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Sectionary Analysis Of Thyroid Function Tests, Vitamin B12 And Folic Acid Levels In Patients With Type 2 Diabetes Mellitus, Hypertension, Chronic Renal Disease And Gastroesophageal Reflux Disease

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Abstract

The most common diseases presenting to the internal medicine outpatient clinic are type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux disease. Thyroid function tests, vitamin B12 and folic acid levels were compared in these diseases. Within the scope of the study, 91 patients were included in the study. Cases with type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux disease as chronic diseases were examined in the study. In this context, besides demographic data and routine biochemical data, TSH, fT3, fT4, vitamin B12 and folic acid levels were also scanned retrospectively from patient files. The mean age of the 91 patients included in the study was 61.29 ± 14.23 and was not statistically different between the groups. The FT3 level was found to be the highest in the first group compared to the other groups, but it was not statistically significant (p=0.863). The highest FT4 level was detected in group 4, but it was not statistically significant (p=0.839). TSH value was found to be the highest in the gastroesophageal reflux disease group and was not statistically significant when compared to other groups (p=0.898). The comparison of folic acid and vitamin B12 levels between the groups was not statistically significant (p=0.605). Spearmens's correlation analysis revealed folic acid was significantly positive correlated with folic acid (rho=0.797, p=0.001). TSH levels were not significantly corelated with fT3, fT4, folic acid and vitamin B12 (rho=0.015, p=0.891; rho= -0.177, p=0.093; rho=0.011, p=0.916; rho=0.153, p=0.147). This study demonstrated that serum TSH, ft3, ft4, vitamin b12 and folic acid levels were found similar in all groups. On the other hand, significant difference was not found between groups in term of TSH, fT3, fT4, vitamin B12 and folic acid.

Keywords: *Type 2 diabetes mellitus, hypertension, chronic renal diseas, gastroesophageal reflux disease*

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Introduction

Patients applying to the internal medicine outpatient clinic are divided into two groups as acute and chronic diseases. Important chronic diseases in the field of internal medicine are diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux disease causing dyspepsia.

Type 2 diabetes mellitus accounts for more than 90 percent of diabetes cases in the United States and Europe. Type 1 diabetes has a share of 5-10%. Genetic and environmental factors play a role in the pathogenesis of diabetes mellitus. In addition, various phenotypic forms of diabetes, defined as "atypical diabetes", which do not fully comply with the definitions of type 1 and type 2 and whose pathogenesis has not been fully elucidated, are emerging. Weight gain due to inactivity and obesity, which are a worldwide problem, also increase the incidence of type 2 diabetes. Type 2 diabetes is the most common phenotypic form of diabetes in adults, and hyperglycemia is characterized by varying degrees of insulin resistance and deficiency. Insulin resistance and insulin deficiency may occur with genetic and environmental effects, which may impair beta cell function in every patient and may make insulin resistance known as glucotoxicity more evident (1,2).

Hypertension has a high prevalence worldwide, and hypertension prescriptions among non-pregnant adults in the United States are a major cause of hospital visits and chronic prescription drug use (3,4). In addition, blood pressure control is not sufficient in approximately half of the patients with hypertension. However, patients do not apply to health professionals because they do not have obvious symptoms. The prevalence of hypertension in the United States is higher in men, older adults, black adults, and rural individuals (5,7). The global prevalence of hypertension is similar to that in the United States, although it varies by country (8). Pooled data using the definition of hypertension as taking antihypertensive medication or having systolic ≥140 mmHg or ≥90 mmHg diastolic blood pressure show that in 1990 approximately 32 percent of the world's adult population (aged 30 to 79 years) had hypertension (9).

Chronic kidney disease is the name given to irreversible deterioration of kidney function. Chronic kidney disease guidelines state the concept of kidney disease, which requires the attention of general internists, to develop strategies for its early detection and management. Chronic kidney failure, regardless of the cause. It is defined as the presence of kidney damage or decreased kidney function for one or more months (10). Damage or diminished function must persist for at least 3 months. Decreased kidney function usually refers to a decreased glomerular filtration rate (GFR) estimated using serum creatinine and one of the existing equations (eGFR).

The passage of gastric contents through the esophagus is a normal physiological process. Gastroesophageal reflux is defined as a disease when it causes macroscopic damage to the esophagus or causes symptoms.

