The Properties of Vitamin B12 Deficiency in the Patients of an Outpatient Clinic

Poliklinik Hastalarında Vitamin B12 Eksikliği ve Özellikleri

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ABSTRACT Objective: The aim of this study is to evaluate the properties of vitamin B12 deficiency and predisposing factors in the patients of an outpatient clinic. **Material and Methods:** Four hundred patients with vitamin B12 deficiency were studied. Anthropometric measures, biochemical analysis, gastric parietal cell antibodies and parasites in stool of the patients, antigliadin antibody survey and upper gastrointestinal system endoscopy were performed. Additionally, randomly selected 100 patients with low and 100 healthy subjects with normal serum vitamin B12 levels were questioned about food intake. **Results:** Overall ratio of vitamin B12 deficiency among outpatients was 4%. Coexisting diseases such as diabetes mellitus (12.3%), hypertension (42.0%), hyperlipidemia (42.0%) and obesity (42.0%) were determined. Nearly a quarter (22,8%) had autoimmune thyroid disease. A group of patients had other problems that may have caused malabsorption such as *Helicobacter pylori* gastritis (66/85= 77.6%), antigastric parietal cell antibody positivity (37/85= 43.5%), antigliadin antibody positivity (40/61= 65.6%), and others (3.3%). The patient group with vitamin B12 deficiency consumed significantly less meat ($p< 0.001$), chicken ($p< 0.001$), fish ($p= 0.002$), milk ($p= 0.027$) and eggs ($p< 0.001$), smaller number of meals ($p= 0.013$) and significantly higher amounts of fiber ($p< 0.001$) and vegetables ($p= 0.037$) when compared with the control group. **Conclusion:** Vitamin B12 deficiency was considered to be related mainly with improper and defective alimentation. However, malabsorption-related diseases may also contribute to vitamin B12 deficiency.

Key Words: Vitamin B12 deficiency; nutrition disorders, gastritis

ÖZET Amaç: Bu çalışmada poliklinik hasta popülasyonunda B12 vitamini eksikliğinin özellikleri ve kolaylaştırıcı faktörlerin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Vitamin B12 eksikliği saptanan 400 hasta incelendi. Antropometrik ölçümler (boy, kilo, beden kitle indeksi) ve biyokimyasal tetkikler, gastrik paryetal hücre antikoru, gaitada parazit, antigliadin antikorları ve gastroskopi incelemeleri yapıldı. İlaveten tesadüfen seçilen, B12 düzeyleri düşük 100 ve B12 düzeyleri normal sağlıklı 100'er hastanın gıda tüketimleri sorgulandı. **Bulgular:** Poliklinik hastalarında B12 eksikliği %4 oranında idi. Birlikte bulunan hastalıklar olarak; diabetes mellitus (%12.3), hipertansiyon (%42.0), hiperlipidemi (%42.0), obezite (%42.0) saptandı. Hastaların yaklaşık dörtte birinde (%22.8) otoimmun tiroid hastalığı tesbit edildi. Bir grup hastada absorbsiyon problemlerine işaret edebilecek çeşitli belirteçler vardı: *Helicobacter pylori* pozitif gastrit (66/85= %77.6), antigastrik pariyetal hücre antikorları (37/85= %43.5) antigliadin antikorları (40/61= %65.6), ve diğerleri (%3.3). B12 eksikliği olan grupta, et ($p< 0.001$), tavuk ($p< 0.001$), balık ($p= 0.002$), süt ($p= 0.027$) ve yumurta ($p= 0.001$) tüketimleri ile öğün sayıları ($p= 0.013$) anlamlı derece düşük, posa ($p< 0.001$) ve sebze ($p= 0.037$) tüketimleri de kontrol grubuna göre anlamlı derecede yüksekti. **Sonuç:** Vakalarımızda vitamin B12 eksikliğinin yanlış ve eksik beslenmeye bağlı olduğu düşünülmüştür. Ancak malborbsiyonuna neden olabilecek hastalıkların B12 vitamin eksikliğine katkısı da yadsınamaz.

