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Research Article

Carotid Intima-media Thickness and Thrombosis Risk in Polycythemia Vera and Essential Thrombocythemia

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Abstract

Objectives: Thrombotic complications are the most important cause of morbidity and mortality in patients with polycythemia vera (PV) and essential thrombocythemia (ET). Carotid intima-media thickness (CIMT) is a surrogate marker used in the noninvasive assessment of subclinical atherosclerosis and cardiovascular event risk. This study aimed to evaluate CIMT in patients with PV and ET and to investigate its usefulness in risk stratification.

Methods: This study was conducted at the Hematology Clinic of Istanbul Training and Research Hospital, Health Sciences University, with patients diagnosed with PV and ET and a control group. CIMT measurement by ultrasonography was performed at the Radiology Clinic of Istanbul Training and Research Hospital, Health Sciences University. The study included 84 patients diagnosed between July 2006 and December 2016, including 42 with PV and 42 with ET, and 46 individuals in the control group.

Results: The median age of the patients was 57 years (min-max, 24-82); 38 were male (45%), and 46 were female (55%). Sixty individuals (71%) had a positive JAK2 mutation. There was no statistically significant difference in CIMT between the patient and control groups (0.83 vs. 0.85 mm; p=0.470). When the relationship between risk factors associated with increased CIMT was examined, a significant increase in CIMT was found in patients with JAK2 mutation, hypertension, and diabetes mellitus (DM) (p<0.05). In the correlation analysis between CIMT increase and age, CIMT was found to be correlated with age (p<0.001, r=0.647). In the univariate analysis, age (B=0.584, p<0.001), JAK2 mutation (B=0.319, p=0.003), hypertension (B=0.395, p<0.001), and DM (B=0.311, p=0.004) were significantly associated with increased CIMT. However, in the multivariate analysis, only age was found to be an independent predictor of increased CIMT (B=0.584, p<0.001).

Conclusion: The lack of an independent association between thrombotic tendency and CIMT in patients with PV and ET suggests that thrombotic risk may not be explained solely by subclinical atherosclerosis.

Keywords: Carotid intima-media thickness (CIMT), essential thrombocythemia (ET), polycythemia vera (PV)

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The majority of patients with BCR-ABL-negative classical chronic myeloproliferative neoplasms (MPNs) are those with polycythemia vera (PV) and essential thrombocythemia (ET); in these patients, the most important causes of morbidity and mortality are thrombotic complications, such as acute coronary syndrome and ischemic stroke.[1-6] Although the pathogenesis of clonal proliferation in PV and ET has not been fully elucidated, the JAK-STAT signaling pathway is known to be an important mechanism. The annual incidence of cumulative thrombosis is approximately 2.5-5% in patients with PV and around 1.9-4% in patients with ET.[1,7-9] Advanced age (>60 years) and a history of thrombosis are the most important risk factors for thrombosis development in both PV and ET.[1,4,7,8,10,11]

Atherosclerosis-related diseases, primarily coronary heart disease and ischemic stroke, are among the most important causes of morbidity and mortality, especially in developed countries.[12-14] The evaluation of carotid arteries by ultrasound and measurement of carotid intima-media thickness (CIMT) for the detection of subclinical atherosclerosis are widely used because of their noninvasive nature, use of nonionizing radiation, low cost, easy accessibility, and lack of disruption to bodily integrity.[13,15-19]

Considering that thrombotic events are a serious cause of morbidity and mortality in PV and ET, CIMT may be important in risk assessment in this patient group. This study aimed to evaluate carotid intima-media thickness in patients with PV and ET and to investigate the usefulness of CIMT in risk assessment.

Methods

This study was conducted at the Hematology Clinic of Istanbul Training and Research Hospital, Health Sciences University, with patients diagnosed with PV and ET and a control group, in accordance with the Declaration of Helsinki. The study protocol was approved by the Istanbul Training and Research Hospital Clinical Research Ethics Committee (Date: 11.11.2016, Approval Number: 2011-KAEK-50).

Ultrasonography-based CIMT measurement was performed at the Radiology Clinic of Istanbul Training and Research Hospital, Health Sciences University.

Patients

A total of 84 patients, including 42 with PV and 42 with ET, who were diagnosed between July 2006 and December 2016 and presented for follow-up to the Hematology Outpatient Clinic of Istanbul Training and Research Hospital, Health Sciences University, were included in the study. The 2016 WHO criteria were used for the diagnosis of polycythemia vera and ET, and patients who did not meet these criteria were excluded from the study. The 46 individuals included in the control group were selected from those who applied to the Internal Medicine Outpatient Clinic of Istanbul Training and Research Hospital, Health Sciences University, and from healthcare professionals. Individuals who did not use any medication, had no additional diseases, and had no risk factors for increased CIMT were selected for the control group. Informed consent forms were signed by the volunteers. The demographic characteristics of the patients; JAK2 V617F and BCR-ABL gene mutation status; complete blood count; blood lipid profile; fasting glucose; medical history and medications used; history of thrombosis and its location, if any; and smoking history were recorded from patient files and the hospital's automation system.

