



Received: 2014.04.11
Accepted: 2014.07.07
Published: 2014.12.18

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Relationship between Initial Lens Transparency and Ocular Circulation in Adolescents with Type-1 Diabetes Mellitus, Unstable Glycaemia and Lipid Parameters

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Summary

Background:

The aim of this study was to determine the relationships between lens opacity, vascular and lipid factors and retrobulbar blood flow parameters in type-1 diabetic (DM) adolescents.

Material/Methods:

Glycated haemoglobin (HbA_{1c}), total cholesterol (TCH), high- and low-density cholesterol, triglycerides (TG) and apolipoprotein B (ApoB) were determined in 28 patients with (DM-1) and without (DM-0) lens opacity and 18 controls. In the ophthalmic, central retinal (CRA) and temporal posterior ciliary (TPCA) arteries, the systolic (PSV), end-diastolic and mean blood flow velocities as well as pulsatility and resistance (RI) indices were measured.

Results:

Ten (35.71%) diabetic patients exhibited lens opacification. Higher TG and TCH levels in the DM-1 group and HbA_{1c} level in the DM-0 and DM-1 groups were observed ($P \leq 0.05$). Diabetic patients had lower PSV and higher RI within CRA and TPCA ($P \leq 0.05$). Significant correlations between biochemical and blood flow parameters were found.

Conclusions:

Glycaemic and lipid factors may play a vasoconstrictive role in retrobulbar endotheliopathy.

MeSH Keywords:

Cataract • Diabetes Mellitus, Type 1 • Dyslipidemias • Hemoglobin A, Glycosylated

PDF file:

<http://www.polradiol.com/abstract/index/idArt/890852>

Background

Diabetes mellitus (DM) is a well-known risk factor for the development of lens transparency abnormalities or cataract, as suggested by the available epidemiological data showing an increased frequency of lens opacity in diabetic patients [1–3]. Hyperglycaemia is generally considered responsible for this increased risk, since both elevated polyol pathway activity in the lens and nonenzymatic glycation of lens proteins have been documented in the experimental and human diabetes [4].

According to the literature, the prevalence of incipient cataract in childhood or adolescent patients ranges from 0.7% to 16% for an age group of 0 to 19 years. However,

the above-mentioned numerical data depend mostly on the size of the analyzed groups [2,5,6]. Also, the so-called acute metabolic cataract in young patients may be a result of spontaneous improvement after starting intensive treatment [5,7,8].

The mechanism of the formation of lens pathology is multifactorial and the potential risk factors have been emphasized, e.g.: genetic predisposition, oxidative stress, long-term hyperglycaemia, poor control and inappropriate treatment of diabetes, lipid metabolism disturbances and nutritional status combined with steroid use. The correlation between lens opacity and diabetes has been documented in older subjects [2,6–13]. It is also known that hyperglycaemia, as seen in diabetes, inhibits the formation

Table 1. Description of examined groups (means were compared using ANOVA and Kruskal-Wallis rank sum test).

Analysed parameters	Group DM-0 (8 females and 10 males)			Group DM-1 (6 females and 4 males)			Control (10 females and 8 males)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Average age (years)	18	18.1	2.7	10	18.8	3.4	18	19.0	4.0
Insulin treatment (years)	18	8.0	2.2	10	8.5	2.5			
Duration of diabetes (years)	18	8.1	3.1	10	8.7	2.1			
Visual acuity	18	1.0	0.0	10	0.95	0.1	18	1.0	0.0
HbA _{1c} (%)	18	7.4 ^a	2.2	10	8.1 ^a	2.8	18	4.9 ^b	1.7
TCH (mg/dL)	18	194.7	35.6	10	203.9 ^a	48.1	18	160.2 ^b	51.0
HDL (mg/dL)	18	69.2	12.0	10	57.8	12.5	18	56.1	11.8
LDL (mg/dL)	18	83.9	25.6	10	99.9	40.9	18	96.4	36.2
TG (mg/dL)	18	109.3	55.0	10	157.1 ^a	111.4	18	98.3 ^b	43.1
ApoB (mg/dL)	18	77.1	18.1	10	86.5	29.4	18	86.5	29.4

