 deficiency. It is known that increased homocysteine may cause damage to the vascular endothelium and cardiovascular disorders [2,3].

Vitamin B12 deficiency is a common but serious condition. While B12 deficiency is 6% in people under the age of 60, it is encountered at rates close to 20% over the age of 60. It has been reported that the incidence is higher in African and Asian countries [4]. Since its deficiency may have clinical symptoms that are not obvious, complex problems can be observed in its diagnosis and treatment. There is no ideal test to detect vitamin B12 deficiency, and therefore the clinical status of patients is extremely important. If clinical findings suggest vitamin B12 deficiency in a patient, it is important to give treatment to prevent neurological complications that may develop even if there is inconsistency between blood results and clinical findings [5]. Hyperpigmentation, jaundice, vitiligo, glossitis symptoms, anemia (macrocytic, megaloblastic), leukopenia, pancytopenia, thrombocytopenia, thrombocytosis, neuropsychiatric, areflexia, cognitive impairment (including dementia-like symptoms and acute psychosis), gait abnormalities, irritability, loss of proprioception and vibration sense, olfactory dysfunction, peripheral neuropathy may occur in vitamin B12 deficiency [6]. Clinical findings may occur in different ways depending on the degree and duration of deficiency and personal sensitivity. Another important point is that clinical findings may occur before anemia or a decrease in serum vitamin B12 levels. Therefore, treatment should be started without delay [7,8]. Considering the laboratory techniques and tests used in the detection of B12 deficiency, difficulties are observed in the diagnosis of clinical and subclinical deficiency states on an individual basis. In the definitive diagnosis of B12 deficiency, serum cobalamin level is one of the most preferred methods, and it has a sensitivity of 97% [7,9,10]. Methylmalonic acid (MA) measurement and homocysteine testing are other methods used [7]. In vitamin B12 deficiency, complete blood counts (MCV and Hb), reticulocyte count, peripheral smear, lactate dehydrogenase levels, bilirubin levels, and bone marrow may be affected to varying degrees depending on individual sensitivity. Macrocytosis is the most common stimulus to control vitamin B12 status. A bone marrow biopsy may be considered in people who are resistant to treatment. Macrocytosis may be masked and not observed in cases such as concomitant iron deficiency or thalassemia in people with B12 deficiency [5].

MPV is a marker of platelet function, and a high MPV indicates an excess of atherogenic platelets [11]. It has been found that MPV values increase during activation periods in inflammatory diseases (such as rheumatoid arthritis and ankylosing spondylitis) [12]. Neutrophil/lymphocyte Ratio (NLR-NLR) values are calculated using hemogram values and are accepted as indicators of subclinical inflammation [13,14].There have also been studies that show NLR can be used to calculate the morbidity and mortality associated with some medical interventions, such as angiography or appendectomy, and even to predict the prognosis in some types of cancer [15,16].However, there is still no consensus on the range of normal NLR values in different age groups and different genders [17]. Waiting for macrocytosis and changes in other blood elements to occur in every B12 deficiency sometimes wastes us time. In this study, it was aimed to examine the changes in blood in patients with B12 deficiency and was followed by primary care physicians.

Methods

This study was designed as a case-control study on 375 patients. 170 patients with low B12 (<130 pg/dL) were accepted as the experimental group, and 205 individuals with normal B12 levels were accepted as the control group (B12>130 pg/dl). Between these two groups, white blood cells (WBC), platelet count (Plt), hemoglobin (Hgb), mean erythrocyte volume (Mean Corpuscular Volume-MCV), mean platelet volume (Mean Platelet Volume-MPV), neutrophil, lymphocyte counts, and neutrophil -lymphocyte ratios (NLR) were examined.

Ethical Approval

Our study was approved by the local ethics committee, dated 11/11/2021 and numbered 2021/11-1, and it was conducted with the permission of the Provincial Health Directorate for the use of personal data.

