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Could Mean Platelet Volume and Red Cell Distribution Width Predict Vitamin B12 Deficiency?

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Authors' contributions

This work has been carried out in collaboration between all authors. Authors GA and MS designed the study, performed the statistical analysis, wrote the first draft of the manuscript. Authors AA and HS managed the analyses of the study, author BKT collected the laboratory data. Authors BKT and HT managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Vitamin B12 deficiency causes an increase in homocysteine levels which is associated with inflammatory conditions. Mean platelet volume (MPV) and red cell distribution width (RDW) are also associated with inflammation. Therefore, we aimed to compare hematological parameters in patients with and without vitamin B12 deficiency to find out whether they could predict vitamin B12 deficiency.
Methods: Patients who underwent vitamin B12 assessment grouped based on the serum level of vitamin B12. We grouped 116 patients, whose B12 level was lower than 250, in first group and 62 patients, whose B12 ≥ 250 pg/ml, in second group.
Results: Red cell distribution width was significantly higher in group 1 (patients with a vitamin B12 level lower than 250 pg/ml) compared to those in group 2 (patients with a vitamin B12 level higher than 250 pg/ml). Mean platelet volume was significantly lower in group 1 compared to group 2.
Conclusion: We suggest that MPV and RDW should be an indicator of vitamin B12

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deficiency especially in early stages of the disease. However, prospective studies with larger cohort are needed to confirm our results.

Keywords: Vitamin B12; mean platelet volume; red cell distribution width; inflammation.

1. INTRODUCTION

Vitamin B12 is an important nutrient which can not be produced in vivo by human. Vitamin B12 deficiency occurs as a consequence of reduced oral intake or impaired absorption. Vegetarian diet, alcohol consumption, smoking, gastric acid suppression and drugs (i.e Metformin) may cause vitamin B12 deficiency [1-4]. Hematologic (anemia alone or accompanied with leukopenia or thrombocytopenia) and neurologic disorders occur usually in later periods of the deficiency [1,5]. Diagnosis of the disease is easy in these stages, however, early diagnosis, which is very important to avoid irreversible neurological damage, is confusing due to laboratory methods and lack of symptoms [6,7]. Macro-ovalocytosis in erythrocytes and hypersegmentation in the nuclei of neutrophil are two major findings of Vitamin B12 deficiency in peripheral blood smear. On the other hand, hematocrit (Htc) and mean corpuscular volume (MCV) might be normal in vitamin B12 deficiency even in cases presented with neurological disorders [8].

Homocysteine levels increase in serum of the patients with vitamin B12 deficiency [9-11] and lead to hyperhomocysteinemia, which is considered as a risk factor for atherosclerosis [11,12]. Treatment of vitamin B12 deficiency not only corrects the level of vitamin B12, but also reduces serum homocysteine levels [13]. On the other hand, inflammation had been found as an underlying pathological mechanism in atherosclerosis [14].

Mean platelet volume (MPV), and red cell distribution with (RDW) are hemogram parameters that authors speculate that both two were associated with inflammation and inflammatory conditions [15,16]. Moreover, atherosclerosis is characterized with subclinical inflammation and data in literature suggest that it is associated with both RDW and MPV [17,18].

In present retrospective study, we aimed to compare hematological parameters in patients with and without vitamin B12 deficiency to find out whether they could predict vitamin B12 deficiency.

2. MATERIALS AND METHODS

Patients who underwent vitamin B12 assessment grouped based on the serum level of vitamin B12. Laboratory data obtained from computerized database of our institution. Patients with chronic inflammatory disease, diabetes mellitus, coronary artery disease and congestive heart failure were excluded from the study because these conditions may affect MPV and RDW levels. We also did not include subjects with an elevated white blood cell count which probably indicates recent infection. Patients with iron deficiency or with a history of iron replacement therapy in last six months were also excluded. Remaining 178 patients grouped into two groups according to the serum B12 level. Previous studies usually grouped patients at a cut point B12 level of 250 pg/ml [19], therefore, we grouped 116 patients, whose B12 level was lower than 250, in first group and 62 patients, whose B12 ≥ 250 pg/ml, in second group. The reference range of serum Vitamin B12 was 191-663 pg/ml in the laboratories of our institution.

The complete blood count analyses were performed in automatic analyser of LH 780 model of Beckman Coulter device (Beckman Coulter In.; Bre CA). Electrochemiluminescent assay performed in the detection of serum vitamin B12 assessment (Roche Cobalt e 601).

Patients' characteristics and laboratory data; white blood cell count (WBC), neutrophil count (neu), lymphocyte count (lym), eosinophil count (eos), hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), red cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW) recorded.

SPSS software (SPSS 15.0 for Windows Chicago, IL, USA) used for statistical analysis. Patients characteristics and laboratory data of the groups compared either with student t test (for normal distributed variables) or with Mann Whitney U test (for non normally distributed variables). A spearman correlation analyze performed to detect correlation of the variables. Statistically significance set on $p<0.05$ level. The study was approved by local ethics committee of Abant Izzet Baysal University.

3. RESULTS

General characteristics and laboratory data of the patients in study groups summarized in Table 1.