^{a, b} Values marked with different letters within rows differ significantly at $P \leq 0.05$, DM-0 – diabetic patients without clinical lens opacity; DM-1 – diabetic patients with lens opacity; n – number of patients; SD – standard deviation; HbA_{1c} – glycated haemoglobin (reference values: 3.6% to 5.2%); TCH – total cholesterol; HDL – high density lipoprotein fraction cholesterol; LDL – low density lipoprotein fraction cholesterol; TG – triglycerides; ApoB – apolipoprotein B. For humans under 30 years of age, the reference values (mg/dL) are as follows: TCH ≤ 180 , HDL > 45 , LDL ≤ 100 , TG ≤ 150 and ApoB ≤ 100 .

of nitric oxide (NO) as well as decreases vascular smooth muscle cell sensitivity to NO, leading to vasoconstriction [14]. The important and additional risk factors for the development of macroangiopathy may be unstable plasma glucose levels and dyslipidaemia in the form of increased or fluctuating levels of cholesterol and triglycerides, whose presence may affect ocular haemodynamics [11]. However, it remains unknown whether glycaemic and lipid factors, along with their influence on vascular and ischemic complications in diabetes, have any impact on lens opacity in young patients, in relation to alterations in retrobulbar haemodynamics.

Hence, in this study, we investigated possible links between the selected biochemical parameters such as: glycated haemoglobin (HbA_{1c}), total cholesterol (TCH), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), apolipoprotein B (ApoB), as well as retrobulbar blood flow velocities and resistance indices in young insulin-dependent diabetic patients with clinical symptoms of incipient lens opacity and microvascular changes in the retina. The aforementioned relationships were then compared with those of healthy individuals.

Material and Methods

Twenty-eight type-1 insulin-dependent young diabetic patients (DM) divided into two groups (DM-0 and DM-1) were examined. The division was made according to the absence (DM-0) or presence (DM-1) of clinical lens opacity. Indirect ophthalmoscopic examination used to evaluate the ocular fundus revealed diabetic angiopathy (DA) in all patients (DM-0 and DM-1 groups), characterized by the dilation of the venules and their irregular calibre

documented by fluorescein angiography (AF). No diabetic retinopathy (DR) complications within either study group or any laser panphotocoagulation features were noticed. For comparison, a control group (CG) of 18 healthy volunteers with mean age and sex distribution similar to those of the DM-0 and DM-1 group was also analysed.

None of the subjects of the control group suffered from any cardiovascular disorders, hypertension or ocular trauma. Carotid or vertebral arterial diseases were excluded during the Colour Doppler Imaging (CDI). The application of topical ophthalmic or systemic medications was not recorded. A full description of all groups is presented in Table 1.

Since the diagnosis of diabetes, adolescent subjects of the DM-0 and DM-1 groups had been under constant long-term supervision of the Outpatient Diabetes Clinic at the Department of Ophthalmology. In all examined patients, ophthalmic examinations, laboratory blood tests and CDI measurements were repeated routinely every 6 months (cohort, prospective study). The follow-up period was eighteen months since lens opacity diagnosis and the means calculated from three consecutive measurements of blood flow parameters were used for statistical analysis. A written consent had been obtained from all the patients or their parents prior to examination. The study was approved by the Local Ethics Committee (F147/08).

Information on the course of diabetes and therapeutic management was collected from the medical records of the patients. Subsequent detailed examinations, including: visual acuity test with optimal correction, slit lamp examination, intraocular pressure measurement by Goldmann applanation tonometry, indirect funduscopy, fluorescein angiography and CDI were performed.

Table 2. Percentage of types of lens disorders in the examined patients (DM-1 group).