Study population

The universe of our study consists of 763 people who had blood tests in a family health center within the scope of the Check-up program. The blood tests of these people were examined. For other information, patient records and those with missing registration information were obtained by using the face-to-face interview method. As exclusion criteria, iron deficiency anemia, folic acid deficiency, thalassemia, infection status, patients under the age of 18, those with high vitamin B12 levels, those who use drugs that affect vitamin B12 levels (such as metformin and antiepileptic), those who have been diagnosed with pernicious anemia, those who have been diagnosed with proton therapy for a long time, pump inhibitor users, those with a history of gastrointestinal surgery, those with chronic inflammatory diseases, and those who are currently on B12 replacement therapy were not included in the study. After these exclusion criteria, our study was completed on the remaining 375 people. The group with a B12 value below 130 pg/dl was considered the study group (n: 170), and the group with a B12 value above it was considered the control group (n: 205).

Evaluate the samples

Hemogram Horiba ABX Pentra DF 120 device and Beckman Coulter DXI 800 device were used to evaluate vitamin B12 levels. Vitamin B12 level below 130 pg/mL was considered low and above 131 pg/mL was considered normal.

Statistical Analysis

Data were entered into the SSPS 20.00 package program (Statistical Package for the Social Science, Inc.; Chicago, IL, USA) and statistical analysis was performed. Categorical variables were represented as numbers (n) and percent (%), while numerical variables mean standard deviation and median (min, max).The data were first evaluated using the Kolmogorov-Smirnov test to see if they fit the normal distribution or not. test was used for pairwise group comparisons since the data did not fit the normal distribution.

Results

The relationships between gender, age, and blood vitamin B12 values of 375 patients who participated in our study are shown in Table 1. The mean age of the patients was 48.45 ±17.497 years in the B12 deficiency group and 51.93 ±16.175 years in the control group.

Table 1. Characteristics of low vitamin B12 level and control group.

	Patients with B12 deficiency (≤130 pg/mL)		Control group		X^2	p
	n	%	n	%		
Gender						
Female	88	51.7	124	60.5	2.878	0.090
Male	82	48.3	81	39.5		
Age (years)						
18-34 years	42	24.7	36	17.6		
35-49 years	42	24.7	50	24.4	5.879	0.118
50-64 years	54	31.8	61	29.8		
≥65years	32	18.8	58	28.2		

Chi-Square Test

In the group with B12 deficiency participating in the study, the mean of vitamin B12 was 101.41 ± 20.50 (min-max; 37-130) pg/mL, the mean MCV 87.61 ±5.82 fL, and the mean MPV 9.11 ±0.95 The mean fL and NLR ratios were determined to be 1.76 ±0.71. In the control group, mean vitamin B12 was 257.24 ±88.13 (131-498) pmol /L, mean MCV 86.67 ±5.91 fL, mean MPV 9.01 ±0.90 fL, and NLR rate 1.68 ± 0.72. When the B12 deficient group and the control group were evaluated as a whole, it was observed that vitamin B12 levels were lower in the elderly and women. It was determined that there was no statistically significant difference between the B12 deficient group and the control group in the neutrophil, lymphocyte, thrombocyte, hemoglobin values, MCV, MPV, and NLR values in the blood (Table 2).