Anahtar Kelimeler: B12 vitamin eksikliği; beslenme bozuklukları, gastrit

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Vitamin B12 deficiency is an important worldwide health problem. The major reason of vitamin B12 deficiency is the deficiency of intrinsic factor. Other causes are absorbtion problems (intestinal factors), rare genetic disorders and inadequate intake.[1-4] The frequency of vitamin B12 deficiency in general population is 3-5% and is assumed to be 5-20% over age of 65.[1,5] The symptoms of vitamin B12 deficiency are usually vague such as fatigue, anorexia, paresthesia, numbness and diziness and sometimes cognitive dysfunction in elderly. Infrequently, macrocytic anemia, peripheral neuropathy and subacute spinal cord degeneration may ensue. The severity of clinical presentation is not correlated with concentration of vitamin B12.[1,6-9] Inadequate alimentation is one of the most common causes of vitamin deficiency. Dietary insufficiency is observed especially among strict vegetarians, alcoholics and the elderly.[1,5,10-12] Sources of vitamin B12 are egg, milk products, meat and fowl.[1,2,4] Vitamin B12 deficiency may occur at any age and varies upon social eating habits among the countries.[2-18]

The deficiency results in hyperhomocysteinemia with several neurologic and hematologic sequelae.[1,5,8,10,13-18] High plasma homocystein levels may be related to inadequency of vitamin cofactors (folate, B12, B6) and defective enzymes participating in homocysteine metabolism. Genetic disorders are the results of defects in enzymes controlling homocystein metabolism and are frequently ethnic in origin. Vitamin B12 plays an essential role in methylmalonic acid metabolism inducing a rise in serum levels. Therefore, hyperhomocysteinemia may be the consequence of vitamin B6, folate or vitamin B12 deficiency, but rise in methyl malonic acid level is a spesific indicator of vitamin B12 deficiency. Hyperhomocysteinemia is a risk factor for cognitive dysfunction, vascular dementia, Alzheimer disease, coronary heart disease, stroke and peripheral vascular disease.[1,5-8,10,11,13-19]

This study was planned in order to evaluate the properties of the patients with low serum vitamin B12 levels.

MATERIAL AND METHODS

This study was performed in the Outpatient Department of the Internal Medicine Clinic in Istanbul. Medical Faculty. Four hundred patients within 10000 consecutive cases who were admitted with different complaints at first or repetitive visits between March 2005 and December 2006, were detected to have low serum vitamin B12 levels. Biochemical analyses were carried out with modular system Roche_Hitachi E-170, Vitamin B12 was measured with Architect I 2000-I 4000, and homocystein was measured with automated chemiluminescence detection system, Immulite-1000. Vitamin B12 normal limits were 191-663 pg/mL. The values below the lower limit were accepted as low serum vitamin B12 levels. These 400 patients were further evaluated for their other comorbidities and some special properties. Besides medical history and clinical examination, anthropometric measure ments (height, weight and body mass index), biochemical analysis including complete blood count, folic acid, homocystein, ferritin, iron levels, total iron binding capacity and in some patients gastric parietal cell antibody and stool examinations for parasites were performed. In appropriate patients on the basis of existing diseases and complaints, other related investigations such as antigliadin antibody survey and upper gastrointestinal system endoscopy were performed. No vegeterian or alcoholic patient was included in the study. Verbal informed consents were obtained from all the patients.

One hundred patients with low and 100 subjects with normal vitamin B12 levels were questioned about their food intake in detail (for two weekdays and one weekend). Normal amount of intake for fiber was accepted as 20 g/day; for meat, fish, chicken and leguminosae 4-5 portion/week; and for milk/yoghurt was 400 cc/day. The results were defined as; none= 1, very low= 2, low= 3, normal= 4, high= 5, and very high= 6.

For statistical evaluation, SPSS (Statistical Package for Social Sciences) v.12 package program was used. “The Kolmogorov-Smirnov test was used to assess the normality of numeric variables”. Chi-

square tests was used for qualitative variables, and Man Whitney-U test and student-t test were used for quantitative variables. Kruskal Wallis test was performed for the comparison of vitamin B12 levels between different age groups.

