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Association between Hypercobalaminemia and Chronic Diseases in Outpatients: A Retrospective Case-Control Study

Ayaktan Tedavi Gören Hastalarda Hiperkobalaminemi ile Kronik Hastalıklar Arasındaki İlişki: Retrospektif Bir Vaka-Kontrol Çalışması

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Abstract

Background: Several studies have shown that high levels of Cobalamin (vitamin B12) are associated with specific diseases, such as solid cancers, chronic liver diseases, cardiovascular diseases, and others. In this study, we aimed to compare the rates the vitamin B12 in adults with and without chronic diseases.

Materials and Methods In the study, 68 (53.1%) participants with chronic disease and 60 (46.9%) participants without chronic disease were included in the study among 128 patients aged 35 and over with high vitamin B12 levels who applied to the Family Medicine Polyclinics as outpatients for a period of 1 year. Patients with vitamin B12 levels of ≥1000 pg/mL were classified as having very high levels, while those with levels between 663 and 999 pg/mL were classified as having high levels.

Results: In our study, a significant relationship was found between the presence of chronic disease and high vitamin B12 levels (p=0.017). Among chronic diseases, high levels of vitamin B12 have been found to be more significant in patients with Diabetes Mellitus (DM) (p<0.006). According to the categorization of high vitamin B12 in itself, it has been observed that vitamin B12 levels are significantly at very high levels in individuals with DM. Logistic regression analysis revealed that the risk of DM diagnosis was 0.67 times higher in those with elevated vitamin B12.

A significant relationship has been found between high levels of vitamin B12 and those with chronic diseases, especially DM.

Conclusions: It has been shown that individuals with common chronic diseases have significantly high levels of vitamin B12. We observed that very high levels of vitamin B12 are a risk factor for chronic diseases, including Type 2 DM.

Keywords: Vitamin B12, Chronic Disease, Diabetes Mellitus, Case-Control Study

ÖZ

Amaç: Çeşitli çalışmalar, kobalaminin (vitamin B12) yüksek düzeylerinin solid tümörler, kronik karaciğer hastalıkları, kardiyovasküler hastalıklar gibi bazı hastalıklarla ilişkili olduğunu göstermektedir. Bu çalışmada, kronik hastalığı olan ve olmayan yetişkin bireylerde vitamin B12 düzeylerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu kesitsel çalışmaya, bir yıl boyunca Aile Hekimliği polikliniklerine başvuran ve vitamin B12 düzeyi yüksek olan 35 yaş ve üzeri 128 hasta dahil edildi. Katılımcıların 68'i (%53,1) kronik hastalığı olan, 60'ı (%46,9) ise kronik hastalığı olmayan bireylerden oluşmaktaydı. Serum vitamin B12 düzeyi ≥1000 pg/mL olanlar "çok yüksek", 663–999 pg/mL arasında olanlar ise "yüksek" olarak sınıflandırıldı.

Bulgular: Kronik hastalığı olan bireylerde vitamin B12 düzeylerinin anlamlı şekilde yüksek olduğu saptandı (p=0,017). Özellikle Diabetes Mellitus (DM) hastalarında bu ilişki daha belirgin olup, bu grupta çok yüksek vitamin B12 düzeylerine daha sık rastlandı (p<0,006). Lojistik regresyon analizine göre, yüksek vitamin B12 düzeyine sahip bireylerde DM saptanma riski 0,67 kat daha fazlaydı.

Sonuç: Yaygın kronik hastalıklara sahip bireylerde vitamin B12 düzeylerinin anlamlı derecede yüksek olduğu görülmüştür. Özellikle Tip 2 DM hastalarında çok yüksek vitamin B12 düzeylerinin bir risk faktörü olabileceği düşünülmektedir.