Table 2. Blood values of patients with low and normal vitamin B12 levels

	Patients with B12 deficiency (≤130 pg/mL)		Control group (>130 pg/mL)			
	mean±SD	Median (min-max)	mean±SD	Median (min-max)	Z	p
WBC (10^g/L)	7.02±1.86	6.70 (3.3-12,6)	6.96±1.89	6.60 (3.3-16.7)	-0.366	0.714
Hgb(g/dL)	14.09±1.37	14.0 (11.0-17.1)	13.91±1.49	13.7 (11.1-17.8)	-1.485	0.138
Plt (10^g/L)	232.19±47.66	232.50 (125.0-397.0)	244.13±64.37	239.0 (98.0-479.0)	-1.579	0.114
Neutrophil(fL)	4.0±1.42	3.69 (1.7-8.7)	3.6±1.32	3,6 (1.3-11.0)	-1.170	0.242
Lymphocyte (10^g/L)	2.37±0.67	2.22 (1.2-4.7)	2.43±0.79	2.27 (1.3-6.9)	-0.265	0.791
MCV (fL)	87.61±5.82	88.2 (59.0-100.0)	86.67±5.91	88.0 (62.0-97.0)	-1.463	0.143
MPV(fL)	9.11±0.95	9.1 (7.0-12.4)	9.01±0.90	8.8 (7.0-12.3)	-1.354	0.176
Neutrophil - Lymphocyte Rate (NLR)	**1.76±0.71**	**1.6 (0.2-5.2)**	**1.68± 0.72**	**1.57 (0.3-6.1)**	**-1.239**	**0.215**

Mann-Whitney U test

When the B12 deficient group was compared with the control group, there was no statistically significant difference between the blood parameters (WBC, leukocyte, lymphocyte, and MCV values) ($p > 0.05$). It was observed that MCV values were not low in the B12 deficient study group. When this B12 deficiency occurred, it was interpreted that erythrocyte volumes did not change in a short period of time. When the B12 deficient group was compared with the control group, there was no statistically significant difference between the blood parameters (WBC, leukocyte, lymphocyte, and MCV values) ($p > 0.05$). It was observed that MCV values were not low in the B12 deficient study group. When this B12 deficiency occurred, it was interpreted that erythrocyte volumes did not change in a short period of time.

Conclusion

When the B12 deficient group was compared with the control group, there was no statistically significant difference between blood parameters (WBC, leukocyte, lymphocyte and MCV values) ($p>0.05$). It was observed that MCV values were not low in the B12 deficient study group. When this B12 deficiency occurred, it was interpreted that erythrocyte volumes did not change in a short period of time.

In a study by Kwok et al. on elderly vegetarian Chinese women, they found that hemoglobin values decreased by 0.90 g/dl in patients with serum vitamin B12 deficiency and increased Mandelic Acid (MA) in the blood. But he reported no increase in mean corpuscular volume (MCV). In this study, it was found that cases of anemia did not increase significantly until serum MA was > 1.00 µmol/L. In other words, a decrease in hemoglobin was associated with an increase in the level of MA in vitamin B12 deficiency. He also stated that anemia due to vitamin B12 deficiency was rarely macrocytic [18]. We did not have the opportunity to evaluate serum MA levels in the public health laboratory to which we are affiliated. Therefore, we could not evaluate MA levels in patients with B12 deficiency, which was a limitation of our study. There is a need for new studies that can evaluate the level of MA due to B12 deficiency and show its effect on whole blood tests.

Mahmut et al.'s study on 68 children with vitamin B12 deficiency found that both platelet counts and MPV values were increased compared to the control group. The advantage of our study was that it was entirely in adult individuals and the number of cases was 170. In our study, it was found that there was no significant difference in platelet counts and MPV in adult patients with B12 deficiency. MPV was 9.11 ±0.95 in the B12 deficient group, and 9.01 ±0.90 in the B12 normal group. It was thought that this difference may occur due to the fact that our study was conducted in adults (the other study was performed on children), or the problems experienced during the collection and study of blood samples [19].

B12 deficiency also causes increases in blood homocysteine levels in the long term. This increase is known to predispose to atherosclerosis. Increased MPV value was found to be an independent risk factor for acute myocardial infarction and acute and/or non-acute cerebral ischemia in a case-control study by Li et al. As it is known, ischemic heart diseases, Type 2 diabetes, and cancers are observed less frequently in vegans than in omnivores (those fed with animal and plant foods). Therefore, since the cardiovascular risk decreases, MPV values are expected to be low. However, increased plasma homocysteine levels and high MPV values are observed due to vitamin B12 deficiency. It is known that an increased MPV value in vegans indicates the presence of larger and activated platelets. In our study, although there was no statistically significant difference in the group with B12 deficiency, we found that the mean MPV value increased, and the platelet count was lower than in the control group. This was in agreement with the work of Li et al. This increase in MPV can be explained by the larger, newly synthesized young platelets to compensate for the decrease in platelets [20].

