ORIGINAL ARTICLE

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Ischemia-Modified Albumin Levels in Essential Thrombocytosis

ABSTRACT

Objective: The aim of this study was to investigate the levels of ischemia-modified albumin (IMA) in people with essential thrombocytosis (ET).

Methods: A total of 30 patients with ET patient group and 30 volunteers with no known disease control group (C group) were included in this study after the approval of ethics committee and written informed consent was obtained. Patients with a history of major thrombosis were excluded. IMA levels and independent variables were investigated and effects on thrombosis susceptibility were also studied. In addition to that; comorbid disease state, drug use and used drugs group were questioned in patient group and effects of them on IMA levels were studied.

Results: In our study, when ET patient group and C group were compared, the mean serum IMA levels in ET patient group and C group was detected as 0,6726 (0,527-0,776) Absorbans Unite (ABSU) and 0,4342 (0,346-0,612) ABSU respectively and in ET patient group was significantly higher than C group (p<0,001). The glucose, total cholesterol and triglyceride values were significantly higher in ET patient group (p= 0,026, p= 0,058, p= 0,004, respectively). There is a correlation between IMA concentration and age (p= 0,042).

Conclusions: In our study IMA levels were found significantly high in ET patient group, this supports increased risk of thrombosis in ET. The difference of metabolic parameters between the ET patient group and C group can be explained by insulin resistance and atherosclerosis background caused by chronic inflammation.

Keywords: Ischemia Modified Albumin, Essential Thrombocytosis, Thrombosis

Esansiyel Trombositozlu Hastalarda İskemi-Modifiye Albumin Düzeyleri

ÖZET

Amaç: Bu çalışmanın amacı, ET olan kişilerde IMA düzeylerini incelemektir.

Gereç ve Yöntem: Çalışma için etik kurul onayı ve yazılı bilgilendirilmiş onam alındıktan sonra ET hastalığı olan 30 kişi ve bilinen herhangi bir hastalığı olmayan 30 gönüllü çalışmaya dahil edildi. Majör tromboz öyküsü olan hastalar çalışma dışı bırakıldı. Çalışmada IMA düzeyleri ile bağımsız değişkenler ve tromboz duyarlılığı arasındaki ilişki değerlendirildi. Ayrıca, hasta grubunda komorbidite, ilaç kullanımı ve kullanılan ilaç grubu sorgulanarak bunların IMA düzeylerine etkisi incelendi.

Bulgular: Çalışmamızda ET hasta grubu ve C grubu karşılaştırıldığında, ET hasta grubu ve C grubunda ortalama serum IMA düzeyleri sırasıyla 0,6726 (0,527-0,776) ABSU ve 0,4342 (0,346-0,612) ABSU olarak saptandı ve ET hasta grubunda C grubundan anlamlı derecede yüksekti (p <0,001). Glukoz, total kolesterol ve trigliserit değerleri ET hasta grubunda anlamlı olarak daha yüksek bulundu (sırasıyla p=0,026, p=0,058, p=0,004). IMA konsantrasyonu ile yaş değişkeni arasında anlamlı bir korelasyon saptandı (p=0,042).

Sonuç: Çalışmamızda ET hasta grubunda IMA düzeyleri istatistikel düzeyde anlamlı olarak yüksek bulundu, bu da ET' de artmış tromboz riskini desteklemektedir. ET hasta grubu ve C grubu arasındaki metabolik parametrelerin farkı, kronik inflamasyonun neden olduğu insülin direnci ve ateroskleroz arka planı ile açıklanabilir.

Anahtar Kelimeler: İskemi Modifiye Albümin, Esansiyel Trombositoz, Tromboz

INTRODUCTION

Essential thrombocytosis (ET) is a myeloproliferative disease which is characterized by hyperplasia in megakaryocytes, splenomegaly, bleeding and increased risk of thrombosis (1, 2). Patients with ET can be clinically asymptomatic or can be presented with complications such as bleeding and thrombosis (3, 4).

Approximately half of the cases are asymptomatic during diagnosis; and these cases are incidentally diagnosed after recognition of thrombocytosis. Symptomatic cases are generally presented with microvascular and vasomotor symptoms (5). Although they are disturbing; microvascular symptoms are not life-threatening. The same situation cannot be said for thrombotic complications. Thrombosis is generally arterial, it can be detected in 11-25% of cases during diagnosis and in 11-22% during follow-up. Hemorrhagic complications are less common (2-5% during diagnosis, 1-7% during follow-up). Hemorrhagic deaths are rare in ET cases and deaths due to thrombosis in ET cases occur in 13-27% (5, 6).

