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The association between endothelial dysfunction and hypertensive retinopathy in essential hypertension

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Background: Endothelial dysfunction, which is characterized by an imbalance between relaxing and contracting factors, procoagulant and anticoagulant substances, and between pro-inflammatory mediators, may play a particularly significant role in the pathogenesis of atherosclerosis. Numerous experimental and clinical reports suggest that a high von Willebrand factor (vWF) level reflects endothelial damage or dysfunction. Hypertensive retinopathy (HR) is a condition characterized by a spectrum of retinal vascular signs in people with elevated blood pressure. The pathophysiological mechanism of HR is not completely understood. Elevated blood pressure alone does not fully account for the extent of retinopathy. Endothelial dysfunction and mechanisms known to be involved in vascular lesions may be involved in the pathophysiological mechanism of HR. Therefore, this study was designed to answer the following questions: (i) Do vWf levels change in HR? and (ii) Is there any relation between degree of HR and vWf levels?

Material/Methods: This study included 80 hypertensive patients with HR. Group 1 comprised 40 patients with grade I HR, and group 2 comprised 40 patients with grade II HR. We selected 40 healthy subjects for the control group.

Results: Level of vWf in group 2 was significantly higher than in group 1 ($p=0.017$) and the control group ($p<0.001$), and it was also higher in group 1 than in the control group ($p<0.005$). Also, vWf showed positive correlation with degree of HR in the hypertensive group ($r=0.284$, $p=0.009$)

Conclusions: Our study suggests that endothelial dysfunction, which is a mechanism known to be involved in vascular lesions, may promote the development of HR.

Key words: von Willebrand factor • endothelial dysfunction • hypertensive retinopathy

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Background

The vascular endothelium serves as an important autocrine and paracrine organ and maintains vascular homeostasis by modulating blood vessel tone, by regulating local cellular growth and extracellular matrix deposition, and controlling homeostatic and inflammatory responses [1]. Endothelial dysfunction (ED), which is characterized by an imbalance between relaxing and contracting factors, procoagulant and anticoagulant substances, and between pro-inflammatory mediators, may play a particularly significant role in the pathogenesis of atherosclerosis [2]. Under physiological conditions, the vascular endothelium produces many substances that are closely involved in hemostasis, fibrinolysis, growth factor synthesis, and the regulation of vessel tone and permeability. One of these substances is von Willebrand factor (vWf), which is synthesized by and stored in endothelial cells. vWf is a multimeric glycoprotein, and it is essential for platelet aggregation and adhesion [3]. Numerous experimental and clinical reports suggest that a high vWF level reflects endothelial damage or dysfunction. The vWF level has been proposed as an indicator of ED [4–6]. Elevated plasma levels of vWF are associated with established cardiovascular risk factors such as hypertension, diabetes mellitus and other endocrine diseases, hyperlipidemia, smoking, and pulmonary arterial hypertension [7–13]. Also, a high vWF level has been shown to have prognostic value in patients with ischemic heart disease, peripheral vascular disease, or inflammatory vascular disease [14].

Hypertension is a well known risk factor for cardiovascular and cerebrovascular events such as heart attacks and strokes. In addition, it is associated with earlier changes in organ systems in the body, such as left ventricular hypertrophy (LVH), proteinuria, and renal failure, retinopathy and vascular dementia, which are grouped under the term "target organ damage" (TOD) [15]. Hypertensive retinopathy (HR) is a condition characterized by a spectrum of retinal vascular signs in people with elevated blood pressure (BP) [16–18]. The pathophysiological mechanism of HR is not completely established. Elevated BP alone does not fully account for the extent of retinopathy. Recently studies have shown that the oxidative stress, low-grade inflammation, and increased platelet activation may be involved in the pathogenesis of HR [19–23]. Endothelial dysfunction, which is a mechanism known to be involved in vascular lesions, may be involved in the pathophysiological mechanism of HR. Therefore, this study was designed to answer the following questions: (i) Do vWf levels change in HR? and (ii) Is there any relation between degree of HR and vWf levels?

