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Role of endothelial dysfunction in relation to prothrombogenesis in polycythemia vera

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Abstract:

BACKGROUND: The morbidity and mortality in polycythemia vera (PV) are closely associated with cardiovascular diseases burden and clonal evolution. These complications were primarily attributed to abnormal rheology consequent to the raised hematocrit, leukocytosis, and thrombocytosis, and *in vivo* activation of leukocytes, thrombocytes, and endothelial cells. It has been established that damage of endothelium determines the release in circulation of specific markers including thrombomodulin (TM), selectins, and von Willbrand factor (vWF) which are released and favor the formation of cellular aggregates.

OBJECTIVES: The objective of this study is to evaluate the pathophysiological role of endothelial dysfunction (ED) in relation to increased risk of thrombosis in PV patients.

PATIENTS AND METHODS: In a case–control study, 53 patients enrolled in this study from Al-Imamain Al-Khadimiyan Medical City, and the National Center for Hematology Diseases and Researches. They comprised of thirty patients with PV with mean age of – 54.87 ± 13.44 years-and another twenty-three patients with secondary polycythemia, whose mean age was 40.13 ± 12.21 years. Another thirty aged- and sex-matched, non-smokers healthy volunteers comprised 16 males and 14 females were also studied, their mean age was = 52.1 ± 11.16 years. JAK2 mutation was assessed for PV group while Serum erythropoietin (Epo), vWF and TM were determined for all patient and control group.

RESULTS: TM was significantly different among the three studied groups ($P < 0.001$) as well as vWF was significantly higher ($P < 0.001$) in patients with PV as compared to the patients with secondary polycythemia and controls. Epo level was significantly lower ($P = 0.004$) in the newly diagnosed patients with PV when compared to those with a history of thrombosis or longstanding disease. There is positive correlation between *JAK2* and TM ($r = 0.431$, $P = 0.017$), while negative correlation with vWF ($r = -0.565$, $P = 0.001$) in PV patients.

CONCLUSION: ED is one of mechanisms that contribute in prothrombogenesis in PV patient.

Keywords:

Endothelial dysfunction, polycythemia vera, thrombogenesis, thrombomodulin, von Willbrand factor

Introduction

Polycythemia vera (PV) is characterized by uncontrolled and autonomous hematopoiesis, especially erythropoiesis leading to hyperviscosity and an increased risk of thrombosis.[1-4]

In 2005, an acquired *JAK2* mutation (termed *JAK2*^{V617F}) was reported in association with PV and related myeloproliferative neoplasms (MPNs). After phosphorylation, it results in continuous signaling by signal transducer and activator of transcription leading to an uncontrolled proliferation of the erythroid cells independently of erythropoietin (Epo).[5,6]

PV is almost always associated with a *JAK2* mutation (98% *JAK2*^{V617F} and 2% other *JAK2* mutations including exon 12 mutations).[7-9]

The morbidity and mortality in PV are closely associated with cardiovascular diseases (CVD) burden and clonal evolution.[10,11]

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They are - attributed to abnormal rheology consequent to the raised hematocrit, leukocytosis, and thrombocytosis, and *in vivo* activation of leukocytes, thrombocytes, and endothelial cells (ECs).[12,13]

The active *JAK2* mutation signaling may directly activate platelets and granulocytes, and indirectly lead to endothelial activation - through binding to ECs [14,15] leading to endothelial injury, endothelial expression of tissue factor, and endothelial release of procoagulant factors such as von Willebrand Factor (vWF)[16,17] as well as releasing other markers such as thrombomodulin (TM) and selectins that favor the formation of cellular aggregates.[18-20]

Endothelial dysfunction (ED) is characterized by - reduced vasodilation, as proinflammatory state with prothrombotic properties. It is associated with most forms of CVD, such as hypertension, coronary artery disease-peripheral vascular disease and diabetes, etc.[21,22]

The release of TM, selectins, and vWF from damaged endothelium will contribute in -pathogenesis of thrombosis in MPNs.[23]

TM is a surface, glycosylated protein that synthesized predominantly, but not exclusively by ECs.[24-26]

It characterized by three independent anticoagulant activities: catalyzing thrombin-induced activation of protein C to activated protein C, binding with thrombin to prevent the conversion of fibrinogen to fibrin and activation of platelets, FV, FVIII, FXI, and FXIII, and catalyzing the inhibition of thrombin by antithrombin.[27,28]

The vWF is a large glycoprotein - that mediates platelet tethering, translocation and finally adhesion to areas of injured endothelium under physiological high arterial blood flow conditions.[29] It is synthesized by ECs and megakaryocytes.[30]

vWF performs its hemostatic function through binding to factor VIII, to platelet surface glycoproteins, and to constituents of connective tissue.[31]

This study aimed to evaluate the pathophysiological role of ED in relation to increased risk of thrombosis in PV patients.