Anahtar Kelimeler: Vitamin B12, Kronik Hastalık, Diabetes Mellitus, Olgu-Kontrol Çalışması

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Highlights

- Final-year nursing and midwifery students face high risk of sharp object injuries during clinical practice.
- Fishbone diagram used to identify root causes: personnel, equipment, environment, and procedures. 86.7% of participants reported experiencing at least one sharp object injury.
- All identified causes were preventable, indicating potential for effective interventions.
- Study offers a novel perspective to enhance safety awareness in clinical education

Introduction

Vitamin B12 is involved in the maturation of blood cells in the body, the functions of the nervous system and DNA synthesis. High levels of vitamin B12 (Hypercobalaminemia) are a frequently encountered abnormality (1). A study conducted in Denmark in 2012 on patients not receiving vitamin B12 treatment showed that high serum vitamin B12 levels were associated with increased haptocorrin levels. The underlying causes in these patients were found to be alcoholism, liver diseases, and cancer (2). Although there are studies that have found an association between patients with chronic diseases and malignancies hospitalized in hospitals or intensive care units and high levels of vitamin B12, there is insufficient data on this issue in outpatient patients. In this study, we aimed to compare the rates of vitamin B12 elevation in adults with and without chronic diseases who were admitted to the hospital as outpatients.

Material and Methods

Study Population

Patients who applied to the Family Medicine outpatient clinic of Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital between 01.06.2021 and 01.06.2022 were included.

The total number of over 35 patients who applied to Family Medicine and had their vitamin B12 levels checked is 8210. Among them, a total of 769 individuals with low levels of vitamin B12 and 6733 individuals with normal vitamin B12 levels were not included in the research. Out of the remaining 708 individuals, 558 were omitted from the research because of insufficient data, while 22 were excluded because they were utilizing vitamin B12 and folic acid-containing supplements. Consequently, a total of 128 individuals, including 85 females and 43 males, who were above the age limit of 35 and had high vitamin B12 levels, were selected to participate in the research.

Patients who applied to the Family Medicine outpatient clinic of the Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital between 01.06.2021 and 01.06.2022 were included. The total number of patients over the age of 35 who applied to Family Medicine and had their vitamin B12 levels checked was 8210. Among them, a total of 769 individuals with low levels of vitamin B12 and 6733 individuals with normal vitamin B12 levels were not included in the study. Out of the remaining 708 individuals, 558 were excluded due to insufficient data, while 22 were excluded because they were using vitamin B12- and folic acid-containing supplements. Consequently, a total of 128 individuals, including 85 females and 43 males, who were above the age of 35 and had high vitamin B12 levels, were selected to participate in the study.

Identification of chronic diseases

Determined International Statistical Classification of Diseases: Oath-Related Health Patients whose diagnosis was entered with one of the Problems (ICD) codes were included in the case group of the study **(Table 1).**

Vitamin B12 and other laboratory tests

Vitamin B12 was measured using Roche Cobas E801 autoanalyzer (Roche Diagnostics, Tokyo, Japan) from the examinations of patients when they were admitted as outpatients. A separate categorization was made in which individuals with vitamin B12 levels of 1000 pg/ml and above were considered very high, and individuals with vitamin B12 levels between 663 and 999 pg/ml were considered high (10,11). In addition, whole blood parameters, urea, creatinine, ALT, and AST values were also analyzed within the scope of the study.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 25.0 was used to analyze the data for Windows. Frequencies and percentages were used in categorical variables for descriptive statistics, and the Chi-square test was applied

to determine the statistical differences of the participants' characteristics. In descriptive statistics of numerical variables mean, standard deviation, median, minimum and maximum values were used. In the statistical analysis comparing vitamin B12 levels, which do not conform to a normal distribution, with demographic characteristics, the Mann-Whitney U test and Spearman correlation analysis were used. Logistic regression analysis was used to investigate the effect of vitamin B12 levels on Type 2 Diabetes Mellitus (Type 2 DM). The level of statistical significance was set at $p<0.05$.

Ethical approve

This study was conducted in accordance with the Declaration of Helsinki and institutional ethical guidelines. The study was approved by the Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Number: 144/01, Date: 15.08.2022). Since this study was retrospective, informed patient consent statement was not obtained.