Types of lens opacification	Number of patients	Percentage
Subcapsular cloudiness ('snow-flake')	6 (P1 n=3 and P2 n=3)	21.43
Posterior capsular lens opacity	2 (P4 n=2)	7.14
Vacuolization of lens cortex	2 (C1 n=1 and C2 n=1)	7.14
Total	10	35.71

The classification of the type and grade of lens transparency was based on a direct slit lamp examination using the Lens Opacities Classification System III (LOCS III) [15], since we were not in the possession of equipment for the direct photographing of lens opalescence.

The evaluated data included: glycaemia (HbA_{1c}) and lipids (TG, ApoB, TCH, HDL and LDL fractions). The above-mentioned tests and CDI assessment took place in the morning, after overnight fasting, and before insulin and light meal were given [16]. The HbA_{1c} was measured with the use of EDTA-treated blood samples through haemolysis by FLPC (Pharmacia AB, Sweden). The values of TG, TCH, LDL, HDL, and ApoB were established using the Roche kits and the Clinilab automatic analyser (bioMerieux).

For retrobulbar CDI, the patients were examined in supine position with the probe placed on a closed eyelid after a 5-min delay to avoid fluctuation of arterial blood pressure [16]. Blood flow parameters such as: peak systolic velocity (PSV, cm/s), end-diastolic velocity (EDV, cm/s), mean velocity (MV, cm/s), pulsatility (PI) and resistance (RI) indices in the ophthalmic artery (OA), central retinal artery (CRA), and temporal posterior ciliary artery (TPCA) were performed by one and the same operator with great experience in a commonly applied CDI technique (Voluson apparatus, 10.5 MHz sector probe) [10–12]. Angle correction was applied to pulsed Doppler recordings to minimize errors in the measured velocities. PSV, also known as the maximum velocity, was defined as the highest value of blood flow velocity during the cardiac systole. EDV was determined as a minimum velocity and the lowest value of blood flow velocity during the cardiac diastole. MV was the mean value of blood flow velocity during the whole cardiac systole [16]. PI was the quotient of the difference between systolic and diastolic peak velocities in relation to the mean blood flow velocity:

$$PI = \frac{PSV - EDV}{MV}$$

RI was calculated as the quotient of the difference between the systolic and diastolic velocities in relation to the systolic peak [16]:

$$RI = \frac{PSV - EDV}{PSV}$$

All parameters for each of the examined vessels were generated by the computer within the ultrasound machine.

The normality of distribution of the data was verified with the Shapiro-Wilk test. The significance of differences

between the mean blood flow velocity and vascular resistance parameters was tested using ANOVA and Duncan's multiple range tests. We also used the Kruskal-Wallis rank sum test for non-normally distributed variables. The measured haemodynamic parameters were statistically analysed in the OA, CRA and TPCA separately for each eye. The coefficients of linear correlation or Spearman's rank correlation were computed between the blood flow indices for each artery and the biochemical blood parameters. Statistical significance of the coefficients and the differences was tested at the significance level of $P \leq 0.05$. The Statistica 10 software (StatSoft Inc., Tulsa, OK, USA) was used for analysis.

Results

The Snellen chart visual acuity of the subjects of CG and DM-0 groups was 1.0, whereas in the patients of DM-1 group it was 0.95 (SD±0.5; Table 1). The evaluated biochemical parameters within the study groups revealed strong variations, considerably exceeding physiological ranges in some cases. In the diabetic subjects (DM-1 and DM-0 groups), a statistically significant increase in the HbA_{1c} level was found compared with CG. Also significantly higher TCH and TG in DM-1 patients were observed (Table 1). The laboratory levels of HDL, LDL and ApoB did not exceed physiological ranges in either DM-0 or DM-1 group (Table 1).

The examination of the anterior segment of the eye in the slit lamp revealed that, among all diabetic patients, 10 (35.71%) were diagnosed with incipient symptoms of lens opacity according to LOCS III [15] (DM-1 group) and the remaining 18 (64.29%) did not exhibit cataract (DM-0 group). Bilateral lens changes were found in 2 patients and unilateral lesions were diagnosed in 8 subjects (Table 2).