In a study involving 605 cases; negative factors on survival are defined as follows; low hemoglobin level (in women <12g/dl, in men <13.5g/ dl), age>60, the number of leukocytes >15 000/μL, smoking, diabetes mellitus, history of venous thrombosis (7). The general purpose of treatment in ET is to decrease thrombo-hemorrhagic complications without increasing the likelihood of a conversion to leukemia and myelofibrosis (6, 7, 8). Risk stratification is done through many factors influencing thrombosis instead of hemorrhage. Therefore, main purpose of the treatment should be reducing symptoms associated with microvascular pathology and preventing thrombosis-related complications. Unless there is a contraindication; low dose aspirin treatment is recommended for all ET cases (8).

The production mechanism of ischemia-modified albumin is unclear. The last amino terminal of albumin structure is a binding region with a high affinity for transition metals such as nickel, copper, cobalt and it was shown that ischemia can decrease the binding of these metals to N-terminal of albumin and is named as "ischemia-modified albumin" (9, 10, 11).

Ischemia modified albumin (IMA) is a novel marker for detecting ischemic events. Serum IMA levels were detected to be increased during many diseases in which ischemia was observed. There are also results of studies showing that IMA is not only specific for cardiac ischemia. It can also increase in many other diseases such as end-stage renal disease, liver failure, cerebrovascular disease, extreme trauma, neoplastic diseases, serious infections (12, 13).

The aim of this study is to investigate IMA levels in ET patient group. Based on the idea that ischemia because of tendency to thrombosis in ET can increase IMA levels; we planned to measure IMA levels in this group of patients. Thus, rates of mortality and morbidity in ET patient group can be significantly reduced by measures taken at early stages.

MATERIAL AND METHODS

This study was conducted between May and October 2015 in the clinics of Internal Medicine and Hematology of Izmir Tepecik Education and Research Hospital. This study was approved by local ethical committee of Izmir Tepecik Education and Research Hospital. Informed consent was obtained from all of the participants. Thirty patients with ET diagnosis according to World Health Organization criteria for ET and 30 volunteer adult individuals with no known disease [control group (C group)] were included in the study. Patients with a history of major thrombosis were excluded. Ischemic stroke, transient ischemic attack, myocardial infarction, peripheral arterial disease, retinal artery or vein occlusion, deep vein thrombosis and pulmonary embolism were accepted as major thrombotic events. Patients with serum albumin levels of 3.5-5.5 mg / dl were included in this study because abnormal serum albumin levels would challenge IMA measurement. Individuals with additional hepatic, cardiac or renal failure history were also excluded.

Laboratory data were obtained with enzymatic method in Olympus AO5800 otoanalyser in our hospital biochemistry laboratory. Normal laboratory ranges are as follows; The fasting blood glucose (74-106 mg / dL), total cholesterol (110-199 mg / dL), LDL cholesterol (62-129 mg / dL), triglycerides (30-200 mg / dL), uric acid (2.6-6 mg / dL), albumin (3.5-5.5 g / dL) hemoglobin (14.1 to 18.1 g / dL), platelets (140000-400000 u / L). IMA test was performed according to spectrophotometric method which was reported by David Bar-Or. Shimadzu UV mini-1240 spectrophotometer was used. Results were recorded with ABSU unit. Venous blood samples for IMA were collected into gelous biochemistry tubes. Serum was removed from blood samples and was stored in - 80 °C as two aliquats. IMA test was made on a monthly basis in the work schedule.

SPSS-20 program was used for the statistical analysis of the study. Shapiro-Wilk test was used for numeric variables. In variables conforming to the normal distribution; T-test was performed for group comparison analysis. For the relations between numerical variables; Pearson's correlation coefficient was used. In all analyses; p values less than 0.05 were considered statistically significant.

RESULTS

The mean age of ET patient group and C group was 58.2 (30-80) and 54.1, respectively.

There was no significant difference between groups (p=0,114). In this study; 63.3% of the subjects were female. Gender distribution was similar in both groups (p=0,592) (Table 1).

When ET patient group was questioned in itself; 20 patients had known additional chronical diseases. No statistically significant difference was detected on IMA levels, when subgroups with and without comorbid disease were compared (p=0,563).

When ET patient group was questioned in itself; 8 patients were not taking any medicine instead of acetylsalicylic acid, 12 patients were taking hydroxy urea-based treatment and 10 patients were taking anagrelide based treatment. When patients were analysed in three sub-groups according to drug groups; no significant difference was detected between sub-groups on IMA levels were compared (p=0,138).