Results

Eighty percent of the participants were female and 20% were male. The mean age was 22.30±0.702 (Min 21-Max 24). Out of the 128 cases examined in the study, 85 (66.4%) were female and 43 (33.6%) were male. The overall median age of the patient population was 54, with women having a median age of 52 and males having a median age of 61 years. The research comprised 68 people (53.1%) with chronic condition and 60 participants (46.9%) without a chronic disease. Out of the patients with chronic illnesses, 14 (10.9%) had coronary artery disease, 51 (39.8%) had hypertension, and 41 (39.8%) had T2DM. The patient had multiple concurrent chronic conditions, including hypertension, coronary artery disease, T2DM, long-standing renal failure, rheumatoid arthritis, chronic myeloproliferative disease, liver disease, and solid tumors.

Table 1. ICD codes of chronic diseases

C81	Hodgkin's disease	E85	Amyloidosis
C83	Burkitt tumor	I10	Hypertension
C85	Non-Hodgkin's disease	I25	Atherosclerotic heart disease
C88	Waldenström macroglobulinemia	I50	Congestive heart failure
C90	Multiple myeloma	K72	Liver failure
C91	ALL, KLL	K76	Liver disease
C92	KML, AML	K77	Liver disorder
C95	Leukemias	M06	Rheumatoid arthritis
D45	Polycythemia Vera	M98	Plasma cell leukemia
D46	Myelodysplastic Syndrome	N18	Kidney failure
D47	Chronic myeloproliferative disease	N28	Kidney and ureter disorder
D75	Essential thrombocytosis	Q82	Mastocytosis
E14	Type 2 DM	R94	Abnormal disturbance of kidney function studies

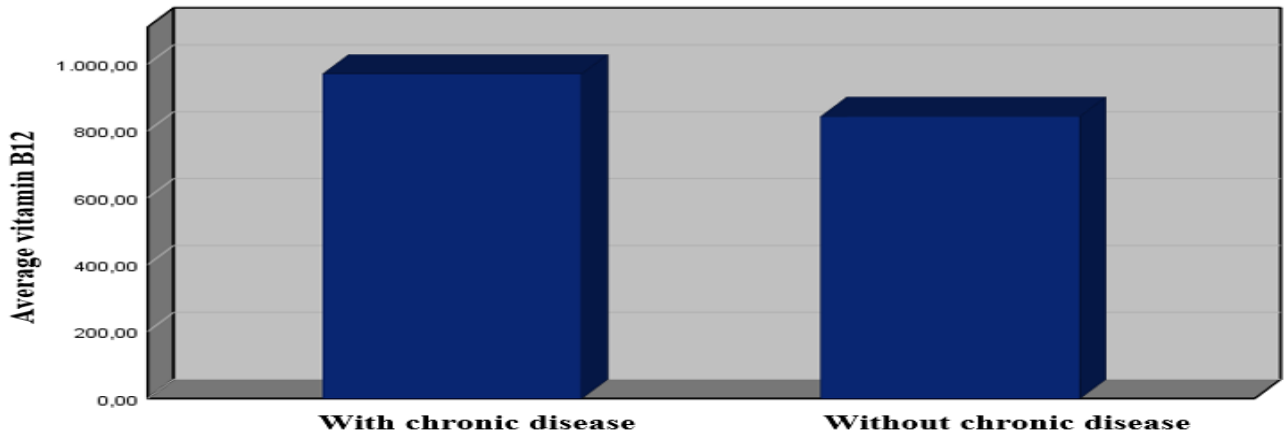

Figure 1. Evaluation of vitamin B12 according to the presence of chronic disease

The research presents the biochemical blood parameters of the individuals, which are displayed in **Table 2**.