Refractive error in the form of myopia (below minus 3.0 Dptr) was found in 8 DM-1 patients (0.33%) and emmetropia was observed in the remaining subjects. Intraocular pressure measured with the applanation method directly prior to CDI remained within the physiological range and its mean values were 13.8 mmHg (DM-0), 14.1 mmHg (DM-1) and 14.6 mmHg (CG). No statistically significant differences were found among them. Before CDI was performed, arterial blood pressure measurement had been done and the values remained below 120 mmHg and 75 mmHg (systolic and diastolic pressure, respectively).

Statistically significantly lower PSV in the CRA was found in patients of both diabetic groups, as compared with CG. MV was significantly altered in the DM-1 group in comparison with CG. In that artery, a significantly higher RI

Table 3. Mean values of blood flow velocity parameters in the ophthalmic artery, the central retinal artery and the temporal posterior ciliary artery in colour Doppler imaging in type 1 diabetic patients compared with healthy control subjects.

	Group DM-0		Group DM-1		Control	
	(n ₀ =18)		(n ₁ =10)		(n _c =18)	
	Mean	SD	Mean	SD	Mean	SD
OA						
PSV	46.70	9.46	49.73	10.63	48.05	13.95
EDV	11.65	4.27	12.99	5.37	14.34	6.44
MV	19.68	5.21	20.83	6.89	22.69	7.66
PI	1.78	0.32	1.83	0.50	1.60	0.42
RI	0.75	0.07	0.74	0.08	0.71	0.07
CRA						
PSV	11.27 ^a	4.57	9.55 ^a	2.63	15.91 ^b	4.28
EDV ¹	4.24	1.32	4.43	0.86	7.50	1.79
MV ¹	6.31	2.54	4.56 ^a	0.53	7.33 ^b	1.84
PI	1.28	0.51	1.39	0.40	1.58	0.33
RI	0.70 ^a	0.11	0.77 ^a	0.07	0.60 ^b	0.09
TPCA						
PSV	9.88 ^a	6.78	12.30 ^a	7.73	20.15 ^b	9.24
EDV ¹	5.04	3.39	5.62	3.17	9.21	4.31
MV ¹	10.99	9.45	14.60	3.03	17.31	5.54
PI	1.15	0.36	1.20	0.40	1.36	0.38
RI	0.69 ^a	0.10	0.73 ^a	0.10	0.60 ^b	0.10

^{a,b} Values marked with different letters within rows differ significantly at $p \leq 0.05$; ¹ Variables strongly deviated from normality, using Kruskal-Wallis analysis; DM-0 – diabetic patients without lens opacity; DM-1 – diabetic patients with lens opacity; n_c – number of controls; n – number of examined patients; SD – standard deviation; OA – ophthalmic artery; CRA – central retinal artery; TPCA – temporal posterior ciliary artery; PSV – peak systolic velocity (cm/s); EDV – end-diastolic velocity (cm/s); MV – mean velocity (cm/s); PI – pulsatility index; RI – resistance index.

was observed in the DM-0 and DM-1 groups with a major prevalence in the DM-1 group (Table 3). In the TPCA, PSV was statistically significantly lower, whereas RI was significantly elevated in the DM-0 and DM-1 groups with a tendency for higher values in the DM-1 group.

In the CRA, slight but significant correlations only in the DM-1 group existed between PSV and HbA_{1c}, PSV and ApoB, RI and HbA_{1c}, as well as RI and ApoB (Table 4). Similar results in the DM-1 subjects were obtained in the TPCA, where significant correlations of PSV and RI with HbA_{1c} were revealed. No statistically significant relationships between the blood flow parameters and biochemical indices in DM-0 patients were found (Table 5).