Material and Methods

Patients

This study was performed at the outpatient clinic of the Department of Internal Medicine of Akdeniz University Hospital. There were 654 adult hypertensive patients [systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg, according to the Eighth report of the Joint National Committee] [24] were registered in the computer files of our departments. Eighty hypertensive patients without exclusion criteria were invited to participate. None of the patients refused to participate in the study. The hypertensive patients were divided into 2 groups according to the Keith-Wagener classification [25]. Group 1 comprised of 40 hypertensive patients with grade I HR, and group 2 comprised of 40 hypertensive patients with grade II HR. Forty normotensive subjects, who were healthy participants and had undergone the checkup program, were used as the control group. The controls had similar body mass index (BMI), age, and sex distribution as the hypertensive group.

The exclusion criteria were: stage 2 hypertension (according to the Eighth report of the Joint National Committee) with BP >160/100 mmHg [24], grade 3 and 4 HR according to the Keith-Wagener Classification (as most of the patients had other complications that could interfere with the vWf results), diabetes mellitus, smoking (smokers and non-smokers were grouped by their current smoking status), alcohol intake more than 30 g/day, dyslipidemia, obesity (BMI ≥30 kg/m^2), cardiac-cerebral-renal (serum creatinine >1.5 mg/dl, blood urea nitrogen >30 mg/dl), and other systemic diseases, recent major surgery or illness, and patients on drugs affecting vWf levels.

Dyslipidemia was defined in the presence of at least 1 of the following conditions: raised plasma triglycerides (>200 mg/dl), total cholesterol (>200 mg/dl), low-density lipoprotein (LDL)-cholesterol (>130 mg/dl), and decreased high-density lipoprotein (HDL) cholesterol (<40 mg/dl for men and <50 mg/dl for women) [26].

Eligible subjects underwent a comprehensive assessment, including documentation of medical history, physical examination, and measurement of laboratory variables. Body weight and height were measured with the subjects in light clothes and without shoes. Body mass index was calculated as the weight (kg)/height squared (m)^2. The resting electrocardiograms of all the subjects were normal. The study protocol was approved by the Ethics Committee of Akdeniz University Faculty of Medicine. All patients gave their informed consent to participate in the study.

Measurement of blood pressure

Arterial BP was measured by a mercury sphygmomanometer after the patient had been in a sitting position for 5 min.

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Table 1. The main characteristics and laboratory results of the study groups.

Parameters	Group 1	Group 2	Control group
n (men/women)	40 (21/19)	40 (20/20)	40 (20/20)
Age (years)	53±2	52±9	53±1
Body mass index (kg/m^2)	25.7±3.1	25.3±3.2	25.4±3.0
Systolic blood pressure (mmHg)	150±4.6**	149±4.8†	127±4.9
Diastolic blood pressure (mmHg)	98±5.7**	98±5.6†	81±4.7
Duration of hypertension (year)	14.9±7.32	13.3±6.88	–
Fasting glucose (mg/dL)	87.4±9.7	87.9±9.8	87.5±9.6
Creatinine (mg/dL)	0.9±0.2	0.9±0.2	0.9±0.2
Alanine aminotransferase (U/L)	25.7±3.5	26.6±3.6	25.9±3.5
Total cholesterol (mg/dL)	170.0±22.5	169.4±22.8	169.8±22.9
LDL-cholesterol (mg/dL)	84.3±11.1	83.9±12.2	84.0±12.3
HDL-cholesterol (mg/dL)	50.2±5.2	50.8±5,0	50.4±5.1
Triglyceride (mg/dL)	127.9±15.8	128.0±16.2	127.7±16.7
vWf (%)	104.14±20.57*	117.26±24.47***,#	89.0±18.64

LDL – low-density lipoprotein (LDL)-cholesterol; HDL – high-density lipoprotein; vWf – von Willebrand factor. * p<0.005, Group 1 *vs.* control group; ** p<0.001, Group 1 *vs.* control group; *** p<0.05 Group 1 *vs.* Group 2; # p<0.001, Group 2 *vs.* control group.