Carotid Intima-media Thickness Measurement

Carotid intima-media thickness measurement was performed at the Radiology Clinic of Istanbul Training and Research Hospital, Health Sciences University, by the same specialist radiologist. As defined by the Mannheim consensus, it was measured from the distal wall of both common carotid arteries 1 cm proximal to the carotid artery bifurcation.[20] (Fig. 1)

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA, 2013). Descriptive statistics were performed for the characteristics of the patient groups. Median (min-max) values and proportions (percentages) were used for the descriptive statistics of the data. Independent samples t-tests, Kruskal-Wallis tests, and

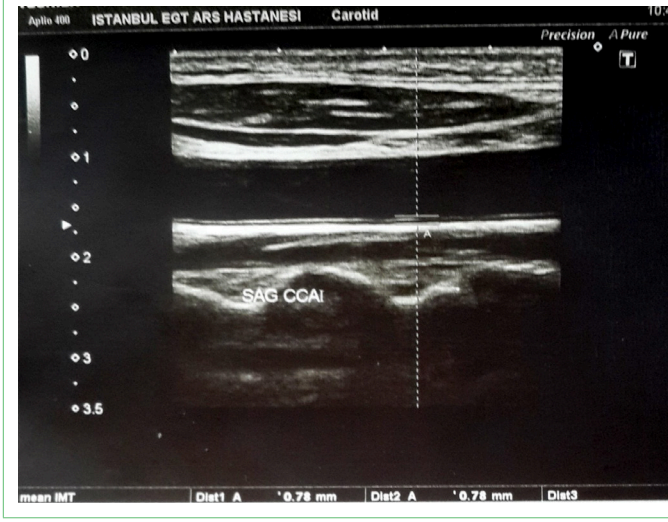

Figure 1. Carotid intima-media thickness measurement using ultrasonography.

Mann-Whitney U tests were used in the analysis of quantitative independent data, while chi-square tests were used in the analysis of qualitative independent data. The relationship between carotid intima-media thickness and certain risk factors was investigated using correlation analysis. Linear regression analysis was performed to examine the effects of classical and potential risk factors on CIMT. A p-value of 0.05 was used as the significance level. Foreign language support and writing assistance in this study were provided with the aid of Claude Sonnet 4.6 (Anthropic), a large language model.

Results

A total of 84 patients, including 42 with PV and 42 with ET, and 46 healthy individuals were included in the study. The median age of the patients was 57 years (range, 24-82), with 38 males (45%) and 46 females (55%). Sixty patients (71%) had a positive JAK2 mutation, while 11 patients (13.1%) had a history of thrombosis. The number of patients with a history of HT was 39 (46.4%), 20 patients (23.8%) had a history of DM, 29 patients (35%) had a history of hyperlipidemia, 26 patients (31%) were obese according to body mass index, and 19 patients (22.6%) were smokers (Table 1).

Hematological and biochemical parameters at the time of measurement did not show a significant correlation with CIMT.

Information comparing age, sex, and CIMT values of the patient subgroups and the control group is summarized in Table 2. No statistically significant difference was found in CIMT between the PV, ET, and control groups.

When the relationship between risk factors associated with increased carotid intima-media thickness was examined, a significant increase in CIMT was found in patients with JAK2 mutation, HT, and DM ($p<0.05$) (Table 3).

In the correlation analysis performed with age, disease duration, lipid levels, Hb, Hct, WBC, and platelet counts during USG, which may be related to increased carotid intima-media thickness, age was found to be correlated with CIMT ($p<0.001$, $r=0.647$).

When the relationship between risk factors and CIMT was examined in the patient group, univariate and multivariate analyses were performed for the factors found to be significant. In the univariate analysis, age, sex, JAK2 mutation, HT, and diabetes were evaluated. For age, B=0.584 and $p<0.001$.

Table 1. General characteristics of patients

Number of patients	**n= 84**
Median age, years, (min-max)	57 (24-82)
Gender, n (%)	
Male	38 (45%)
Female	46 (55%)
MPN subtype, n (%)	
PV	42 (50%)
ET	42 (50%)
JAK-2 mutation, n (%)	
Yes	60 (71%)
No	24 (29%)
History of thrombosis, n (%)	
Yes	11 (13.1%)
No	73 (86.9%)
HT, n (%)	
Yes	39 (46.4%)
No	45 (53.6%)
DM, n (%)	
Yes	20 (23.8%)
No	64 (76.2%)
Hyperlipidemia, n (%)	
Yes	29 (35%)
No	55 (65%)
Body mass index, n (%)	
<30 kg/m^2	58 (69%)
> 30 kg/m^2	26 (31%)
Smoking, n (%)	
Yes	19 (22.6%)
No	65 (77.4%)

MPN: Myeloproliferative neoplasm; PV: Polycythemia vera; ET: Essential thrombocythemia; JAK-2: Janus Kinase 2 gene; HT: Hypertension; DM: Diabetes mellitus.