Table 2. Biochemical blood parameters of the individuals

Parameters	Mean ± SD	Median (IQR)
Vitamin B12	910.93 ± 335.40	764.50 (664-2000)
Urea	32.14 ± 14.43	29.91 (10-130.81)
Creatinine	0.80 ± 0.24	0.75 (0.47-2.20)
AST	23.31 ± 26.27	18.70 (9.50-295.10)
ALT	19.05 ± 26.21	19.03 (5.10-382.47)
WBC	7.74 ± 2.57	7.24 (3.50-24.85)
Hb	13.82 ± 2.57	13.82 (8.20-18.10)
HCT	41.92 ± 4.45	41.48 (28.8-53.86)
MCV	86.74 ± 6.63	87.86 (63.51-103.32)
PLT	265.77 ± 71.55	263 (46-508)

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White Blood Cell, Hb: Haemoglobin, HTC: Haematocrit, MCV: Mean Cell Volume, PLT: Platelets

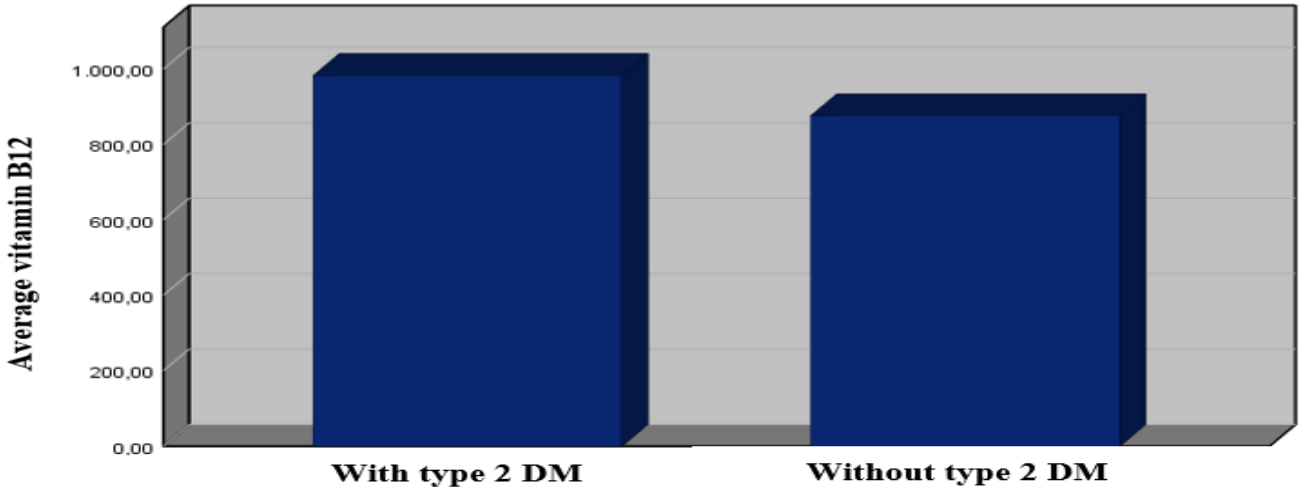

Figure 2. Evaluation of vitamin B12 according to the presence of Type 2 DM

Upon comparing vitamin B12 levels among various types of chronic illnesses, it was shown that individuals with chronic diseases had significantly higher vitamin B12 levels compared to those without chronic illnesses ($p = 0.017$). Furthermore, it was shown that individuals with T2DM had notably elevated vitamin B12 levels compared to other chronic illnesses examined according to the ICD-10 classification ($p = 0.006$).
(Table 3).

Table 3. Correlation between chronic illnesses, different kinds of diseases, and levels of vitamin B12

Vitamin B12 Level (pg / ml)	n (%)	Median (IQR)	Mean ± Sd	p
Presence of Chronic Disease	68(53.1)	823(665-2000)	970.6 ± 373.8	[a] 0.017 *
Coronary Artery Disease	14(10.9)	776(665-1842)	877.5 ± 307.6	[a] 0.781
Hypertension	51(39.8)	812(665-2000)	978.3 ± 393.8	[a] 0.190
Type 2 DM	41(32.0)	863(665-2000)	983.0 ± 337.0	[a] 0.006 *
Chronic renal failure	2(1.6)	970(946-994)	970.0 ± 33.9	[a] 0.244
Rheumatoid Arthritis	4(3.1)	832(691-1063)	854.5 ± 157.6	[a] 0.737
Chronic Myeloproliferative Diseases	2(1.6)	730(719-742)	730.5 ± 16.2	[a] 0.487
Liver Diseases	1(0.8)	843(843-843)	843	[a] 0.737
Solid Tumors	8(6.3)	825(667-2000)	1095.3 ± 535.6	[a] 0.488