Patients and Methods

In a case–control study, 53 patients were recruited from the outpatient clinic of the Clinical Hematology in Al-Imamain Al-Khadimiyan Medical City, and the National Center for Hematology Diseases and Researches, College of Medicine, Al-Mustansyria University. They comprised of thirty patients with PV (13 males and 17 females with age range between 18 and 78 years with mean age of 54.87 ± 13.44 years) and another twenty three patients with secondary polycythemia (22 males and one female with age range between 25 and 65 years with mean age 40.13 ± 12.21 years).

Polycythemia had confirmed clinically by expert hematologist and via the laboratory parameters according to the WHO, 2008 criteria for polycythemia[32,33] to define either primary or secondary type.

The patient was randomly selected as it defined with Hb 18.5 g/dL in men, 16.5 g/dL in women, or other evidence of increased red cell volume for newly diagnosed cases.

The PV patients group was subdivided into three subgroups (long standing who are under follow-up, those with thrombotic complication and newly diagnosed). The long-standing subgroup (13 patients) include those patients whose the diagnosis is already established for a long time. While the second subgroup for those with thrombotic events (7 patients), it includes any PV patients who had previous or recent thrombotic complication like (stroke, pulmonary embolism, DVT, etc.). The last subgroup included all newly diagnosed cases (10 patients).

Another thirty age- and sex-matched, non-smokers healthy volunteers comprised 16 males and 14 females were also studied. Their ages were between 20 and 68 years (mean ± standard deviation [SD] = 52.1 ± 11.16 years).

For all patients, and control group, CBC parameters were recorded, in addition, to report of JAK2 mutation for PV group (Quantitative PCR kit, Bioneer company/Korea). Serum Epo (Human EPO ELISA Kit, Elabscience, China), vWF (Human vWF ELISA Kit, Elabscience, China), and TM (Human TM ELISA Kit, Elabscience, China) were assessed for all patients.

The work was done in laboratories of Al-Imamain Al-Khadimiyan Medical City, and the National Center for Hematology Diseases and Researches, College of Medicine, Al-Mustansiriya University.

The study design is already approved by institutional review board by Al Nahrian University, college of medicine. All patients were informed and verbal consent was taken before enrollment in this study.

All statistical analysis was performed using statistical package for social science software (version 16, Chicago, SPSS Inc). Continuous variables were expressed by means ± SD. The analysis of variance test was used to compares between different groups where there is continuous variable. The association between different variables was examined with binary correlation test.

The causal relationships between some variables were investigated with regression test. $P < 0.05$ was considered statistically significant.

Results

Epo level was significantly higher ($P < 0.001$) in patients with secondary polycythemia than patients with PV and controls. Meanwhile, no difference was noticed between the latter two groups [Table 1].

TM was significantly different among the three studied groups ($P < 0.001$) as well as vWF was significantly higher ($P < 0.001$) in patients with PV as compared to the patients with secondary polycythemia and control subjects but no difference in their level was noticed between the latter two groups [Table 1].

Epo level was significantly lower ($P = 0.004$) in the newly diagnosed patients with PV when compared to those with a history of thrombosis or longstanding disease. While no difference between the latter 2 groups. On the contrary, vWF was significantly higher ($P = 0.001$) in those newly diagnosed as compared with the other two subgroups in whom no difference was demonstrated in Table 2.

On the other hand, TM level was significantly lower ($P < 0.001$) in those with the longstanding disease when compared to the other two subgroups. Moreover, the latter two subgroups show no difference in the level of TM as shown in Table 2.

Considering ED markers (TM and vWF), patients with PV demonstrate positive correlation between *JAK2* and TM (r = 0.431, $P = 0.017$). In addition, TM was negatively correlated with vWF ($r = -0.565$, $P = 0.001$) as shown in Table 3 and Figures 1 and 2.