Table1. Sociodemographic Variables of ET Patient Group and C Group

		ET Patient Group (n=30)	C Group (n=30)	p
		Mean ± SD (Min-Max)	Mean ± SD (Min-Max)	
Age/ Year		58,2 ± 11,84 (30-80)	54,1 ± 7,41 (41-75)	0,114
		n (%)	n (%)	
Gender	**Female**	18 (60%)	20 (66,6%)	0,592
	Male	12 (40%)	10 (33,3%)	
Comorbid Diseases	**DM**	17 (56,67)	-	-
	HT	8 (26,67)	-	-
Drugs	**ASA**	8 (26.7%)	-	-
	Hydroxyurea	12 (40%)	-	-
	Anagrelide	10 (33,3%)	-	-

ET: Essential Thrombocytosis, C: Control, HT: Hypertension, DM: Diabetes Mellitus, SD: Standart Deviation, Min: Minimum, Max: Maximum

The mean blood glucose levels in ET patient group and C group were 102 mg / dL (73-181 mg / dL) and 90.43 mg / dL (69-124 mg / dL), respectively. The mean blood glucose level in ET patient group was significantly higher than that of C group (p=0,026) (Table 2).

The mean serum triglyceride levels in ET patient group and C group were detected as 154,4 mg/dl (56-254 mg/dl) and 111 mg/dl (39-244 mg/dl), respectively. The mean serum triglyceride level in ET patient group was significantly higher than that of C group (p=0,004) (Table 2).

The mean serum LDL levels in ET patient group and C group were detected as 111,83 mg/dl (48-185 mg/dl) and 123,43 mg/dl (55-182 mg/dl), respectively. There was no statistically significant difference between ET and C in terms of serum LDL values. (p=0,167) (Table 2).

The mean serum uric acid levels in ET patient group and C group were 6,523 mg/dl (3,7-11 mg/dl) and 5,09 (2,5-8,8 mg/dl), respectively. The mean serum uric acid level in ET patient group was significantly higher that of C group (p=0,002) (Table 2).

The mean hemoglobin levels in ET patient group and C group were 11,94 gr/dl (8,8-15,5 gr/dl) and 13,83gr/dl (9,5-17,1 gr/dl), respectively. The mean hemoglobin level in ET patient group was significantly lower than C group (p<0,001) (Table 2).

The mean serum IMA levels in ET patient group and C group was detected as 0,6726 ABSU (0,527-0,776 ABSU) and 0,4342 ABSU (0,346-0,612 ABSU), respectively. The mean serum IMA level in ET patient group was significantly higher than C group (p<0,001) (Table 2).

Table 2. Laboratory Parameters in ET Patient Group and C group

	ET Patient Group	C Group	p
	Mean ± SD (Min-Max)	Mean ± SD(Min-Max)	
Glucose (mg/dl)	102 ± 24,49 (73-181)	90,43 ± 12,42 (69-124)	0,026
Total Cholesterol (mg/dl)	183,57 ± 45,46 (95-279)	203 ± 30,90 (131-262)	0,058
Triglycerides (mg/dl)	154,4 ± 55,71 (56-254)	111 ± 56,211 (39-244)	0,004
LDL (mg/dl)	111,83 ± 34,01 (48-185)	123,43 ± 30,121 (55-182)	0,167
Uric acid (mg/dl)	6,52 ± 1,82 (3,7-11)	5,09 ± 1,60 (2,5-8,8)	0,002
Albumin (g/dl)	4,39 ± 0,67 (3,5-5,2)	4,37 ± 0,44 (3,5-5,1)	0,910
Creatinine (mg/dl)	1,07 ± 0,71 (0,5-1,3)	0,91 ± 0,15 (0,6-1,1)	0,244
Hemoglobin (gr/dl)	11,94 ± 1,99 (8,8-15,5)	13,83 ± 1,51 (9,5-17,1)	<0,001
Leukocyte (x10^3/µL)	8336,67 ± 2456,31(4800- 13700)	6873,33 ± 1387,61 (4300- 10100)	0,007
Thrombocyte (x10^3/µL)	733133,33 ± 398601,671 (223000-1766000)	250366,67 ± 46219,479 (145000-351000)	0,000
IMA (ABSU)	0,67 ± 0,052 (0,53-0,78)	0,43 ± 0,61 (0,35- 0,61)	<0,001

Statistical analysis: Student-T Test
ET: Essential Thrombocytosis, C: Control, IMA: Ischemia Modified Albümin, ABSU: Absorbans Unite, SD: Standart Deviation

When the effects of laboratory parameters and demographic data on the IMA levels were investigated in the ET patient group and C group, the correlations between demographic data, laboratory values, anagrelide, acetylsalicylic acid and hydroxyurea groups and IMA levels are given in Table 3.