Abbreviations: [a] Mann Whitney U Test * A significance threshold of $p<0.05$ was used to ascertain statistical significance

Comparison of the relationship between individuals with and without chronic diseases for other laboratory parameters except vitamin B12 in Table 4. According to a separate categorization (11,12), in which participants with vitamin B12 levels above 1000 pg/mL were considered very high, and patients with levels between 663 and 1000 pg/mL were considered high, the relationship with T2DM was evaluated. Accordingly, participants with T2DM had substantially elevated vitamin B12 levels compared to those without a history of T2DM (p=0.010). According to the results of the Cremers V test, the positive linear relationship between the two variables was low (r =0.228, p = 0.010) (Table 5).

A logistic regression analysis, using elevated levels of vitamin B12 as the reference category, revealed that individuals with high vitamin B12 levels were 2.122 times more likely to have T2DM compared to those with low vitamin B12 levels (Exp(B) = 2.122). Based on this result, the estimated probability of having T2DM among individuals with high vitamin B12 levels was approximately 67% (P = 2.122 / [1 + 2.122] ≈ 0.67). Conversely, the probability of having T2DM in individuals with low vitamin B12 levels was estimated at approximately 33% (1 – 0.67). The logistic regression model demonstrated an overall prediction accuracy of 68.0%, indicating a moderate level of model performance **(Table 6).**

Table 4. Comparison of lab parameters (without vitamin B12) by chronic disease status

Parameters	With chronic disease	Without chronic disease	p
Urea	33.8 ± 16.2	30.2 ± 11.9	[a]0.170
Creatinine	0.84 ± 0.30	0.75 ± 0.15	[a]0.170
AST	21.0 ± 11.5	25.8 ± 36.3	[a]0.430
ALT	22.2 ± 16.0	29.2 ± 48.9	[a]0.940
WBC	7.77 ± 2.11	7.70 ± 3.11	[a]0.310
Hb	13.8 ± 1.6	13.8 ± 1.8	[b]0.820
HCT	41.6 ± 0.6	42.1 ± 0.5	[b]0.500
MCV	86.3 ± 6.14	87.2 ± 6.9	[a]0.120
PLT	264.5 ± 78.2	267.0 ± 63.5	[a]0.590

Abbreviations: [a]Mann Whitney U Test [b]Independant T Test, * A significance threshold of p<0.05 was used to ascertain statistical significance, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White Blood Cell, Hb: Haemoglobin, HTC: Haematocrit, MCV: Mean Cell Volume, PLT: Platelets

Table 5. Classify Type 2 DM based on vitamin B12 levels

	Vitamin B12 (pg /ml) (n=128)			Statistical analysis		
	Vitamin B12>1000, n (%)	**VitaminB12<1000, n (%)**	**Total, n (%)**	**x^2**	**SD**	**p**
Type 2 DM	15(36.6)	26(63.4)	41(100)	6.679	one	**0.010***

Abbreviations: * Continuity Correction, Chi-square χ2: Chi-square, A significance threshold of p<0.05 was used to ascertain statistical significance

Table 6. Regression between vitamin B12 levels and Type 2 DM

	B.	sh	Wald	sd.	p	Exp B)	95% for Exp (B) CI	
							Low	High
Vitamin B12 (continuous variable)	0.001	0.001	0.565	one	0.452	1.001	0.999	1.003
Vitamin B12 (categorized)	-1.576	0.769	4.197	one	0.040*	0.207	0.046	0.934

Abbreviations: Univariant logistic regression analysis *p<0.05 was considered significant. CI: confidence interval