RESULTS

Overall ratio of vitamin B12 deficiency among 10000 patients was 4%. The demographic and biochemical characteristics of 400 patients included in this study is designated in Table 1. One hundred and eleven (27.8%) of the patients were males and 289 (72.2%) were females. Median age was 47.2 ± 15.1 years, median height 1.6 ± 0.1 m, weight 75.3 ± 13.7 kg and body mass index was found as 29.3 ± 5.5 kg/m^2.

In the total patient population, vitamin B12 levels decreasing with age. However, there was no statistically significant difference between age groups (Table 2) [15-24 (n: 45, mean 150.01 ± 28.9); 25-34 (n: 34, mean 153.4 ± 36.0); 35-44 (n: 77, mean 153.3 ± 31.8); 45-54 (n: 109, mean: 150.6 ± 35.01), 55-64 (n: 82, mean: 142.5 ± 37.01); >65 (n: 53 mean: 137 ± 39.5) p 0.05]. Similarly, no difference was found between genders in terms of B12 levels. One third of the patient group had iron deficiency and 7.4% had folic acid deficiency along with vitamin B12 deficiency. Anemia (hemoglobin <12 g/dL) was detected in 18% of the patients (Table 1). However, Hb, Hct, serum iron and ferritin levels were significantly lower in females.

Table 3 denotes the diseases accompanying vitamin B12 deficiency. Among 400 patients, 51.25% were also followed by dietary outpatient clinics owing to coexisting chronic diseases such as diabetes mellitus (12.3%), hypertension (42%), hyperlipidemia (42%) and obesity (42%). A group of the patients had other problems that may have caused malabsorption: Gastrointestinal surgery in six, colon tumor in one, colitis in three and antiobesity treatment in three. Gastroscopic examination detected *Helicobacter pylori* positive gastritis in 66 of 85 patients (77.6%), while antigastric parietal cell antibodies were positive in 37 of 85 patients (43.5%) and antigliadin antibody positivity was 65.6% (40/61). The frequency of autoimmune thyroiditis was 22.75%. Stool examinations for parasites were negative for all the patients. The patient group with vitamin B12 deficiency consumed significantly less meat ($p< 0.001$), chicken ($p< 0.001$), fish ($p= 0.002$) milk ($p= 0.027$) and eggs ($p< 0.001$), smaller number of meals ($p= 0.013$) and significantly higher amounts of fiber ($p< 0.001$) and vegetables ($p= 0.037$) compared to the control group (Table 4). As expected, Vitamin B12 levels were inversely correlated with erythrocyte volume (MCV) and hematocrit (Htc) ($p= 0.01$) but positively correlated with folic acid levels ($p= 0.01$). TSH levels were found to be correlated with hematocrite, MCV, folic acid, iron ($p< 0.001$) and homocystein levels ($p= 0.007$). Homocysteine levels were found to be high (>12 μmol/L) in 53.4% of the patients. After the B12 replacement therapy for two months, most of the clinical symptoms disappeared and there was a rise in vitamin B12 levels.

DISCUSSION

Vitamin B12 deficiency which mainly is a result of intrinsic factor deficiency, can be observed at any age. Other factors causing deficiency are improper social eating habits, malabsorption problems (*Helicobacter pylori* gastritis, drugs, intestinal factors) and rare genetic disorders. The most common reason accounting for deficiency is inadequate intake.[1-5,9,11,12,15,20-29] Our study also displays the importance of inadequate intake of Vit B12-rich food items in the occurence of serum Vit B12 deficiency. As well known, dietary deficiency is most commonly observed among strict vegetarians, alcoholics and elderly.[1,5,10,11] Although neither vegetarians nor alcoholics are present in our series, nearly half of the subjects had other chronic diseases and have been visiting both internal medicine and dietary outpatient clinics regularly (Table 3). The patients whose dietary habits were questioned, were educated about a well-balanced diet, inscribed diet programs and they did not have any apparent malabsorption problems. Nevertheless, it was observed that owing to the effect of health programs through media, an exaggerated fear of atherosclerosis and hypercholesterolemia resulted in less consumption of nutrients which are rich

TABLE 1: General properties of the patients with vitamin B12 deficiency.