For each subject, we recorded the average of 3 readings obtained within 5 min. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, as recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [24].

Funduscopic examination

For the HR evaluation, direct and indirect ophthalmoscopy was performed in all subjects after dilation of the pupils. A single-blinded observer performed the funduscopic examinations. The grade of HR was determined according to the Keith-Wagener classification [25].

Biochemical measurements

Blood samples were collected from the antecubital vein without the use of a tourniquet, between 08.30 and 09.00 hours, after an overnight fast to avoid the differences of diurnal variation. Enzymatic colorimetric assay method (Roche Diagnostic GmbH, Mannheim, Germany) was used to measure of lipid profile. Fasting glucose level was measured by the enzymatic colorimetric assay method (GLU, Roche Diagnostic GmbH, Mannheim, Germany). Serum vWf levels were measured quantitatively by STA-LIATEST [(Diagnostica Stago (France)]. All of the samples measured were done at the same run.

Statistical analysis

Statistical analysis was done by SPSS statistical software (SPSS for Windows 16.0, Chicago, IL, USA). For α=0.05 (between each group) and a power of 80%, a sample size per group >31 subjects was needed to detect an actual difference. The normality of the distribution was checked by stem and leaf plots, and also using the Kolmogorov-Smirnov test. vWf values across groups were compared with one-way analysis of variance (ANOVA) followed by the post-hoc Bonferroni test. In addition, Pearson's correlation was used to evaluate the correlation between vWf and grade of HR, and also the correlation between blood pressures and vWf levels. Summary data for vWf and other continuous variables are expressed as the mean ±SD. Statistical significance was defined as p<0.05.

Results

The main characteristics, BPs, and laboratory results of study populations are reported in Table 1. Age, gender distribution, and BMI did not differ among the groups. Similarly, metabolic parameters were not different among the study groups as a result of the selection process. Durations of known hypertension were not different among the hypertensive groups (14.9±7.32 *vs.* 13.3±6.88 year, p>0.05) and there was no correlation between vWf levels and duration of known hypertension (p>0.05).

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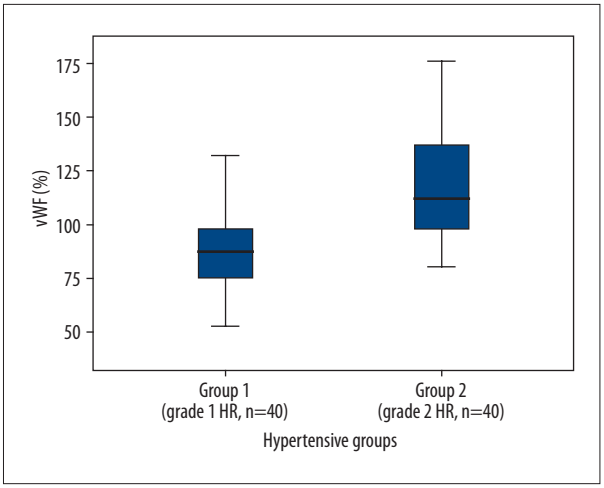

Figure 1. The correlation between von Willebrand factor (vWf) levels and grade of hypertensive retinopathy (HR) in hypertensive groups (Pearson's correlation test, (r=0.284, p=0.009).

The level of vWf in group 2 was significantly higher than in group 1 (117.26±24.47% *vs.* 104.14±20.57%, p=0.017) and the normotensive control group (117.26±24.47% *vs.* 89.0±18.64%, p<0.001) and it was also higher in group 1 than in the normotensive control group (104.14%±20.57% *vs.* 89.0±18.64%, p<0.005). Also, vWf showed a positive correlation with grade of HR in the hypertensive group (r=0.284, p=0.009) (Figure 1). There was no significant correlation between blood pressures (systolic and diastolic) and vWf levels (p>0.05).

