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Original Research Article

Can vitamin D, B12, folic acid, inflammatory markers and *H. pylori* effective in the process of chronic spontaneous urticaria?

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ABSTRACT

Background: Etiopathogenesis in Chronic Spontaneous Urticaria (CSU) is not completely clear. Some vitamins, inflammatory markers and even some microorganisms have been held responsible for this process. There are limited number of publications in this field in the literature. The aim of this study is to shed light on the etiology of chronic urticaria.
Methods: This study included a total of 90 patients that 45 with CSU patients and 45 healthy subjects who admitted to Allergy and Clinical Immunology and Internal Medicine outpatient clinics of University of Health Sciences, Bursa Postgraduate Research and Training Hospital between October 2018 and June 2019. They were between the ages of 18-55. Both groups were examined for CRP, Procalcitonin (PCT), Erythrocyte Sedimentation Rate (ESR), Vitamin B12, vitamin D, folic acid and *Helicobacter pylori* (*H. pylori*) antibody.
Results: ESR, CRP, PCT, Vitamin B12 and Vitamin D levels were not statistically different according to the groups ($p>0.05$). Folic acid levels were significantly different between groups ($p=0.026$; $p<0.05$); the low folic acid ratio in the healthy group is higher than in the urticaria group. There was no statistically significant difference between the groups according to *H. pylori* antibody positivity ($p>0.05$). In urticaria group, sufficient vitamin D ratio was higher in who were *H. pylori* antibody negative. In healthy group; insufficient and sufficient vitamin D ratio was higher in who were *H. pylori* antibody positive.
Conclusions: There is no direct correlation between urticaria and Vitamin B12, Vitamin D, folic acid deficiencies and inflammatory biomarkers. CRP, ESR and PCT levels may be generally normal as in patients with urticaria. However, CRP may also increase slightly in patients with severe urticaria. It may be wrong to see *H. pylori* as a direct cause of urticaria.

Keywords: Chronic spontaneous urticaria, C-reactive protein, Folic acid**,** *Helicobacter pylori***,** Procalcitonin, Vitamin B12

INTRODUCTION

Urticaria is an inflammatory skin disease, characterized by the development of wheals, angioedema, or both.[1] Chronic Urticaria (CU) is described as a duration of the disease for more than six weeks. The lifetime prevalence of urticaria is 8.8% to 20% and 1.8% for CU in particular.[2] Chronic Spontaneous Urticaria (CSU) can be defined as a mast cell and basophil associated inflammatory disease of the skin a by acute phase response.[3] This process is demonstrated by increased concentration of biomarkers IL-6 and C Reactive Protein (CRP).[4-6] This is accompanied by activation of the coagulation fibrinolysis system, not activation of platelets.[6-10] CRP is a marker of systemic CSU activity. It reflects the systemic effects of inflammatory mediators, associated with the disease, including IL-6.[4,5] Fibrin degradation products, D-dimer and serum CRP levels

increased in exacerbation of CU and their levels decreased as the disease inactivated.[5] Unfortunately, these biomarkers may reflect not only the activity and severity of CU, but also correlate with a systemic response to infections.[4,11] In contrast, Procalcitonin (PCT) seems to be more specifically associated with the presence of microbial infection. PCT may elevate only slightly in rare cases of immune mediated inflammatory diseases.[12-14] Determination CRP and PCT together was found superior than CRP alone for diagnosing active or severe inflammatory bowel diseases.[15] There has been increasing evidence showing that vitamin D deficiency or insufficiency is associated with increased incidence and severity or activity of the immune inflammatory diseases. Vitamin D has immunomodulatory properties and it may suppress the inflammatory circle including IL-6 and CRP synthesis.[16-18]

In the literature, there are studies investigating the relationship between vitamin B12, folic acid, vitamin D levels and *H. pylori* in patients with CU. Different results were obtained in these studies.[19] In these researches was also found that eradication of *H. pylori* positively affected urticaria healing.

Etiopathogenesis in CSU is not completely clear. Some vitamins, inflammatory markers and even some microorganisms have been held responsible for this process. There are limited number of publications in this field in the literature. The aim of this study is to shed light on the etiology of CU.

METHODS

This study included a total of 90 patients that 45 with CSU patients and 45 healthy subjects who admitted to Allergy and Clinical Immunology and Internal Medicine outpatient clinics of University of Health Sciences, Bursa Postgraduate Research and Training Hospital between October 2018 and June 2019.