Patients presenting to general internal medicine outpatient clinics describe symptoms that are independent of each other. For this reason, many diseases should be considered in the differential diagnosis and appropriate diagnostic tests should be requested. Thyroid dysfunction, iron deficiency anemia, vitamin B12 deficiency and folic acid deficiency should also be considered in the differential diagnosis of weakness and fatigue, which are two important complaints seen in internal medicine outpatient clinics. In this study, the frequency of possible accompanying

thyroid dysfunction and other causes of anemia in patients diagnosed with type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux were investigated.

Materials and methods

Study groups

315 patients who applied to the internal medicine outpatient clinic were included in the study. Acute diseases were not included in the evaluation. The patients were evaluated in terms of chronic disease. Among the chronic diseases, hypertension was defined as type 2 diabetes mellitus, chronic kidney disease and gastroesophageal reflux. 91 patients with chronic disease were included in the study. Exclusion criteria for the study were type 2 diabetes mellitus, chronic kidney disease, hypertension, and having a chronic disease other than gastroesophageal reflux. Demographic, clinical and laboratory data of the patients were collected retrospectively from patient files. Glucose, urea, creatinine, uric acid, albumin, globulin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, lactate used in the study. The standart reference ranges were as follows: fT4 0.61-1.45 ng/dL, fT3 2,5-3,9 ng/dL, vitamin B12 180-914 ng/L, and folic acid 5.9-24.8 ug/L. Dehydrogenase, total bilirubin, calcium, phosphorus, vitamin B12, folic acid, thyroid stimulating hormone, free T3 and free T4 levels were obtained retrospectively. The diagnoses of the patients were diagnosed using the diagnostic criteria determined by the international guidelines, or the patients who were previously diagnosed and using active treatment were considered to have a previous diagnosis. The study protocol was made with the permission of Gaziantep University ethics committee.

Statistical analysis

In the present study, compliance of variables with normal distribution have been evaluated using histograms, variation coefficients, skewness, sharpness, detrended normality graph and Kolmogorov–Smirnov test. Median (minimum/maximum) has been used to present descriptive statistics of variables without normal distribution. Mean standard deviation (SD) values of variables with normal distribution are provided (mean ± SD, 95% CI). ANOVA test has been used to evaluate differences between groups in terms of fT3, fT4,TSH, vitamin B12, and folic acid. When the ANOVA test was applied, no statistically significant difference could be detected between the variances, so post hoc analysis was not needed and was not used. The Pearson correlation test has been used for continuous variables that showed a normal distribution. IBM SPSS version 24 (IBM Corp., Armonk NY, USA) have been used for statistical analysis and calculations. Statistical significance level has been defined as $P < 0.05$.

Results

The mean age of the patients was 61.29 ±14.23. 49.5% (n:45) of the patients were female and 48.4% (n:46) were male. Biochemical and hormonal parameters of the entire study population are given in the table. The patients were divided into groups according to the main diagnostic groups. The first group consists of hypertension, the second group consists of type 2 diabetes mellitus, the third group consists of chronic kidney disease and the fourth group consists of gastroesophageal reflux disease. The first group consisted of 30 patients with hypertension, the second group consisted of 39 patients with type 2 diabetes mellitus, the third group consisted of

20 patients with chronic kidney disease, and the fourth group consisted of 2 patients with gastroesophageal reflux. According to the groups, the values of the biochemical parameters of the patients at the time of application are given in the table. Among the patients included in the study, the rate of smokers in the 1st group was 18.5%, 15.7% in the 2nd group, 14.8% in the 3rd group and 13.97% in the 4th group. There was no statistically significant difference in terms of body mass index (BMI) of the patients (p=0.672). The FT3 level was found to be the highest in the first group compared to the other groups, but it was not statistically significant (p=0.863). The highest FT4 level was detected in group 4, but it was not statistically significant (p=0.839). TSH value was found to be the highest in the gastroesophageal reflux disease group and was not statistically significant when compared to other groups (p=0.898). The comparison of folic acid and vitamin B12 levels between the groups was not statistically significant (p=0.605).