Table 1. Characteristics and laboratory data of the study groups

		Group 1 (VitaminB12<250pg/ml)	**Group 2 (VitaminB12≥250pg/ml)**	**p**
Gender (n)	Male	27	14	0.91
	Female	89	48	
		Median (Min-Max)		
Age (years)		23.5 (20-73)	25 (19-75)	0.23
WBC (u/mm^3)		6.4 (4.1-9.8)	6.7 (4.3-9.6)	0.24
Neu (u/mm^3)		3.7 (1.7-7)	3.7 (1.7-6.7)	0.87
Lym (u/mm^3)		1.9 (0.6-4)	2 (0.8-3.9)	0.27
Eos (u/mm^3)		0.1 (0-0.5)	0.1 (0-0.9)	0.21
RDW(%)		16.5 (15.6-18.8)	16.3 (14.4-18.1)	0.031
MPV (fL)		8.2 (6.3-11.4)	8.6 (4.9-12)	0.026
PDW (%)		13.7 (11.6-28.9)	13.8 (11.5-27.4)	0.48
VitB12 (pg/ml)		180 (150-247)	315 (250-899)	<0.001
		Mean±Standard Deviation		
Hb (g/dL)		13.6±1.1	13.7±1.2	0.89
Htc (%)		40.1±3.4	40.5±3.4	0.58
MCV (fL)		87±4.7	87.7±5.2	0.40
PLT (u/mm^3)		262±60	268±94	0.62

Age was not significantly different between groups ($p=0.23$). Similarly, gender was not different between groups ($p=0.91$), either. There was no significant difference between study groups in terms of following laboratory parameters: WBC, Neu, Lym, Eos, Hb, Hct, MCV, PLT and PDW (all $p>0.0.5$).

RDW was significantly higher in group 1 (patients with a vitamin B12 level lower than 250 pg/ml) compared to those in group 2 (patients with a vitamin B12 level higher than 250

pg/ml) [16.5 (15.6-18.8) in group 1 and 16.3 (14.4-18.1) in group 2]. The difference was statistically significant (p=0.031).

Mean platelet volume was significantly lower in group 1 compared to group 2 [8.2 (6.3-11.4) in group 1 and 8.6 (4.9-12) in group 2], and the difference reached statistically significance (p=0.026).

Serum vitamin B12 level was significantly lower in group 1 [180(150-247pg/ml)] compared to group 2 [315(250-899pg/ml)] (p<0.001).

In correlation analysis, we figured out that vitamin B12 was significantly correlated with MPV (p=0.017) (r=0.178). However, serum vitamin B12 level was not correlated with any other hemogram parameters.

4. DISCUSSION

We found that RDW and MPV were significantly different in patients with vitamin B12 deficiency compared to the patients with normal vitamin B12 serum levels.

MPV refers the size of circulating platelets and red cell distribution width refers the size variability of erythrocytes. Literature is full of data reported association between both these two hemogram parameters and overt or subclinical inflammatory processes [16,20-23]. Vitamin B12 deficiency may be associated with occult inflammation by homocysteine increasing pathway. It is well established that serum homocysteine levels increase in vitamin B12 deficiency [9] and homocysteine is considered to be associated with inflammation [24]. Because homocysteine plays important role in inflammation, one can conclude that vitamin B12 deficiency should be associated with inflammatory conditions. The results of our study encourage this hypothesis.

Elevation in serum homocysteine has been described as a risk factor for atherosclerosis, and for arterial and venous thromboembolism [11] and similarly, MPV has been found to be associated with such conditions too [18,25]. Therefore, we can suggest that homocysteine and MPV act interrelated in the course of inflammation. The results of Mohan et al's study reporting that homocysteine promoted platelet activation, suggest this hypothesis [26].

Why RDW increase in Vitamin B12 deficiency? A deficiency in vitamin B12 results on a defect in DNA synthesis, therefore, leads to unbalanced growth and impaired division of hematopoietic cells. Thus, larger and normal sized erythrocytes should be produced in bone marrow which causes an elevation in RDW. Another explanation could be about the association between vitamin B12 deficiency and inflammation. Since RDW has been found to be related with inflammatory conditions and vitamin B12 deficiency is considered to be connected with inflammation via homocysteine increase, an elevated RDW in vitamin B12 deficiency should reflect the inflammatory burden of the disease. Similar to the results of present study, elevated RDW in vitamin B12 deficiency has been reported in literature by Ponstaporn et al. [27] and Bhatia et al. [28].

We showed that MPV was lower in patients with vitamin B12 deficiency than in the patients without vitamin B12 deficiency. Similar to our results, some authors pointed an involvement of MPV in inflammation [16,20]. Furthermore, changes in MPV have been found to be related with acute myocardial infarction, an important outcome of atherosclerosis (18). Possible reasons for this difference in MPV in vitamin B12 deficiency may be include

inflammation related to vitamin B12 deficiency may interact with megakariopoesis in bone marrow and cause production of smaller platelets. Another explanation should be that active platelets tend to be larger in diameter and they involve in inflammatory conditions. After utilization of active platelets in inflammatory processes, remaining smaller platelets may be responsible of the reduction in MPV.

Our results indicated that RDW and MPV changes occur in such an early stage of the deficiency before other well established hematological changes developed are very important. Because, authors do not rely on MCV in the diagnosis of vitamin B12 deficiency due to that it has been reported to be normal between reference range even in patients with suspected vitamin B12 deficiency [28,29]. Besides, Loikas et al reported that neither anemia nor macrocytosis predicted vitamin B12 deficiency [30].

Retrospective design and relatively small study population are two important limitations of present study. Moreover, we could not discuss the homocysteine levels of our study population because of retrospective design.

5. CONCLUSION

In conclusion, we think that MPV and RDW should be an indicator of vitamin B12 deficiency especially in early stages of the disease in patients without cytopenias. However, prospective studies with larger cohort are needed to confirm our results.

CONSENT

Not applicable.

ETHICAL APPROVAL

Present study was approved by local ethics committee of Abant Izzet Baysal University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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