This research included the people with urticaria, and healthy who are between the ages of 18-55. Forty-five patient with CSU and 45 healthy volunteers without any known disease were included in the study. Both groups were examined for CRP, PCT, ESR, vitamin B12, vitamin D, folic acid and *H. pylori*.

Routine investigations had been performed to exclude any known causes of the diseases or the concomitant diseases. In all cases, any known causes of CSU were ruled out by appropriate investigations. Each patient underwent the following tests: routine laboratory tests (full blood count, urine analysis, ESR, CRP, serum glucose, hepatic functions, and creatinine), stool (for parasites, *H. pylori* Ag), hepatitis serology, antinuclear and antithyroid microsomal antibodies, thyroid function tests, vitamin B12 and folic acid). In addition, Vitamin D, *H. pylori* IgG antibody and PCT were also evaluated in patients with CSU.

The control group comprised 45, sex, age matched the healthy subjects. Healthy volunteers without any known disease were included in the study. This group was examined for CRP, PCT, ESR, Vitamin B12, Vitamin D, folic acid and *H. pylori* IgG antibody.

UAS according to EAACI/GALEN/EDF guidelines was estimated during four days and on the day of blood sampling: (no wheals = 0, 1-10 wheals = 1, 11-50 wheals = 2, >50 wheals = 3) and pruritus intensity (no = 0, mild = 1, moderate = 2, and severe = 3). UAS scores were as follows: daily (minimum = 0; maximum= 6) and four days by adding the daily score values (minimum = 0; maximum=24).[20] The UAS was graded as follows: mild (0-8), moderate (9-16) and severe (17-24). The study comprised 45 patients with moderate-severe urticaria symptoms.

None of the examined subjects had taken oral corticosteroids within 2 months, or antihistamines within at least 4 days before the study.

All blood samples were obtained at 9 a.m. by antecubital puncture. As the circulating levels of 25 (OH)D vary depending on the season, the concentration was evaluated in summer (June).

Assay of CRP: Serum CRP concentration was measured by the turbidimetric latex agglutination method (CardioPhase hsCRP, Siemens Healthcare Marburg, Germany) with a detection limit of 1.0 mg/l. Elevated serum CRP was defined as higher than 5.0 mg/l.

Assay of 25(OH)D: Serum 25(OH)D concentration, and serum *H. pylori* IgG levels, and PCT were measured with the use of an automated ELISA which Microplate reader RT 2100 C and Microplate washer RT 2600 C (Human 25-OH Elisa kit, Human PCT Elisa kit, Human *H. pylori* Elisa kit. Sinegeneclon Co., Ltd, China). Serum 25(OH)D concentration was defined as: a) sufficiency (30 ng/ml), b) insufficiency (between 20 and 29 ng/ml), c) deficiency (< 20 ng/ml). Assay of *H. pylori* antigen: Feces *H. pylori* antigen levels was measured with the use of a one-step rapid test (Safecare Biotech, Zhejiang China).

Assay of Vitamin B12, folic acid: Serum vitamin B12 and folic acid levels were measured with the use of an automated ELISA (Elcys Vitamin B12 II, Human Elcys folate III, Germany).

This study was approved by the ethics committee of Bursa High Specialization Training and Research Hospital. Written informed consent was obtained from all subjects.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The suitability of

the quantitative data for normal distribution was tested with the Shapiro-Wilk test and graphical analysis. Student t test was used to compare the normal distribution of quantitative variables between two groups. Pearson chi-square test, Fisher's Exact test and Fisher-Freeman-Halton test were used to compare the qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

This research was included the patients with CSU who were admitted to the allergy and clinical immunology outpatient clinics between March and June 2019. Control group was included volunteers who were not any known diseases. The study was conducted with 90 cases; 50.0% (n=45) in the CSU group and 50.0% (n=45) in the healthy group.

In this study; 52% (n=47) of the cases were female and 48% (n=43) were male. Their ages ranged from 18 to 55 years with an average of 36.36±10.56 years. Evaluation of Descriptive Properties by Groups were shown in (Table 1).

Distribution of ESR, CRP, PCT and general inflammation status by groups were shown in (Figure 1).

Folic acid levels were significantly different between groups ($p=0.026$; $p<0.05$); the low folic acid ratio in the healthy group is higher than in the urticaria group.

Vitamin B12 and vitamin D levels were not statistically difference between the groups ($p>0.05$). There was no statistically significant difference between the groups in terms of vitamin status ($p>0.05$).

