Blood sICAM-1 levels in type 2 diabetes mellitus patients with various grades of DME

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Background: *Diabetic macular edema (DME) is a major cause of visual impairment in type 2 diabetes mellitus (DM) patients. Non-specific inflammation is an important factor of the underlying processes of DME. Intercellular adhesion molecules (ICAM), particularly, soluble ICAM-1 (s-ICAM-1), are a local inflammatory mediator involved in the pathogenesis of diabetic injury to the layers of the eye. The literature is scant on the assessment of sICAM-1 blood levels in type 2 DM patients with diabetic injury to the neurovascular system of the eye.*

Purpose: *To investigate serum sICAM-1 levels in type 2 DM patients with various grades of DME.*

Materials and Methods: *Eighty-two type 2 DM patients (145 eyes) were involved in the study; they were divided into four groups based on DME severity. Patients underwent laboratory examination (glycated hemoglobin A1c, HbA1c) and comprehensive eye examination. Inclusion criteria were voluntary informed consent, age above 18 years, and presence of type 2 DM. Exclusion criteria were pregnancy, presence of endocrine disorders that may lead to type 2 DM (Cushing's syndrome, acromegalia, dispituitarism, polycystic ovaries syndrome, etc.), coagulation system impairment, neurodegenerative disorders of the central nervous system, type 1 DM, acute infectious disorders, cancer, decompensation of concomitant medical conditions, mental disorders, administration of neuroleptics and/or antidepressants, or presence of proteinuria, glaucoma or mature cataract. Serum sICAM-1 levels were determined by enzyme-linked immunosorbent assay (ELISA). Single-factor analysis of variance was used for statistical analysis.*

Results: *The median serum sICAM-1 level value for DME0 group (Me = 600.3 ng/mL (593.1 ng/mL – 610.1 ng/mL)) was statistically significantly (p = 0.01) higher than for conventionally amalgamated (DME1 – DME3) group (Me = 558.5 ng/mL (506.9 ng/mL – 607 ng/mL)).*

Conclusion: *The median serum sICAM-1 level value for patients with DME0 (Me = 600.3 ng/mL (593.1 ng/mL – 610.1 ng/mL)) was statistically significantly (p = 0.01) higher than for those with DME1 to DME3 (Me = 558.5 ng/mL (506.9 ng/mL – 607 ng/mL)).*

Introduction

Diabetic macular edema (DME) is a major cause of visual impairment in diabetic patients as type 2 diabetes mellitus (DM) has a high prevalence worldwide. The available data on the principal pathogenetic components of DME evidence that non-specific inflammation is an important factor of the underlying processes of DME [1]. Intercellular adhesion molecules (ICAM), particularly, soluble ICAM-1 (s-ICAM-1), are a local inflammatory mediator involved in the pathogenesis of diabetic injury to the retina. ICAM-1 molecules are available at low concentrations on the membranes of white cells and endothelial cells. ICAM-1 expression on the cytoplasmic membrane abruptly increases after stimulation with cytokines, especially interleukin-1 (IL-1) and tumor necrosis factor (TNF). ICAM-1 is a ligand of lymphocyte function-associated antigen-1 (LFA-1) found on the white blood cells which after recruiting are activated, become bound to the endothelium due to the ICAM-1/LFA-1 complex, and penetrate to the site of inflammation [2]. Thus, the white cell adhesion mediated by ICAM-1 and

CD18 increases in the retina of diabetic mice or under conditions of experimental hypergalactosemia and may explain many of important blood-retinal barrier injuries in diabetic retinopathy [3]. Unfortunately, the literature is scant on the assessment of sICAM-1 blood levels in type 2 DM patients with diabetic injury to the neurovascular system of the eye [4].

Purpose: To investigate serum sICAM-1 levels in type 2 DM patients with various grades of diabetic macular edema.

Materials and Methods

Eighty-two type 2 DM patients (145 eyes; mean age, 65.25±10.85 years; mean diabetes duration, 14.0±7.05 years; mean HbA1c, 8.40±1.58%) were involved in the study; they were divided into four groups based on DME severity. Patients underwent laboratory examination (glycated hemoglobin A1c, HbA1c) and comprehensive eye examination. They were divided into four groups based on DME severity as per the International Diabetic Macular Clinical Edema Severity Scale [5] (DME0, DME apparently absent; DME1, mild DME; DME2, moderate DME; DME3, severe DME).

Inclusion criteria were voluntary informed consent, age above 18 years, and presence of type 2 DM. Exclusion criteria were pregnancy, presence of endocrine disorders that may lead to type 2 DM (Cushing's syndrome, acromegalia, dispituitarism, polycystic ovaries syndrome, etc.), coagulation system impairment, neurodegenerative disorders of the central nervous system, type 1 DM, acute infectious disorders, cancer, decompensation of concomitant medical conditions, mental disorders, administration of neuroleptics and/or antidepressants, or presence of proteinuria, glaucoma or mature cataract.