Nagelkarke R^2 =0.074, Omnibus Chi-square=6.938, df:2, p=0.000, Hosmer and Lemeshow >0.05

Based on the normal distribution of vitamin B12 levels, Spearman correlation analysis revealed a statistically significant but weak positive correlation between vitamin B12 levels and both age (p = 0.041) and AST levels (p = 0.006). As age (r = +0.181) and AST (r = +0.243) increased, a significant increase in vitamin B12 levels was observed. No significant correlation was found between vitamin B12 levels and other blood parameters (**Table 7**)

Table 7. Evaluation of the relationship between vitamin B12 levels and Age and AST value

	Vitamin B12 levels		
	n	**r**	**p**
Age	128	0.181	0.041*
AST	128	0.243	0.006*

Abbreviations: Spearman correlation analysis *p<0.05 was considered significant.

Discussion

We found that vitamin B12 levels in individuals with chronic illnesses were significantly higher compared to those without chronic illnesses. Especially those with Type 2 Diabetes Mellitus (T2DM), we found that the number of individuals with vitamin B12 levels above 1000 pg/ml were significantly high. Additionally, we found a weak positive correlation between age and vitamin B12 levels.

In hypercobalaminaemia, the patient's treatment with pharmacological doses of vitamin B12 explains this condition, as the treatment will lead to an increase in TC saturation (4).

While a low vitamin B12 level does not directly indicate deficiency, abnormally high levels serve as a warning that underlying serious pathologies should be ruled out. Most of the causes of hypercobalaminemia are related to quantitative anomalies involving transcobalamin (1). It is thought that pathogenic causes include increased concentrations of circulating cobalamin-binding proteins, TC and HC, either one or both (4). There are several pathophysiological mechanisms in hypercobalaminaemia:

- A direct increase in plasma vitamin B12 due to excessive intake or administration
- A direct increase in plasma vitamin B12 released from body stores
- An increase caused by overproduction of TC or decreased clearance
- An affinity deficiency of TC for vitamin B12

Prolonged parenteral intake of vitamin B12 can lead to the development of anti-TC-II autoantibodies, which may result in decreased clearance of TC-II. This induced autoimmunization has been observed in 30% of a group of Danish patients receiving treatment for pernicious anemia. In cases of liver cancer, the mechanisms causing hypercobalaminemia include a decrease in the hepatic clearance of the HC-vitamin B12 complex and an increase in plasma levels of TC due to extensive hepatocyte destruction. The decrease in hepatic clearance is thought to be associated with poor hepatic vascularization and a reduction in the number of HC receptors on the surface of cancerous hepatocytes. In other solid tumors, the cause of hypercobalaminemia is primarily thought to be related to the tumor's excessive synthesis of TC or an increase in HCs due to the stimulation of leukocytosis. In myeloid proliferations, hypercobalaminemia is primarily associated with the release of HCs by tumor granulocytes and their precursors. Since the liver is involved in vitamin B12 metabolism, acute and chronic liver diseases also play a role in high serum vitamin B12 levels. In acute hepatitis, it is thought that excessive release of cobalamin by the liver and a decrease in hepatic synthesis of TC-II, which is necessary for the binding of vitamin B12 to tissues, occur. In patients with cirrhosis, the main mechanisms involve a decrease in the hepatic uptake of vitamin B12 and HC-vitamin B12 complex at the tissue and cellular levels, which has been characterized by biopsy. In a study conducted on alcoholic liver diseases, an increase in the plasma levels of TC-I and TC-III was observed, which binds to vitamin B12 and prevents the eventual elimination of plasma vitamin B12. The same study showed that a decrease in TC-II levels led to impairments in the transfer of vitamin B12 to tissues. It is thought that the TC-II receptor, which is abundantly found in the kidney, may impair the cellular uptake of vitamin B12 (1). In a study conducted by Arendt et al., it was found that as age increases, there are more patients with high blood levels of vitamin B12 (2). In the study conducted by Kansal et al., it was found that individuals aged 65 and above had higher vitamin B12 levels compared to those aged 18-64, and that vitamin B12 levels showed a positive correlation with age (5). Research has been conducted on different patient groups to use vitamin B12 levels as a prognostic marker of mortality (6-8). Especially in patients with HCC (Hepatocellular Carcinoma) or hepatic metastasis, hypercobalaminemia has been found to have a positive association with the risk of mortality. These studies have led to the introduction of the BCI (Vitamin B12 to CRP levels ratio index) as a mortality indicator, but its use in clinical practice has not yet become widespread (4-9-10). "In the study conducted by Couderc et al. on elderly cancer patients, a significant relationship was found between BCI and mortality (11). In similar studies, it has been found that patients with a BCI level above 40,000 have a shorter survival time (12-13). As a result of all these studies, more research on vitamin B12 and BCI is needed to explore new prognostic markers in diseases and aid in early diagnosis, especially in malignancies. Comprehensive studies are required.