Distribution of folic acid, B12, vitamin D and general vitamin status by groups were shown in (Figure 2).

No statistically significant difference was found between the groups according to age and gender distributions ($p> 0.05$). Although CRP was high in 9 patients with severe CSU, there was no statistically significant difference when compared to the healthy group($p>0.05$).

Table 1: Evaluation of descriptive properties by groups.

		Urticaria (n=45)	Healthy (n=45)	p
Age (year)	Min-Max (Median)	18-55 (39)	18-51 (36)	[a]0,086
	Mean±Standard deviation	38,27±11,43	34,44±9,35	
Gender	Female	25 (55,6)	22 (48,9)	[b]0,527
	Male	20 (44,4)	23 (51,1)	
ESR	Normal	33 (73,3)	29 (64,4)	[b]0,362
	High	12 (26,7)	16 (35,6)	
CRP	Normal	36 (80,0)	40 (88,9)	[b]0,245
	High	9 (20,0)	5 (11,1)	
PCT	Normal	45 (100)	43 (95,6)	[c]0,494
	High	0 (0)	2 (4,4)	
Inflamation Status	Normal	31 (68,9)	27 (60,0)	[b]0,378
	High	14 (31,1)	18 (40,0)	
	All normal	31 (68,9)	27 (60,0)	
	1 measurement high	7(15,6)	14 (31,1)	
	2 measurement high	7 (15,6)	3 (6,7)	
	3 measurement high	0 (0)	1 (2,2)	
Folic acid	Low	0 (0)	6 (13,3)	[c]0,026*
	Normal	45 (100)	39 (86,7)	
Vitamin B12	Low	2 (4,4)	0(0)	[c]0,494
	Normal	43 (95,6)	45 (100)	
Vitamin D	Deficiency	32 (71,1)	32 (71,1)	[d]1,000
	Insufficiency	4 (8,9)	4 (8,9)	
	Sufficiency	9 (20,0)	9 (20,0)	
Vitamin Status	Normal	8 (17,8)	9 (20,0)	[b]0,788
	Low	37 (82,2)	36 (80,0)	
	All normal	8 (17,8)	9 (20,0)	
	1 measurement low	36 (80,0)	30 (66,7)	
	2 measurement low	1 (2,2)	6 (13,3)	
H. Pylori Antibody	Negative	35 (77,8)	33 (73,3)	[b]0,624
	Positive	10 (22,2)	12 (26,7)	

[a]Student t Test, [b]Pearson Chi-Square Test, [c]Fisher's Exact Test, [d]Fisher Freeman Halton Test, *p<0,05

ESR, and PCT levels were not statistically different according to the groups (p>0.05). There was no statistically significant difference between the groups in terms of inflammation status (p>0.05). There was no statistically significant difference between the groups according to *H. pylori* antibody positivity (p>0.05).

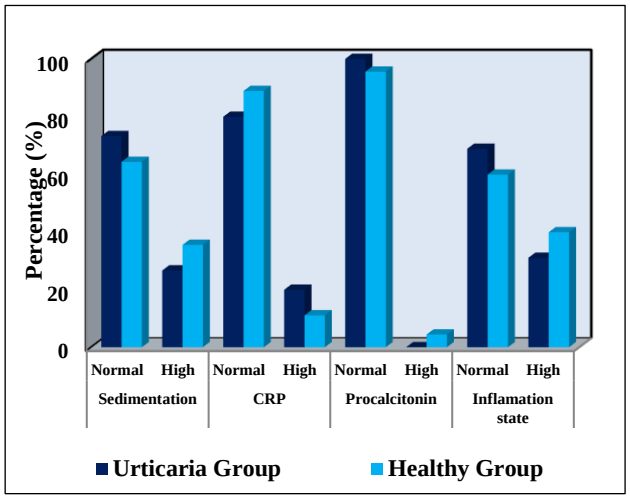

Figure 1: Distribution of ESR, CRP, PCT and general inflammation status by groups.

Relationship between *H. pylori* antibody and *H. pylori* Ag in urticaria group was shown in Table 2.

There was no statistically significant relationship between *H. pylori* Antibody and *H. pylori* Ag positivity in the urticaria group (p>0.05).