Table 2. Comparison of demographic characteristics and CIMT between patient subgroups and the control group

	PV n=42	**ET n=42**	**Control group n=46**	**p**
Median age, years (min-max)	57 (27-74)	58 (24-82)	55 (26-77)	0.672
Gender, n (%)				
Male	21 (%50)	25 (%59.5)	24 (%52.2)	0.655
Female	21 (%50)	17 (%40.5)	22 (%47.8)	
CIMT, median (min-max)	0.78 (0.5-2)	0.85 (0.42-1.13)	0.85 (0.33-1.21)	0.782

PV: Polycythemia vera; ET: Essential thrombocythemia; CIMT: CIMT: Carotid intima-media thickness.

Table 3. Relationship between CIMT and risk factors

n=84	CIMT Median, mm	CIMT Min-max, mm	p
Gender			
Female	0.83	0.42-2	0.828
Male	0.8	0.33-1.13	
Body mass index			
<30 kg/m^2	0.82	0.42-2	0.289
>30 kg/m^2	0.83	0.6-1.13	
JAK-2 mutation			
Yes	0.85	0.54-2	**0.001**
No	0.72	0.42-1.13	
Thrombosis			
Yes	0.85	0.5-1.06	0.790
No	0.81	0.42-2	
HT			
Yes	0.92	0.6-2	**0.000**
No	0.73	0.42-1.13	
DM			
Yes	0..89	0.7-2	**0.009**
No	0.78	0.42-1.13	
Hyperlipidemia			
Yes	0.85	0.42-2	0.083
No	0.78	0.5-1.13	
Smoking			
Yes	0.80	0.42-1.13	0.295
No	0.85	0.5-2	

CIMT: Carotid intima-media thickness; JAK-2: Janus Kinase 2 gene; HT: Hypertension; DM: Diabetes mellitus.

Discussion

This study found that carotid intima-media thickness values in patients with PV and ET were similar to those in the control group. Considering that PV and ET are high-risk diseases for thrombosis, the failure to demonstrate an increase in CIMT suggests that the tendency for thrombosis may not be directly related to structural atherosclerotic changes.

In subgroup analyses, higher CIMT values were found in patients with hypertension, diabetes, and JAK2 mutation. However, in the multivariate analysis, only age was found to be an independent predictor of increased CIMT. The literature has demonstrated a strong and linear relationship between age and CIMT.[12,14,21] This finding supports that the increase in CIMT in our study primarily reflects age-related vascular changes.

The association between hypertension and increased CIMT has been well established in the literature.[13,22-25] The association between diabetes and increased CIMT has also been well established.[14,16,19,26-28] In our study, these variables were also found to be significant in the univariate analysis but failed to maintain their independence. Similarly, while the higher CIMT values observed in JAK2-positive patients are noteworthy, the fact that this relationship was not independent in the multivariate analysis suggests that the observed increase may be related to accompanying classical cardiovascular risk factors.

The relationship between the JAK2 mutation and thrombosis has been demonstrated in previous studies.[29-34] However, the finding in our study that JAK2 positivity did not constitute an independent structural atherosclerotic burden via CIMT raises the possibility that the thrombosis-enhancing effect of this mutation may occur through inflammatory, endothelial dysfunction, and procoagulant mechanisms rather than structural atherosclerosis.

No statistically significant association was found between obesity, hyperlipidemia, male sex, smoking, and CIMT in our study.

One of the strengths of this study is that CIMT was evaluated in patients with PV and ET in comparison with a control group, and the effects of potential confounding factors were examined using multivariate analysis. Furthermore, the inclusion of a disease-specific molecular variable, such as the JAK2 mutation, in the analysis contributes to the biological interpretation of the findings. However, the cross-sectional and single-center design of the study limits the establishment of causal relationships. The limited sample size and the fact that CIMT reflects only the structural atherosclerotic burden are among the other limitations of the study.

Conclusion

In conclusion, the fact that the presence of PV and ET alone is not associated with an increase in CIMT suggests that the development of thrombosis in these diseases may not be fully explained by classical atherosclerotic burden. Larger prospective studies evaluating the role of disease-specific biological processes in the pathogenesis of thrombosis are needed.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Istanbul Training and Research Hospital Clinical Research Ethics Committee (Date: 11.11.2016, Approval Number: 2011-KAEK-50).

Informed Consent: Informed consent forms were signed by the volunteers.

Conflict of Interest: The author declare that there is no conflict of interest.

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Use of AI for Writing Assistance: The authors used Claude Sonnet 4.6 (Anthropic) to provide foreign language support and writ-

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Authorship Contributions: Concept: MB, ES; Design: MB,ES; Supervision: ES; Fundings: MB; Materials: MB; Data Collection and/or Processing: MB, OK; Analysis and/or Interpretation: MB, ES; Literature Search: MB, ES; Writing: MB; Critical Reviews: MB, OK, ES.

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