Discussion

The vascular endothelium plays a role in the production of many essential substances involved in cardiovascular pathophysiology. One of these substances, which is synthesized by and stored in endothelial cells, is vWf [3]. It has been previously shown that increased vWF levels reflect ED and may also have prognostic value in patients with atherosclerotic disease [14]. Recent epidemiologic and clinical studies have reported a strong association between vWf and hypertension [27]. Our findings are consistent with previous work. However, this is the first study, to our knowledge, specifically to evaluate vWf levels in hypertensive patients with HR. Our study results demonstrate that hypertensive patients with retinopathy have increased vWf activity, a marker of ED. Also, vWf levels showed positive correlations with degree of HR in the hypertensive group. The endothelium is a major organ with an enormous surface area; therefore, it is highly unlikely that the vascular surface of the retina will in anyway influence vWf levels. However, retinopathy in essential hypertension may reflect systemic dysfunction of the vascular endothelium, a structure intimately involved in permeability, hemostasis, and fibrinolysis [28]. This abnormality may have important physiopathological implications and expose these patients to increased cardiovascular risk.

Few studies have explored the relationship between vWf and TOD in hypertensive patients. Spencer et al. found a relationship between TOD and the vWf in essential hypertension [29]. Similarly, Xu et al. reported a correlation between ED and TOD [30]. Left ventricular hypertrophy is an index of hypertensive TOD. Vaziri et al. reported that the levels of vWf were related to left ventricular mass index and left ventricular posterior wall and septal thickness in essential hypertension [31]. Microalbuminuria, another index of hypertensive end-organ damage, is also related to ED, suggesting that microalbuminuria reflects systemic dysfunction of the vascular endothelium. Pedrinelli et al. found higher vWf levels in hypertensive patients with microalbuminuria compared to hypertensive patients without microalbuminuria or controls [28].

In previous research, retinal signs have been linked to major risk factors of disability, including hypertension, diabetes, metabolic syndrome, heart disease, and stroke [18]. Hypertensive retinopathy is an important complication and a major site of target organ damage from hypertension. It is known that the autoregulation of the retinal circulation fails as BP increases beyond a critical limit. However, elevated BP alone does not fully account for the extent of HR [32–24]. There are cases in which retinopathy resolved despite the persistence of high BP [35]. Although the BP levels and duration of hypertension in group 1 and group 2 were similar, levels of vWf were higher in group 2 than in group 1 in our study. Thus, the presence of high vWf levels in HR and the correlation of the amount of vWf with the severity of HR imply that ED may be involved in the pathophysiological mechanism of HR. However, with the current data, it is not possible to know if high vWf levels are the cause or the results of HR.

This study has some limitations. Firstly, endothelial function can be measured in a variety of ways using invasive and non-invasive techniques [e.g. ultrasound flow-mediated dilation, flow-mediated magnetic resonance imaging, and biochemical markers of endothelial function (endotehelin-1, soluble E-selectin, soluble P-selectin] in the coronary and peripheral circulation [36]. Unfortunately, in our study we could not perform measurements using other techniques. Secondly, since we excluded patients with clinically overt cardiovascular-cerebrovascular diseases, diabetes mellitus, dyslipidemia, and other systemic diseases (these were excluded to clarify the specific levels of vWf-related abnormalities). However, hypertension is frequently associated with these diseases. For this reason, our results cannot be extrapolated

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to all hypertensive patients. However, regardless of the mechanism, higher vWf represent a risk factor for atherothrombotic disease. Thus, this limitation does not lessen the clinical relevance of our results. Thirdly, we accept that our study is a case-control design; it is not easy to predict exactly whether the high vWf levels precede retinopathy or vice versa. Future cohort studies will be helpful in providing an answer. Fourth, the study was conducted while the patients were taking antihypertensive treatment. However, distribution of drug use was similar in both hypertensive groups. Finally, grade 1–2 HR is not specific to hypertension.

Conclusions

Our findings suggest that there is a relationship between HR and vWf levels in essential hypertension. Endothelial dysfunction, which is a mechanism known to be involved in vascular lesions, may promote the development of HR. Future studies will determine whether or not vWf is a predictor of hypertensive vascular outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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