Hypercobalaminemia has been associated with many causes, primarily serious and life-threatening diseases. Available data and studies have raised numerous questions and prompted further research. Investigating vitamin B12 metabolism in certain diseases, treating hypercobalaminemia in clinical practice, and measuring TC and/or HC in laboratory tests highlight the importance of early intervention in these conditions (4). As a result of the study conducted by Anwaar et al., higher vitamin B12 levels were found in diabetics compared to individuals with abnormal and normal glucose homeostasis (14). Another study investigated the relationship between glycemic fluctuations and vitamin B12 levels in patients with Type 2 DM, finding that individuals with more frequent glycemic fluctuations had higher vitamin B12 levels (15). Meta- analyses have found that the prevalence of vitamin B12 deficiency in patients with Type 2 DM using metformin is higher compared to those who do not use it. Additionally, the daily dose and duration of metformin use play a role in this association (16-17). Similarly, in the study by Khattab et al., a positive correlation was found between long-term metformin use and vitamin B12 deficiency (18). While previous studies have shown vitamin B12 deficiency due to metformin use in DM patients, our study and several supporting studies reveal the opposite findings, indicating that more research is needed in this area. Although the exact mechanism by which Type 2 DM causes elevated vitamin B12 levels is not yet clearly understood, we hypothesize that this may result from impaired liver or kidney functions associated with the disease.

Study limitations

There are some limitations in our study. It is a single-center, retrospective study conducted over a certain period and includes a small number of patients. Although there were a variety of chronic diseases in our study, the number of patients analyzed in each category was insufficient. When the additions of the study to the literature are considered, it is seen that the relationship between vitamin B12 levels and chronic diseases is complicated by several factors, as the patients' dietary habits, lifestyles, and whether they receive additional nutritional support are based on subjective responses, which may act as confounding factors affecting vitamin B12 levels. It has been observed in the literature that there is a clear need for large-scale, multicenter, randomized controlled cohort studies on this subject.

Conclusion

When considering the contributions of the study to the literature, it should not be overlooked that there may not be a direct relationship between vitamin B12 levels and chronic diseases; given that diet, medications, supplements, and the metabolic effects of aging are confounding factors, there is a natural difficulty in establishing this relationship. In addition to the adverse effect of metformin, the first choice in the treatment of Type 2 DM, on vitamin B12 levels, we believe it is worth investigating whether there are mechanisms in the pathogenesis of diabetes itself that may hinder the accumulation and metabolism of vitamin B12.

It has been shown that individuals with common chronic diseases have significantly high levels of vitamin B12. We observed that very high levels of vitamin B12 are a risk factor for chronic diseases, including Type 2 DM. There is a need for mechanism-focused cohorts to clearly establish the relationship between chronic diseases and vitamin B12 levels.

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Ethical Approval: *This Study approval was obtained from the Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Number: 144/01, Date: 15.08. 2022). Since this study was retrospective, informed patient consent statement was not collected.*

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Data Availability: *The data used to support the findings of this study are available from the corresponding author upon reques*

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