Unlike significant realtionship in primary polycythemia; in secondary polycythemia group, there was no correlation reported between Epo and either TM or vWF as parameters of ED (r = 0.089, $P = 0.688$ and r = 0.186, $P = 0396$, respectively) as shown in Table 4 as well as in Control groups (r = 0.035, $P = 0.854$, r = 0.154, $P = 0.417$, respectively) as shown in Table 5.

Table 1: Biochemical parameters of patients with polycythemia and control subjects

Parameter	Polycythemia patients		Control subjects (*n*=30)
	Primary (*n*=30)	Secondary (*n*=23)	
Epo (pg/ml)	2323.3±656.29	3355±271.05[‡]	2186.3±220.5
TM (pg/ml)	3327.4±222.58*	2875.7±302.1**	2223.7±338.9[ı]
vWF (ng/ml)	58.99±14.84[ǁ]	43.26±5.47	42.64±5.54

[‡]*P*<0.001 (secondary vs. primary polycythemia and control), **P*<0.001 (primary vs. secondary polycythemia), ***P*<0.001 (secondary polycythemia vs. control), [ı]*P*<0.001 (control vs. primary polycythemia), [ǁ]*P*<0.001 (primary vs. secondary polycythemia and control). Epo=Erythropoietin, TM=Thrombomodulin, vWF=von Willbrand factor

Table 2: Biochemical parameters of polycythemia vera subgroups

Parameter	Polycythemia vera patients		
	Newly diagnosed (*n*=10)	with thrombosis (*n*=7)	Longstanding (*n*=13)
Epo (pg/ml)	1853±485.58[ǁ]	2838.1±414.14	2407.9±656.99
TM (pg/ml)	3659.5±232.59	3774.3±166.73	3483.9±123.06[‡]
vWF (ng/ml)	75.66±12.58[†]	50.93±8.68	50.52±5.35

[ǁ]*P*=0.004 (newly diagnosed vs. with thrombosis and longstanding), [‡]*P*=0.001 (longstanding vs. newly diagnosed and those with thrombosis), [†]*P*<0.001 (newly diagnosed vs. with thrombosis and longstanding). Epo=Erythropoietin, TM=Thrombomodulin, vWF=von Willebrand factor

Table 3: The correlations between JAK2 and erythropoietin with thrombomodulin and von Willebrand factor parameters in polycythemia vera group

Parameter	JAK2	Epo	TM	vWF
JAK2				
r	1	−0.040	0.431*	−0.048
P		0.834	0.017	0.802
Epo				
r		1	0.238	−0.307
P			0.205	0.099
TM				
r			1	−0.565**
P				0.001
vWF				
r				1
P				

*Correlation is significant at the 0.05 level (two-tailed), **Correlation is significant at the 0.01 level (two-tailed). Epo=Erythropoietin, vWF=von Willebrand factor, TM=Thrombomodulin

Discussion

It is clear that Epo level is markedly higher in secondary polycythemia, a result which goes in accordance with that of other researchers,[34-36] which can signify that secondary polycythemia is limited to overproduction of RBCs as a consequence of a high secretion of Epo to achieve an improvement of the O_2 carrying capacity of the blood.

The TM level also found to be remarkably increased in PV when compared to other two groups, similar to Falanga *et al*. when compared with controls (57 ± 8 ng/ml vs. 27 ± 2 ng/ml).[37]

Physiologically, the endothelium facilitates blood flow by providing an antithrombotic surface that inhibits platelet adhesion and coagulation activation[38]. The increased hypercoagulable TM marker level confirm the ECs damage in PV patients which indicate an endothelium perturbation.[16]

In addition, membrane-bound TM is likely shed and released into the circulation by the action of leukocyte-derived proteases and cytokines from

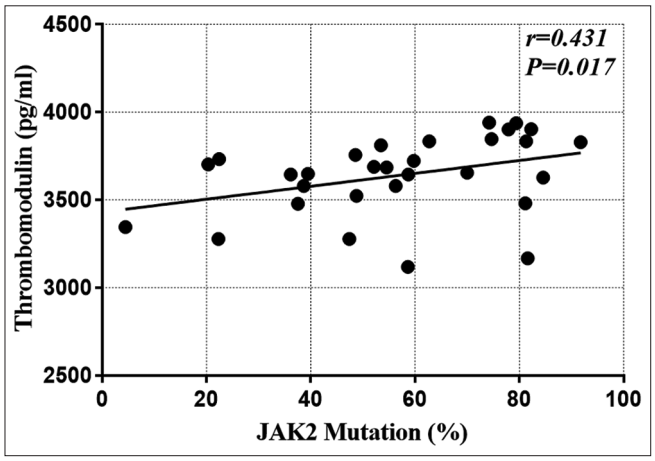

Figure 1: The correlation between *JAK2* mutation rate and thrombomoduin level in polycythemia vera group