This study was performed in full compliance with the treatment and examination guidelines provided in the Helsinki declaration (as revised in 2008) and relevant orders issued by the Ministry of Health of Ukraine (No. 281 issued 01.11.2000, No. 355 issued 25.09.2002, No. 356 issued 22.05.2009 (as revised in Order No. 574 issued 05.08.2009), and No. 1118 issued 21.12.2012).

HbA1c levels were measured by high-performance liquid chromatography, with Bio-Rad D10 analyzer (Bio-Rad Laboratories, CA) and assay. Serum sICAM-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) with IEMS Reader MF analyzer (Labsystems, Helsinki, Finland) and Human sICAM-1 Platinum ELISA Kit, Extra Sensitive (Bender MedSystem GmbH, Austria).

The eye examination included measurements of visual acuity, perimetry, tonometry, refractometry, biomicroscopy, gonioscopy, ophthalmoscopy, optical coherence tomography with angiography, and fundoscopy (with fundus photography).

Statistical analyses were performed using MedCalc v 18.11 software (MedCalc Software Inc, Broekstraat, Belgium). The Shapiro–Wilk test was used to control quantitative data for normality. Single-factor analysis of variance (Kruskal-Wallis test) was used to compute the differences among the three or more groups. Data are presented as median (Me) (with first quartile (Q1) and third quartile (Q3) in parenthesis) and minimum and maximum values. The level of significance $p \leq 0.05$ was assumed [6].

Results

Table 1 presents serum sICAM-1 levels in type 2 DM patients with various grades of diabetic macular edema.

There were no significant differences among groups of type 2 DM patients with various grades of DME in serum sICAM-1 levels ($p = 0.09$). However, the median serum sICAM-1 level value for DME0 group (Me = 600.3 ng/mL (593.1 ng/mL – 610.1 ng/mL)) was statistically significantly higher than for conventionally amalgamated (DME1 – DME3) group (Me = 558.5 ng/mL (506.9 ng/mL – 607 ng/mL)).

Discussion

The median serum sICAM-1 levels for our type 2 DM patients with DME were 2.34 to 2.61 times higher than the reference levels for healthy donors specified in kit instructions. In addition, the median serum sICAM-1 level value for conventionally amalgamated (DME1 – DME3) group was statistically significantly lower than for DME0 group.

It has been reported [7] than vitreous levels of both VEGF and sICAM-1 were significantly higher in patients with hyperfluorescent DME than in those with minimally fluorescent DME ($P = 0.0027$ and $P = 0.0005$, respectively). The vitreous levels of both VEGF and sICAM-1 were significantly correlated with retinal thickness at the central fovea ($P < 0.0001$ and $P = 0.0005$, respectively). These results suggested that VEGF and ICAM-1 are related to the increase of vascular permeability in DME patients [6].

In the study by Zhu et al [8], aqueous sICAM-1, VEGF and MCP-1 levels in DME group were statistically significantly higher than in controls [11].

Hiller et al [9] investigated aqueous humor cytokine level changes in response to intravitreal ranibizumab therapy for the management of DME. Aqueous ICAM-1 levels were decreased compared to baseline as early as month 2, and continued decreasing at month 3 [9].

In general, type 2 DM impairs the balance between neurotropic factors contributing to cell survival (neurotrophins) and proinflammatory mediators, leading to hyperactive inflammatory responses in the retinal endothelium, micro- and microglia, and emergence of inflammatory mediators, which causes increased vascular permeability, arrest of capillary blood flow ICAM-1, VCAM-1, PAI-1) [10, 11], apoptosis of endothelial cells, macular edema and neovascularization (VEGF).

Conclusion

The median serum sICAM-1 level value for DME0 group (Me = 600.3 ng/mL (593.1 ng/mL – 610.1 ng/mL)) was statistically significantly higher than for conventionally amalgamated (DME1 – DME3) group (Me = 558.5 ng/mL (506.9 ng/mL – 607 ng/mL)).

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All authors declare that they have neither financial nor non-financial competing interests.

Table 1. Serum sICAM-1 levels in type 2 diabetes mellitus patients with various grades of diabetic macular edema

Characteristi	Me (Q_I – Q_{III}) [Min; Max]				Level of significance, p
	DME0 (n=12)	DME1 (n=18)	DME2 (n=25)	DME3 (n=27)	
sICAM-1, ng/mL	600,3 (593.1–610.1) [581.2; 686.4]	558.45 (504.7–603.8) [453; 660.5]	569.4 (511.3–608.6) [470.9; 686.7]	539.4 (508.3–604.3) [463.1; 667.4]	0.09

Note: Kruskal-Wallis test was used to compute the differences among the three or more groups. Data are presented as median (Me), with first quartile (Q1) and third quartile (Q3) in parenthesis and minimum (Min) and maximum (Max) values in square brackets.