It was performed Spearmen's correlation analysis to evaluate the associations between serum TSH, fT3,fT4, folic acid and Vitamin B12. Spearmens's correlation analysis revealed folic acid was significantly positive correlated with folic acid (rho=0.797, p=0.001). TSH levels were not significantly corelated with fT3, fT4, folic acid and vitamin B12 (rho=0.015, p=0.891; rho= -0.177, p=0.093; rho=0.011, p=0.916; rho=0.153, p=0.147). FT3 was positively correlated with TSH and folic acid (rho=0.015, p=0.891; rho=0.797, p=0.001) and negative correlated with fT4 and vitamin B12 (rho= -0.040, p=0.709; rho= -0.109, p=0.309). FT4 was positively correlated with vitamin B12 (rho=0.022, p=0.837 and negative correlated with TSH, fT3, vitamin B12 and folic acid (rho= -0.177, p=0.093; rho= -0.040, p= -0.030; rho=0.776). Vitamin B12 was positively correlated with TSH, fT4 and folic acid (rho=0.153, p=0.147; rho=0.022, p=0.837; rho= 0.056, p=0.601) and negative correlated with fT3 (rho= -0.109, p=0.309). Folic acid was positively correlated with TSH, fT3 and vitamin B12 (rho=0.011,p=0.916; rho=0.767,p=0.01; rho=0.056, p=0.601).

Table 1. The clinical characteristics of all patients

	Mean± Standart deviation
Glucose (mg/dL)	162.40 ± 68.82
Urea(mg/dL)	83.74 ± 62.22
Urıc acid(mg/dL)	7.19 ±3.94
Creatinine(mg/dL)	1.44 ±1.43
Albumin (g/dL)	3.20 ±1.90
Globulin (g/dL)	3.04 ±0.83
Total protein (g/L)	11.50 ±52.11
AST (U/L)	197.02 ±487.10
ALT(U/L)	108.97 ±285.18
ALP(U/L)	179.08 ± 182.94
GGT(U/L)	136.60 ±195.23
Total Bilirubin(mg/dL)	1.24 ±2.33
LDH (U/L)	390.40 ±165.87
Calcium(mg/dL)	8.44 ±1.40
Phosphorus(mg/dL)	4.60 ±1.96
Vitamin B12(pg/mL)	575.97 ±442.46
Folic acid(ng/mL)	8.48 ±7.43
TSH(mU/L)	2.67 ±6.19
fT3 (pg/mL)	6.01 ±23.04
fT4(pg/mL)	1.22 ±0.64

Table 2 The clinical characteristics of all patients separated by groups

	Mean ±Standart deviation	95% CI (Lower-Upper)	*p*
Free T3			
1.Group	8.03 ± 28.68	-2.88 - 18.93	
2.Group	6.50 ± 25.08	-1.74 - 14.74	0.863
3.Group	2.47 ± 0.53	2.23 - 2.72	
4.Group	2.36 ± 0.61	-3.10 - 7.82	
Free T4			
1.Group	1.24±0.811	0.94 - 1.54	
2.Group	1.23±0.64	1.02 - 1.44	
3.Group	1.12±0.28	0.99 - 1.25	0.839
4.Group	1.37±0.70	-4.98 - 7.72	
TSH			
1.Group	2.09±2.86	1.02 - 3.16	
2.Group	3.30±8.78	0.45 - 6.15	
3.Group	2.16±3.47	0.54 - 3.79	0.898
4.Group	3.79±4.89	-40.23 - 47.80	
Folic acid			
1.Group	8.85±8.34	1.52 - 5.74	
2.Group	8.81±8.18	1.31 - 6.16	
3.Group	7.48±4.47	0.99 - 5.39	0.882
4.Group	6.36±0.29	3.69 - 9.03	
Vitamin B12			
1.Group	602.00±469.14	426.82 - 777.18	
2.Group	524.85±417.54	389,50 - 660.19	
3.Group	659.60±469.92	439.67 - 879.53	0.605
4.Group	346.00±219.20	-1623.46 - 2315.46	

Table 3 Perason's correlation analysis between laboratory variables and clinical features for patients

	TSH	fT3	fT4	Vitamin B12	Folic acid
TSH					
rho	1	0.015	-0.177	0.153	0.011
p		0.891	0.093	0.147	0.916
fT3					
rho	0.015	1	-0.040	-0.109	0.797
p	0.891		0.709	0.309	0.001
fT4					
rho	-0.177	-0.040	1	0.022	-0.030
p	0.093	0.709		0.837	0.776
Vitamin B12					
rho	0.153	-0.109	0.022	1	0.056
p	0.147	0.309	0.837		0.601
Folic acid					
rho	0.011	0.767	-0.030	0.056	1
p	0.916	0.001	0.776	0.601	