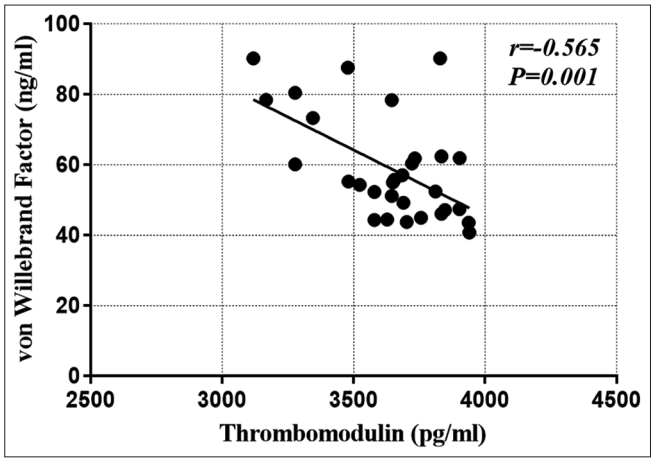

Figure 2: The correlation between thrombomodulin and von Willebrand factor levels in polycythemia vera group

Table 4: The correlations between erythropoietin with thrombomodulin and von Willebrand factor parameters in secondary polycythemia group

Parameter	Epo	TM	vWF
Epo			
r	1	−0.089	−0.186
P		0.688	0.396
TM			
r		1	−0.147
P			0.502
vWF			
r			1
P			

Epo=erythropoietin, vWF=von Willebrand factor, TM=thrombomodulin, Epo=Erythropoietin

Table 5: The correlations between erythropoietin with thrombomodulin and von Willebrand factor parameters in control group

Parameter	Epo	TM	vWF
Epo			
r	1	0.035	0.154
P		0.854	0.417
TM			
r		1	−0.324
P			0.080
vWF			
r			1
P			

Epo=Erythropoietin, vWF=von Willebrand factor, TM=Thrombomodulin

inflammation site that can induce detachment or lysis of ECs, affecting functions involved in thromboregulation. Hence, greater neutrophil activation could render PV patients more susceptible to vascular damage.[10,38]

Besides, high circulating levels of endothelial activation markers, such as TM, selectins, and vWF, are released and favor the formation of cellular aggregates as proved by other studies.[20]

An elevated TM level in secondary polycythemia as compared to the control group can be attributed to the hyperviscosity of blood that may cause shedding of the ECs membrane. However, smoking history has a positive significant correlation with TM levels. In addition to role of other accompanied chronic diseases (i.e., hypertension, diabetes mellitus and myocardial infarction) may enhance the shedding of ECs.[39,40] However still, there is no definite evidence that secondary polycythemia *per se* increases the risk of thromboembolism.[41]

Similar to the results of TM, marked increase in the level of vWF is documented in PV compared to the other two groups that is similar to report Falanga *et al*. in view of to control (180% ± 12% vs. 105% ± 13%, $P < 0.01$).[37]

Whenever there is vascular damage, vWF will get activated and facilitate platelets adhesion as well as aggregation.[42] In addition, to role of hyperviscosity induced by high hematocrit in PV.[43]

Constitutively, the active *JAK2* signaling may directly drive activation of platelets and granulocytes and indirectly lead to endothelial activation through platelet and leukocyte binding to ECs.[14,15,17]

Such interactions may provoke further endothelial injury by inducing detachment or lysis of ECs and may turn it into a proadhesive and procoagulant surface,[10] with increasing endothelial expression of TF, and release of procoagulant factors such as vWF. Furthermore, activated leukocytes, platelets, and ECs secrete microparticles, which express procoagulant factors important for forming the fibrin clot.[17,44]

Therefore, PV patient has some degree of ED induced by hyperviscosity as well as inflammation

resulting in overexpression of endothelial markers of prothrombogenesis such as TF, TM, and vWF that collectively contribute in relation to the effect of JAK2 mutation in increasing chance of thrombotic complication.[45]

Conclusion

Endothilial dysfunction is one of mechanisms that contribute in prothrombogenesis in polycythemia patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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