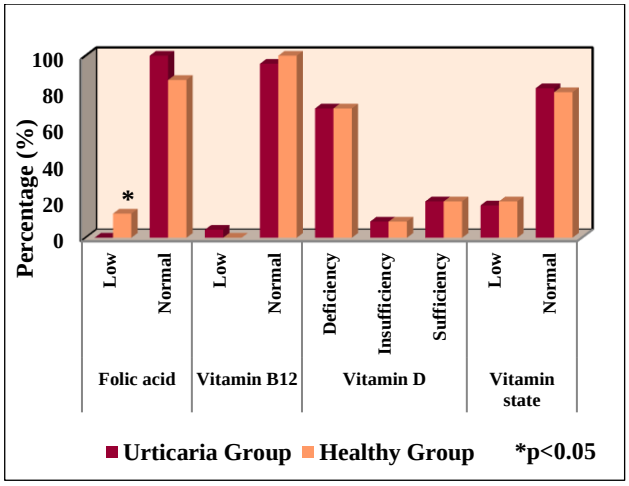

Figure 2: Distribution of folic acid, B12, vitamin D and general vitamin status by groups.

Table 2: Relationship between *H. pylori* antibody and *H. pylori* Ag in urticaria Group.

		H. pylori antibody		p
		Negative (n=35)	Positive (n=10)	
H. pylori Ag	Negative (n=41)	33(94,3)	8(80,0)	[c]*0,209*
	Positive (n=4)	2(5,7)	2(20,0)	

[c]Fisher's Exact Test

Evaluation of Folic Acid, B12 and Vitamin D by *H. pylori* Antibody Positivity were shown in Table 3.

Table 3: Evaluation of folic acid, B12 and vitamin D by *H. pylori* antibody positivity.

		H. pylori antibody		p
		Negative	Positive	
Urticaria group		n=35	n=10	
Folic acid	Low	0(0)	0(0)	-
	Normal	35(100)	10(100)	
Vitamin B 12	Low	1(2,9)	1(10,0)	c0,399
	Normal	34 (97,1)	9(90,0)	
Vitamin D	Deficiency	32(91,4)	0(0)	d0,001**
	Insufficiency	3(8,6)	1(10,0)	
	Sufficiency	0(0)	9(90,0)	
Healthy group		n=33	n=12	
Folic acid	Low	6(18,2)	0(0)	c0,171
	Normal	27(81,8)	12(100)	
Vitamin B 12	Low	0(0)	0(0)	-
	Normal	33(100)	12(100)	
Vitamin D	Deficiency	32(97,0)	0(0)	d0,001**
	Insufficiency	1(3,0)	3(25,0)	
	Sufficiency	0(0)	9(75,0)	

cFisher's Exact Test dFisher Freeman Halton Test **p<0,01

In the urticaria group

Because folic acid levels were normal in all cases, no evaluation was performed.

According to *H. pylori* antibody positivity, B12 level did not show statistically significant difference (p>0.05).

According to *H. pylori* antibody positivity, vitamin D level was statistically significant (p=0.001; p<0.01). In the *H. pylori* antibody negative group, the ratio of deficient vitamin D was higher than in the *H. pylori* antibody positive group. In the *H. pylori* antibody positive group, sufficient vitamin D ratio was higher than the *H. pylori* antibody negative group.

In healthy group

According to *H. pylori* antibody positivity, folic acid level did not show statistically significant difference (p> 0.05).

Because B12 level was normal in all cases, no evaluation was performed.

According to *H. pylori* antibody positivity, vitamin D level was statistically significant (p=0.001; p<0.01). In the *H. pylori* antibody negative group, the ratio of deficient vitamin D was higher than in the *H. pylori* antibody positive group. Insufficient and sufficient vitamin D ratio was higher in *H. pylori* antibody positive group than *H. pylori* antibody negative group.

Evaluation of Folic Acid, B12 and Vitamin D by *H. pylori* Ag Positivity in Urticaria Group were shown (Table 4).

Table 4: Evaluation of Folic Acid, B12 and Vitamin D by *H. pylori* Ag Positivity in urticaria group.

Urticaria group (n=45)		*H. pylori* Ag		p
		Negative (n=41)	**Positive (n=4)**	
Folic acid	Low	0(0)	0(0)	-
	Normal	41(100)	4(100)	
Vitamin B 12	Low	2(4,9)	0(0)	c1,000
	Normal	39(95,1)	4(100)	
Vitamin D	Deficiency	30(73,2)	2(50,0)	d0,325
	Insufficiency	4(9,8)	0(0)	
	Sufficiency	7(17,1)	2(50,0)	

[c]Fisher's Exact Test, [d]Fisher Freeman Halton Test

In the urticaria group

Folic acid levels were normal in all cases and no evaluation was performed.