	Female	Male	Total	
	n= 289 (72.3%)	n= 111 (27.7%)	n= 400 (100%)	P values
Mean age	47.4 ± 14.99	47.73 ± 15.82	47.66 ± 15.82	0.681
Height (m)	1.57 ± 0.06	1.70 ± 0.07	1.6 ± 0.08	<0.001
Weight (kg)	74.04 ± 14.15	79.09 ± 11.59	75.35 ± 13.7	0.005
BMI (kg/m²)	30.07 ± 5.86	27.37 ± 3.81	29.37 ± 5.55	0.002
Mean Systolic BP (mmHg)	132.48 ± 24.96	132.7 ± 12.32	132.54 ± 23.98	0.875
	Median: 130 Iqr: 20	Median: 130 Iqr: 30	Median: 130 Iqr: 20	
Mean BP (Diastolic)mmHg	84.12 ± 13.28	83.42+-12.32	83.92 ± 13.01	0.715
	Median: 80 Iqr: 10	Median: 80 Iqr: 10	Median: 80 Iqr: 10	
Mean TSH (mIU/L)	3.48 ± 9.81	1.7 ± 1.95	2.98 ± 8.42	0.001
	Median: 1.23 Iqr: 1.10	Median: 1.77 Iqr: 169	Median: 1.6 Iqr: 1.6	
Mean Anti Tg (IU/ml)	147.86 ± 677.8	94.3 ± 456.4	132.59 ± 629.62	0.005
	Median: 28.2 Iqr: 69	Median: 19Iqr: 17.8	Median: 25 Iqr: 46.8	
Mean Anti TPO (IU/ml)	209.1 ± 851.1	82.8 ± 295.4	178.2 ± 755.3	0.006
	Median: 18 Iqr: 101	Median: 14.5 Iqr: 12	Median: 17 Iqr: 55.2	
Vit. B12 (Pre-treatment) (<191 IU/ml)	149.66 ± 37.02 IU/ml	144.91 ± 6.87 IU/ml	147.77 ± 36.75 IU/ml	0.281
	Median: 158.2 Iqr: 44.45	Median: 155.4 Iqr: 46.9	Median: 157 Iqr: 46.1	
Vit B12 (Post-treatment)	779 ± 188.24 IU/ml	551 ± 434.81 IU/ml	730.51 ± 1073 IU/ml	0.341
	Median: 474 Iqr: 542	Median: 412 Iqr: 328	Median: 456.5 Iqr: 455.6	
Folic acid ng/ml	8.32 ± 3.40 ng/ml	7.43 ± 3.67 ng/ml	8.07 ± 3.5 ng/ml	0.044
Iron (Fe)	72.37 ± 41.15 µg/dl	83.76 ± 41.78 µg/dl	75.37 ± 41.54 µg/dl	0.005
	Median: 65 Iqr: 40	Median: 79Iqr: 56	Median: 69Iqr: 45	
Fe <50 µg/dl	107 (%37.02)	36 (%32.43)	133%33.25	0.391
Ferritin ng/ml	48.48 ± 64.70 ng/ml	106.26 ± 10.5 ng/ml	64.30 ± 83.78 ng/ml	0.001
	Median: 31.9 Iqr: 44.8	Median: 79.9 Iqr: 103.6	Median: 39.3 Iqr: 59.8	
Hb (Hemoglobin) gr/dl	12.73 ± 1.76	14.47 ± 1.63	13.21 ± 1.89	0.001
	Median: 13.1 Iqr: 1.48	Median: 14.6 Iqr: 1.75	Median: 13.4 Iqr: 1.8	
Hb<12 gr/dl	61 (%21.1)	11 (9.9)	72 (%18)	0.009
Htc (Hematocrit)	37.73 ± 4.38	42.18 ± 4.29	38.97 ± 4.79	0.001
	Median: 38.1 Iqr: 4.53	Median: 42.6 Iqr: 4.3	Median: 39.5 Iqr: 5.1	
MCV (mean corpuscular volume	86.22 ± 9.01	88.43 ± 7.78	86.85 ± 8.72	0.078
	Median: 86.5 Iqr: 7.4	Median: 87.9 Iqr: 7.15	Median: 87.2I qr: 7.65	
MCV<80fl	68 (23.52%)	26 (23.42%)	94 (23.5%)	0.982
MCV>100 fl	18 (6.22%)	6 (5.4%)	24 (6%)	0.756
Homocystein pmol/L	14.11 ± 7.42	16.2 ± 16.2	14.3 ± 7.94	0.580
	Median: 12.6 Iqr: 8.52	Median: 11.5 Iqr: 7.64	Median: 12.6 Iq: 7.72	
Homocystein>12 pmol/L	145 (50.17%)	68 (61.26%)	213 (53.4%)	0.047