Discussion

In the present study, it is found that the serum levels of vitamin B12, folic acid, TSH, free T3 and free T4 were not statistically different between patients groups but the levels of these parameters were found insignificantly different in terms of groups. The highest TSH value, the lowest folic acid and vitamin B12 levels were found in the gastroesophageal reflux disease group. This indicates that patients with gastroesophageal reflux disease should use acid-suppressing therapy, which is an important goal of treatment. It is known that the bioavailability of levothyroxine preparations used in the treatment of hypothyroidism is also low due to drug interactions, and it shows that acid suppressive treatments cause an increase in TSH level for this reason. These results are important evidence that the treatment of patients with gastroesophageal reflux disease differs in some hormone and vitamin parameters, which are the basic needs of the body.

The prevalence of gastroesophageal reflux disease is increasing worldwide and causes deterioration in quality of life (11,12). Dyspepsia is a disease characterized by abdominal pain, retrosternal pain, belching, bloating, and nausea, usually originating from the upper gastrointestinal tract. Reflux symptoms such as heartburn and regurgitation are considered typical symptoms of gastroesophageal reflux disease. However, other dyspeptic complaints may be seen in patients with non-erosive gastroesophageal reflux disease (13,14). In the pathogenesis of dyspeptic patients, increased gastric acidity is treated by suppressing it with acid-suppressing drugs. In these patients, different clinical symptoms may accompany due to multiple pathogenesis of endocrine disorders. Hormonal interactions between systems are not clearly known. Gastrointestinal symptoms or signs may also cause thyroid disease symptoms to occur and, if ignored, may lead to misdiagnosis or delay in diagnosis (15).

Acid-suppressing treatments used in the treatment of reflux are proton pump inhibitors and histamine 2 receptor antagonists. These drugs are defined as acid-suppressing therapies (ALA) and are commonly used drugs for the gastrointestinal tract. Although the use of ALA is generally considered a safe therapeutic agent, long-term use of ALA raises concerns about vitamin B12 deficiency. The hypothesis of this situation can be explained by understanding how vitamin B12 is obtained in the human body. Diet is the only source of vitamin B12 for humans. Vitamin B12 is naturally protein bound. The human body uses stomach acid and pepsin to convert the vitamin to free vitamin B12, which then binds to the R-protein in the stomach. Once it reaches the less acidic duodenum, vitamin B12 is released from the R-proteins by pancreatic enzymes and binds to intrinsic factor. Vitamin B12 bound to intrinsic factor is then absorbed into the body via terminal ileum cubilin receptors (16,17). There are 2 reasons why chronic ALA use can cause vitamin B12 deficiency. First, it inhibits the absorption of vitamin B12 by lowering stomach acidity. Vitamin B12 cannot be separated from dietary protein. Secondly, a higher pH value in the intestine may cause malabsorption by causing bacterial growth (18,19).

Levothyroxine, which is used in the treatment of thyroid, changes its absorption in case of increased gastric acidity (20). Various studies have confirmed that patients with impaired gastric acid secretion due to disease or using proton pump inhibitors may require higher doses of levothyroxine to achieve targeted TSH(21,22). This effect proves clinically important in patients with chronic ALA administration (23). Although the proton pump inhibitors pantoprazole and esomeprazole do not seem to change the pharmacokinetic parameters of levothyroxine, the data are insufficient to prove their safety (23,24).

This study had some limitations. In this study, which was designed as a cross-sectional study, the chronic disease duration of the patients, the information on whether they use additional treatment, the active ingredients of the drugs they use, the duration of drug use, whether they use active drugs and their nutritional status are not known. These conditions are also factors that may affect the hormone and vitamin values screened within the scope of the study.

In coclusin, this study demonstrated that there is no statistically significant difference in vitamin B12, folic acid, TSH, Ft3 and F4 values among patients with type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux diseases screened in this study. Although the highest TSH and lowest vitamin B12 values did not reach statistical significance, they were found in individuals with gastroesophageal reflux disease. This suggests that molecules related to acid-suppressing drugs may impair their absorption into the body. This result emphasizes controlling the achievement of treatment goals in situations where multiple drug use is required.

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