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Levels of adhesion molecules in peripheral blood correlat with stages of diabetic retinopathy and may serve as bio markers for microvascular complications

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ABSTRACT

Background: Proliferative diabetic retinopathy is a devastating complication of diabetes mellitus, developing within 15 years in 50% of patients with type 1 diabetes mellitus (DM) and in 10% of patients with type 2 DM. The correlation between levels of inflammatory markers in the peripheral blood and retinopathy staging has not been studied yet, and the purpose of this prospective study was to find a possible association between inflammation and staging of diabetic retinopathy.

Methods: A prospective (pilot) study that measured level of adhesion molecules in the peripheral blood of 10 healthy subjects and 30 patients with type 2 diabetes mellitus. Patients were grouped by the degree of retinopathy: 10 without retinopathy, 10 with non-proliferative retinopathy [NPDR] and 10 with proliferative retinopathy [PDR]. After signing the consent form, an ophthalmologic examination was performed, and 10 mL of blood was drawn. In order to assess adhesion molecules' level serum samples were collected, frozen, and stored at a temperature of −80 °C until analysis was performed as one batch.

Results: 10 healthy volunteers and 30 patients were enrolled. Healthy volunteers were younger (36.6 ± 7.9 years) compared to patients (no retinopathy 64.5 ± 10.8 years, NPDR 71.4 ± 8.9 years, and PDR 63.3 ± 11.6 years) ($p = .0003$ for all groups of patients in comparison with the healthy subjects). VCAM-1 levels were increased by retinopathy staging – starting from 81.86 ± 3.80 ng/ml (healthy), 105.55 ± 1.37 ng/ml (no retinopathy), 111.78 ± 4.14 ng/ml (NPDR), and 123.45 ± 3.99 ng/ml (PDR), with a significant difference between healthy and patients without retinopathy ($p = .03$), between no retinopathy and NPDR ($p = .001$), and between NPDR and PDR ($p < .0001$). E selectin was increased in correlation with severity of the retinopathy, with a significant difference between groups of patients ($p = .03$ between healthy subjects and T2DM patients without retinopathy, $p = .001$ between patients with T2DM no retinopathy and NPDR, $p < .0001$ between NPDR and PDR).

Conclusions: We found a significant increase in levels of adhesion molecules (VCAM-1) and selectins (E-selectin) in parallel with increased severity of diabetic retinopathy, with a significant difference of inflammatory markers between stages of retinopathy.

1. Introduction

Proliferative diabetic retinopathy is a devastating complication of diabetes mellitus, developing within 15 years in 50% of patients with type 1 diabetes mellitus (DM) and in 10% of patients with type 2 DM [1–3]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy has shown a 72% survival rate in older onset patients without retinopathy, and a 52% in patients with proliferative diabetic retinopathy [PDR] [4]. Patients older than 50 years had a higher rate of ischemic stroke with a strong correlation to the severity of the retinopathy [4,5]. The paradigm today is that there is a link between inflammation and retinopathy (and other micro-vascular and macro-vascular complications observed in diabetes) – however, the correlation between levels of inflammatory markers and retinopathy staging has not been studied yet, and the purpose of this prospective study was to find a possible association between inflammation and staging of diabetic retinopathy that will be studied step by step in different stages of retinopathy. If markers of inflammation will correlate with retinopathy staging – they will be used

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as biomarkers of diabetic retinopathy and microvascular complications.

2. Methods

A prospective study that studies levels of inflammatory markers in the peripheral blood of patients with type 2 diabetes mellitus. 10 healthy subjects (36.6 ± 7.9 years old) served as the control group, 10 diabetic patients without retinopathy (64.5 ± 10.8 years old), 10 diabetic patients with non-proliferative diabetic retinopathy (NPDR) (71.4 ± 8.9 years old), and 10 diabetic patients with proliferative diabetic retinopathy (PDR) (63.3 ± 11.6 years old). The study was approved by the ethics committee of the hospital and all subjects had to sign a consent form before enrollment. All subjects had an ophthalmologic examination by a specialized ophthalmologist in the outpatient clinic of the hospital. Neither of them had any laser treatment or injections of AVASTIN before enrollment to the study. After signing the consent form, an ophthalmologic examination was performed, and 10 mL of blood was drawn early in the morning after 12 h fast from the left cubital vein. In order to assess adhesion molecules' level serum samples were collected, frozen, and stored at a temperature of −80 °C until analysis was performed.

The concentration of adhesion molecules was determined (Human sVCAM-1/CD106 immunoassay kit (R&D Systems Minneapolis, MN, USA) with a sensitivity of minimum detectable dose (MDD) of sVCAM-1 ranged from 0.17 to 1.26 ng/mL. Human sE-Selectin/CD62E Immunoassay kit (R&D Systems, Minneapolis, MN, USA) with a sensitivity range of 0.003–0.027 ng/mL.

2.1. Data analysis

Statistical analysis was performed using the student T test for paired parameters. A p-value of < .05 was considered statistically significant.