*: TSH: Thyroid stimulating hormone.

sources of vitamin B12 (Table 4). Hence, this study unravels the necessity of an argument about the education of patients with chronic diseases in hospitals, patients' consistency on inscribed diet programs and the influence of media on public health. The high prices of meat products in our country was also supposed as an important factor responsible for reduced consumption.

The severity of clinical presentation is not correlated with concentration of vitamin B12.[1,6-8,10,13] The symptoms of vitamin B12 deficiency are usually vague such as fatigue, anorexia, paresthesia,

TABLE 2: Serum B12 levels in different age groups.

Age group	B12 levels (mean IU/L)
15-24 (n:45)	150.01 ± 28.9
25-34 (n:34)	153.4 ± 36.0
35-44 (n: 77)	153.3 ± 31.8
45-54 (n: 109)	150.6 ± 35.01
55-64 (n: 82)	142.5 ± 37.01
>65 (n: 53)	137 ± 39.5

(p= 0.05).

numbness and diziness and sometimes cognitive dysfunction in elderly. Infrequently, macrocytic anemia, peripheral neuropathy, subacute spinal cord degeneration may ensue.[1,6-8,10,13,30-33] Most of the subjects in our study had similar complaints. Palpitations, amnesia, oral lesions and especially weakness of lower extremities constituted the other frequent complaints.[34] Otoimmune thyroiditis may provoke similar symptoms; in fact a quarter (22.75%) of our study group consisted of patients with otoimmune thyroiditis. Therefore, vitamin B12 levels must be determined especially in such patients as they can present with similar clinical symptoms.

Vitamin B12 deficiency may cause hyperhomocysteinemia with diverse neurological and hematological sequelae.[1,5,8,10,13,14,30,33] High plasma homocystein levels may be due to deficiency of vitamin cofactors (folate, vitamin B12, B6) or defects of enzymes acting in homocystein metabolism. Vitamin B12 plays an essential role in methylmalonic acid metabolism, inducing a rise in serum levels.

TABLE 4: Diseases coexisting with vitamin B12 deficiency in the study group.

Sex	Female	Male	Total	P values
Number	N= 289	N= 111	N= 400	
Hypertension	122 (42.2%)	46 (41.4%)	168 (42%)	0.888
Diabetes	34 (11.8%)	15 (13.5%)	49 (12.3%)	0.633
Hyperlipidemia	95 (32.9%)	36 (32.4%)	168 (42%)	0.933
Obesity	141 (48.8%)	27 (24.3%)	168 (42%)	0.0001
Arthrosis	48 (16.6%)	10 (9%)	58 (14.5%)	0.053
Thyroiditis	78 (27%)	13 (11.7%)	91 (22.75%)	0.001
Anti-Gliadin antibodies >20 (n= 61)	25/39 (64.1%)	15/22 (68.18%)	40/61 (65.57%)	0.487
Helicobacter pylori (+) (n= 85)	46/60 (76.66%)	20/25 (80%)	66/85 (77.64%)	0.489
Antigastric parietal cell antibody (+) (n= 85)	23/60 (38.3%)	14/25 (56%)	37/85 (43.52%)	0.105
Others (colitis, gastrointestinal surgery, anti obesity treatments etc.)			13 (3.25%)	

TABLE 4: Characteristics of thediets of the patients questioned for dietary habits.