According to *H. pylori* Ag positivity, B12 level did not show statistically significant difference (p>0.05).

According to *H. pylori* Ag positivity, vitamin D level did not show statistically significant difference (p>0.05).

DISCUSSION

CSU is a skin disease and it has unclear etiology. It is common and it affects people's work, school, family and social lives. In the literature, there are publications investigating the relationship of this disease with vitamin B12, vitamin D, folic acid, *H. pylori*, and its possible correlations with biomarkers such as CRP, PCT, ESR. However, in these publications, a few parameters have been examined and it is very difficult to find a publication that contains all of them together. In this study, we aimed to investigate biomarkers such as CRP, PCT, ESR and vitamins such as B12, vitamin D, folic acid. We also examined whether *H. pylori* was associated with CSU.

Cheng-Han Wu et al, in their study; vitamin D levels determined in the United Kingdom population were higher in patients with CSU than in the normal population.[21] Thorp et al, did not find statistically a significant difference according to vitamin D levels between 25 patients with CU and 5 healthy controls.[22] According to vitamin D levels; there was no statistically significant difference in between 45 patients with CSU and 45 healthy controls in this study. In both of group according to *H. pylori* antibody positivity, vitamin D level was statistically significant difference (p=0.001; p <0.01). In the *H. pylori* antibody negative group, the ratio of deficient vitamin D was higher than in the *H. pylori* antibody positive group. In the *H. pylori* antibody positive group, sufficient vitamin D ratio was higher than the *H. pylori* antibody negative group. In urticaria group, sufficient vitamin D ratio was higher in who were *H. pylori* antibody negative. In healthy group; insufficient and sufficient vitamin D ratio was higher in who were *H. pylori* antibody positive.

Vitamin B12 deficiency were found in 11 of 33 patients with CU by Mete et al.[23] Cheng-Han Wu and colleagues found that vitamin B12 levels in CU were within the normal range compared to the general population of England, but they were low significantly according to statistically.[21] In this study, there was no significant statistically difference in vitamin B12 levels between CU and healthy controls.

Mete et al, found that folic acid levels in patients with chronic urticaria were within normal limits.[22] In the literature review, author found no other study investigating folic acid levels in patients with CU. In this study, there was no significant statistically difference in folic acid levels between CU and healthy controls. But folic acid levels were significantly different between groups (p=0.026; p<0.05); the low folic acid ratio in the healthy group was higher than in the urticaria group.

There are shown that there is a relationship between *H. pylori* and CU and its eradication therapy is beneficial for healing urticaria in the studies at literature.[24,25,26]

In this study, *H. pylori* IgG were evaluated in CU and healthy group. In CU group, fecal *H. pylori* antigen was also evaluated. No significant relationship was found between *H. pylori* and CU. There was no statistically significant difference between the groups according to *H. pylori* antibody positivity ($p > 0.05$).

PCT was found to be within normal limits except in cases of severe urticaria.[6] PCT is also more valuable than CRP in discriminating of infection in patients with CU.[6,11] In this study, PCT levels were normal. Since there was no infection in this patient, CRP levels were also normal except for 9 patients with severe urticaria. There was no elevation in PCT levels associated with urticaria.

CONCLUSION

Folic acid levels were significantly different between groups ($p=0.026$; $p<0.05$); the low folic acid ratio in the healthy group is higher than in the urticaria group. In urticaria group, sufficient vitamin D ratio was higher in who were *H. pylori* antibody negative. In healthy group; insufficient and sufficient vitamin D ratio was higher in who were *H. pylori* antibody positive. There is no direct correlation between urticaria and vitamin B12, vitamin D and folic acid deficiencies. In patients with urticaria, vitamin deficiencies may also be seen due to malnutrition or other causes and may accompany the course of urticaria. Elevations in acute phase reactants may also be more correlated with possible concomitant viral or bacterial infections. This infection can even trigger urticaria. Excluding infections, CRP, ESR and PCT levels may be generally normal as in patients with urticaria. However, CRP may also increase slightly in patients with severe urticaria. It may be wrong to regard *H. pylori* as a direct cause of urticaria. However, the relationship between *H. pylori* and vitamin deficiencies remains controversial.

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