3. Results

40 subjects were enrolled to the study. 10 healthy subjects served as the control group, 10 patients with type 2 diabetes mellitus had no retinal changes, 10 patients had mild retinal changes (non-proliferative retinopathy), and 10 patients had type 2 diabetes mellitus with proliferative retinopathy (Table 1). There was a significant age difference between the healthy subjects and all other groups (0.0003), but no difference in age between the 3 groups of patients (NS).

Table 2 summarizes the results of levels of the adhesion molecules and selectins measured in patients with type 2 diabetes mellitus at different stages of diabetic retinopathy.

We found that vascular cell adhesion molecule 1 (VCAM-1) was increased as the severity of the retinopathy was increased (Table 1) with a significant difference between the groups (p value of less than .0001).

The selectin E selectin was also increased in the same way – in correlation with severity of the retinopathy, with a significant difference between groups of patients (p = .03 between healthy subjects and T2DM patients without retinopathy, p = .001 between patients with T2DM no retinopathy and NPDR, p < .0001 between NPDR and PDR).

Table 1
Clinical characteristics.

	Healthy (10)	T2DM (10)	NPDR (10)	PDR (10)
Age (years)	36.6 ± 7.9	64.5 ± 10.8	71.4 ± 8.9	63.3 ± 11.6
P value	.0003	NS	NS	
No. females	5 (50%)	4 (40%)	3 (30%)	4 (40%)

Table 2
Level of Adhesion Molecules and Selectins in Patients with Type 2 DM.

	Healthy	T2DM	NPDR	PDR
Number	10	10	10	10
VCAM-1 ng/ml				
Mean	81.86	105.55	111.78	123.45
SD	3.80	1.37	4.14	3.00
P value between groups	< .0001	< .0001	< .0001	
E-selectin ng/ml				
Mean	24.64	27.22	32.86	59.09
SD	2.52	1.71	3.38	7.14
P value between groups	.03	.001	< .0001	

T2DM – type 2 diabetes mellitus.
NPDR – non-proliferative diabetic retinopathy.
PDR – proliferative diabetic retinopathy.

4. Conclusions

We found a significant increase in levels of adhesion molecules (VCAM-1) and selectins (E-selectin) in parallel with increased severity of diabetic retinopathy. Atherosclerosis is a long-standing process (for many years, starting during childhood) that starts with activation of endothelial cells with increased expression of adhesion molecules and selectins, that are first expressed in different cells' surfaces, but eventually shed from the cell surface to the blood. The increased expression and communication between different cells –monocytes, lymphocytes, macrophages, endothelial cells, platelets – leads to functional processes described as rolling, activation, firm adhesion, and transmigration of different cells involved in atherosclerosis [6–10]. The binding of these cells to the endothelium is through interaction of integrins on the cells' surfaces of white blood cells and adhesion molecules of the immunoglobulin family – intercellular cell adhesion molecule 1 and vascular cell adhesion molecule 1 – on one hand, and with selectins – on the other hand [9]. The firm adhesion step of white blood cells activated by different cytokines to the activated endothelium is conducted by the adhesion molecules that belong to the immunoglobulin superfamily – ICAM-1 and VCAM-1 – expressed on endothelial cells, adhering to integrins expressed on the white blood cells' surface, like LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18) – both adhere to ICAM-1, while VLA-4 (CD49/CD29) tends to adhere to the endothelial VCAM-1 [11].

Studies have shown a long-standing process of endothelial activation that leads to atherosclerosis – adhesion molecules sICAM-1 and VCAM-1 and E selectin were enhanced in children and adolescents with risk factors for atherosclerosis – obesity, hypertension, and diabetes [12,13]. Adults with advanced atherosclerosis showed a significant increase of cell adhesion molecules (sICAM-1 and VCAM-1) in patients with coronary artery disease who developed myocardial infarction or sudden death [14]. Paul Risker's study[15] that an increase in one of the adhesion molecules – sICAM-1 – in apparently healthy men predicted the development of myocardial infarction, and could serve as a biomarker that can predict a grave outcome.

VCAM-1 has been demonstrated to be involved in macrovascular complication of diabetes [16] and in the development of retinal vascular complications. The interaction of VCAM-1 with its ligand, integrin VLA-4, plays a key role in the progression to diabetic retinopathy (DR). In an animal model of DR, hyperglycemia upregulated VCAM-1 expression on blood vessels in the retina [17].

Besides, VLA-4 mediated increased leukocytes' adhesion to the retinal vessels, and blocking VLA 4 inhibited vascular inflammation [18]. In parallel to E selectin, increased levels of VCAM-1 have been found in diabetic patients with microvascular complications [19], and soluble VCAM-1 level is increased in the vitreous of patients with PD [20,21].

Soluble VCAM-1 has an angiogenic effect on endothelial cells through the VLA-4 dependent mechanism, in common with E selectin [22,23].

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