Table 3. Comparative Analysis of Data with IMA

	Correlation With IMA			
	ET Patient Group		C Group	
	p	r	p	r
Comorbid Diseases	0,456	-0,141	-	-
Age	0,826	0,042	0,093	0,312
Glucose	0,793	0,050	0,072	0,333
Total Cholesterol	0,070	-0,335	0,764	0,057
Triglycerides	0,200	-0,240	0,263	0,211
LDL	0,096	-0,310	0,126	0,286
Uric acid	0,910	0,021	0,281	0,204
Albumin	0,075	-0,330	0,669	0,081
Creatinine	0,401	0,159	0,584	-0,104
Hemoglobin	0,266	-0,210	0,163	0,261
Leukocyte	0,466	0,138	0,190	0,310
Thrombocyte	0,816	-0,044	0,981	-0,004
ASA	0,775	-0,121	-	-
Hydroxyurea	0,455	0,239	-	-
Anagrelide	0,216	-0,429	-	-

Statistical analysis: Pearson's correlation coefficient

ET: Essential Thrombocytosis, C: Control, IMA: Ischemia Modified Albümin, ABSU: Absorbans Unite, ASA: Acetylsalicylic Acid, SD: Standart Deviation

DISCUSSION

When ET patient group and C group were compared in our study; IMA levels were significantly higher in the ET patient group (p<0,001). This situation reinforces the thesis that there is a predisposition to thrombosis in ET patient group. Age is one of the factors affecting survival in ET patient group. Risk of complications increases as the duration of disease extends (14,15). There were few studies showing that there is no correlation between IMA concentration and age (16). Our study is in parallel with the literature in terms of the relationship between age variation and IMA levels (p:0,826).

A relation among chronic inflammation, obesity, insulin resistance and diabetes mellitus was shown (17, 18). In our study; glucose and triglycerides values were detected as significantly high in ET patient group (p:0,026, p:0,004). This can be explained by insulin resistance and atherosclerosis background caused by chronic inflammation. When the close relationship of chronic inflammation with insulin resistance and inflammation with cardiovascular diseases is considered; impaired glucose tolerance development can be expected in MPN patients and prospective studies are needed for this topic. In many diseases such as diabetes mellitus (DM) and hypertension (HT), level of IMA increases (38). In our study; 12 patients had DM, 3 patients had HT and 5 patients had both DM and HT. When effect of comorbid diseases on level of IMA was investigated; no significant difference was detected (p:0,456). C-reactive protein (CRP) increase in MPN patients is believed to be related with in vivo cell activation because of clonal myeloid proliferation (19). In a study of Barbui et al., high sensitivity CRP (hs CRP) levels were found to be substantially similar with JAK2V617F allele burden (20). According to this; chronic inflammation can be a secondary condition elicited by clonal cells. But leukocyte and platelet increase in MPNs cannot only reflect clonal myeloid proliferation. Due over cytokine production of these neoplasms; chronic inflammation may occur (19, 20). In general population; Hyperuricemia is associated with chronic inflammation, cardiovascular diseases and kidney diseases (17). In our study; uric acid levels in ET patient group were significantly high (p:0,002). This can be due to chronic inflammation in addition to high cell turnover in ET. Two of the factors that affect surveillance in ET are low hemoglobin level (in female <12 g / dL and in males <13.5 g / dL) and number of leukocytes >15000 u/L. In the general population leukocytosis is a well-known risk factor for cardiovascular disease (21). And it has been shown to be an important risk factor for the development of thrombosis in patients with MPN in recent studies (22, 23). When effect of leukocyte count and hemoglobin values in ET patient group in our study was investigated; no certain cut-off value was detected which was effective on IMA. In some clinical studies about ET recently; the relation

between chronic inflammation and thrombosis susceptibility had been investigated.

CONCLUSION

In our study, the IMA levels in the ET patient group were significantly higher than the control group. IMA levels may be considered in future studies as a possible early marker candidate for increased tissue hypoxia and thrombosis susceptibility in ET patients. In tissue ischemia; chronic inflammation also plays a role. As a limitation of our work; any inflammatory and tissue hypoxic marker or molecule is not studied. The effects of chronic inflammation on ischemia can be more clearly defined by the simultaneous study of markers of inflammation and tissue hypoxia, IMA.

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