	Patients with normal vitamin B12 levels N= 100 mean ± sd	Patients with low vitamin B12 levels N= 100 mean ± sd	P values
Fiber	4.06 ± 1.13/4	5.04 ± 0.72/5	<0.001
Leguminosae	4.06 ± 1.36/5	4.48 ± 1.24/5	=0, 135
Meat	3.68 ± 0.81/ 4	2.50 ± 1.44 /2	<0.001
Chicken	4.02 ± 0.76 / 4	2.94 ± 1.36/3	<0.001
Fish	3.74 ± 0.94 /4	2.92 ± 1.44/3	=0.002
Egg	3.34 ± 0.93/ 4	1.96 ± 1.02/2	<0.001
Milk	3.92 ± 0.94 / 4	3.22 ± 1.59/3.5	=0.027
Tea	4.18 ± 0.59/4	3.56 ± 1.01/4	<0.001
Vegetables	3.88 ± 0.98/ 4	4.42 ± 1.51/5	=0.037
Number of daily meals	3.66 ± 0.74 / 4	3.00 ± 0.8/3	=0.013

Therefore hyperhomocysteinemia may be the consequence of vitamin B6, folate or vitamin B12 deficiency, but rise in methyl malonic acid level is a spesific indicator of vitamin B12 deficiency.[8,10,13,14,17,18] Among our patients, ratio of patients with hyperhomocysteinemia was 53.4% which seems proportional with B12 deficiency.

Intestinal absorption disorders is another cause of vitamin B12 deficiency. Gastric bypass surgery, gluten enteropathy, some drugs and *Helicobacter pylori* gastritis are common causes of vitamin B12 malabsorption[1,5,16,21-29] Although only 85 patients underwent endoscopic evaluation in our study, *Helicobacter pylori* positive gastritis rate was found quite frequently (77.6%), which is concordant with the findings of a previously published paper.[25] In that article, authors noted that *Helicobacter pylori* IgG values were not statistically different between the patients with low and normal vitamin B12 levels, although they were slightly higher in low B12 group. In some studies, *Helicobacter pylori* posivity rates were found between 50%-90% in general Turkish population.[35] We did not compare the patients with low vitamin B12 to the normal patients regarding *Helicobacter pylori* positivity rate. Considering the high *Helicobacter pylori* prevalence in the normal population, it seems hard to indicate *Helicobacter pylori* as a cause of low B12 levels. Furthermore, as we did not do *Helicobacter pylori* eradication treatment and obtained post eradication results, we cannot explain the low B12 levels by the existence of *Helicobacter pylori* infection. On the other hand, although out of 61 patients who were examined for anti-gliadin antibodies, 40 had higher levels than normal, these findings can not allow us to be able to speculate that those patients had a vitamin B12 absorbtion defect.

Vitamin B12 deficiency can also cause pernicious anemia.[1,30-33] However, among our patients, the frequency of macrocytosis was very low (the patients with MCV >100 fl was %6 while overall anemia rate was 18%). Another study carried out in our outpatient clinics among 10 000 patients pointed out that frequency of iron deficiency anemia was 2.7%. This discrepancy may be explained by the fact that there was 33.75% iron deficiency among the patients. These results may be due to improper alimentation, malabsorption or another accompanying chronic diseases.

In conclusion, although some absorbtion problems were suspected at least in a group of patients, vitamin B12 deficiency was mostly associated with improper and defective alimentation in our study. In addition to high prices of meat in our country, negative effect of health programs through media may cause fear of atherosclerosis and hypercholesterolemia resulting in less consumption of nutrients which are rich sources of vitamin B12. Consequently, the influence of health programs on media over public health is an issue that should be investigated and discussed throughly. Furthermore, patients'consistency with the diet education given in dietary outpatient clinics has to be questioned recurrently.

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