Toplak et al. conducted a study to examine the MPV value in obese patients. Higher MPV values were found in the obese group compared to the control group. No significant difference was observed between the obese and non-obese groups in terms of platelet counts. It was observed that MPV values of obese individuals increased 8 weeks after weight loss but returned to their previous levels 48 weeks later. As it is known, positive changes are observed in metabolic parameters such as blood sugar, cholesterol, and triglycerides in obese patients with weight loss. As a result, cardiovascular risks are reduced. Therefore, decreases in MPV values are expected and these decreases are expected to be permanent. However, it was determined that this was not the case and that they returned to previous levels [21]. Zhou et al. discovered no significant difference in MPV values between pre- and postoperatively in cases with more than 30% weight loss after obesity surgery [22].

The blood samples taken in our study were taken in the morning, collected in one place, and could only be studied towards noon. As stated in the literature, MPV values are affected by conditions such as storage conditions, time, temperature difference, characteristics of the device, and long waiting time in ethylene diamine tetra acetic acid (EDTA) tubes. Even when ethylene diamine tetra acetic acid (EDTA) is used, it is known that MPV values increase with the direct effect of EDTA on platelets [23,24,25,26].

The study by Noris et al. reminded us that we need to reconsider what we know about MPV. He states that it is not known exactly whether the increased platelet size (MPV) is the cause or the result of thrombosis. He stated that the differences in MPV between patients and control groups were usually exceedingly small and that standardization for MPV measurement could reach statistical significance with large numbers of patient data. However, in real life, we observed that MPV may vary depending on platelet count, gender, age, and ethnicity. The differences between the control group and selected patient groups are small, and it is impossible to comment on normal or slightly increased MPV because there is extremely poor standardization in the methodologies used for MPV measurement [27,28,29]. Beyan et al. state that MPV values are actually an indicator of platelet production, not platelet function. He says that this may be related to the production of large-volume platelets due to the stimulation of megakaryopoiesis as a result of the consumption of platelets in the area of inflammation. As it is known, as a result of the consumption of platelets in the inflammatory region, their number decreases, megakaryocytes in the bone marrow are stimulated, resulting in the production of large platelets [30]. In our study, a decrease in platelet counts and a slight increase in MPV values were observed in the vitamin B12 deficient group.

Neutrophil-lymphocyte ratio (NLR ratio) is a parameter that has been used as an indicator of inflammation. It has been investigated, especially in conditions such as inflammatory diseases and metabolic diseases. In a study by Baş et al. they found that the rate of NLR increased in the group with vitamin D deficiency [31]. NLR values in the B12 deficient experimental group (1.76 ± 0.71) were higher than those in the control group (1.68 ± 0.72). Statistically, this difference was not significant. There are not enough studies on this subject in the literature, so new studies are needed.

Limitations

The fact that a certain period of time passed until the blood samples were collected and started to be studied and the lack of a complete standardization of NLR rates were the factors limiting our study. Previously, there was little data on NLR rates and B12 deficiency. This revealed the lack of literature to guide us in our research.

Conclusion

The prevalence of vitamin B12 deficiency is observed to be between 5–60% in the population. It is important to observe an increase in homocysteine levels and MA in the detection of its deficiency. It is more common in older people and women (32).In conclusion, in our study, we found that no immediate changes were observed in complete blood counts in the end period in patients with B12 deficiency. We found no statistically significant changes in blood parameters, MPV, MCV, or NLR rates.

Conflict of interest: None.

Author Contributions		Author Initials
SCD	Study Conception and Design	AD
AD	Acquisition of Data	AD
AID	Analysis and Interpretation of Data	AD
DM	Drafting of Manuscript	AD
CR	Critical Revision	AD

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