Discussion

Type-1 DM is known to cause damage of the sight organ in patients of various age. Deterioration in vision acuity is usually related to lens cloudiness or eye fundus lesions,

such as DA or DR [8,12,15,17]. According to our study, the mean values of glycaemia and lipids were significantly elevated, especially in type-1 DM patients, with lens cloudiness. It is accepted that the HbA_{1c} level above 7.0% (or above 8.2% according to others) predisposes to cataract, as in the study group (8.1–11.5%). However, this is contrary to diabetic patients without lens opacity, in whom the average HbA_{1c} level was 7.4% [7,18]. Besides hyperglycaemia, dyslipidaemia may probably increase the risk of lens lesions through its influence on blood flow dysregulation. Our observations showed statistically significantly increased TCH and TG levels in DM-1 patients, possibly confirming the aforementioned hypothesis (Table 1) [3,19,20]. Lens opacity or cataract may develop as a complication of diabetes, and in some cases at an early stage of young-onset diabetes before any retinal lesions are seen [21]. It is also known that DA escalates the risk of lens opacity [2,9,20]. Vascular pathology in diabetes develops as a result of impaired autoregulatory mechanisms of small arterioles and venules. The consequences include altered vessel

Table 4. Correlations between blood flow parameters measured in selected retrobulbar arteries and biochemical blood parameters in diabetic patients with lens opacity (DM-1, n₁=10).

	HbA _{1c} % ¹	TCH ¹	HDL	LDL ¹	TG	ApoB ¹
OA						
PSV	-0.24	0.19	-0.28	-0.16	-0.28	-0.27
EDV	-0.36	-0.13	-0.46	0.20	-0.26	-0.25
MV	-0.17	-0.22	-0.21	-0.11	-0.12	-0.27
PI	0.07	0.32	0.27	0.22	0.18	0.10
RI	0.28	0.31	0.24	0.30	0.12	0.33
CRA						
PSV	-0.77*	-0.30	-0.27	-0.29	-0.22	-0.57*
EDV ¹	-0.22	-0.27	-0.23	-0.26	0.43	-0.43
MV ¹	-0.18	0.17	-0.27	-0.20	-0.39	-0.33
PI	0.26	0.10	0.05	0.17	-0.18	0.51
RI	0.75*	0.31	0.07	0.29	-0.29	0.75*
TPCA						
PSV	-0.57*	0.04	-0.05	0.03	-0.01	-0.48
EDV ¹	-0.15	0.09	-0.04	-0.08	-0.12	-0.18
MV ¹	-0.29	0.05	0.02	0.03	-0.07	-0.15
PI ¹	0.22	0.30	0.30	0.38	0.19	0.35
RI	0.59*	0.11	0.21	-0.16	0.08	0.40

* Significant at p≤0.05. ¹ Variables strongly deviated from normality, using Spearman rank correlation; OA – ophthalmic artery; CRA – central retinal artery; TPCA – temporal posterior ciliary artery; HbA_{1c} – glycated haemoglobin; TCH – total cholesterol; HDL – high density lipoprotein fraction cholesterol; LDL – low density lipoprotein fraction cholesterol; TG – triglycerides; ApoB – apolipoprotein B; PSV – peak systolic velocity (cm/s); EDV – end-diastolic velocity (cm/s); MV – mean velocity (cm/s); PI – pulsatility index; RI – resistance index.

diameter, reduced perfusion pressure and dysregulation of vascular resistance in the retino-choroidal circulation [10–13,22,23]. Microvascular complications, such as vasculopathy, have been shown to be linked to an increased risk of diabetes [24]. The study by van Hecke et al. [25] demonstrated that abnormalities in the microvascular circulation are the basis of diabetes, i.e. retinal venule dilation correlated with macrovascular complications such as a significant increase in carotid intimal thickness. Diabetic angiopathy was observed in all studied patients, not only in the adolescents with lens opacity. In those patients, CDI revealed a statistically significantly decreased systolic velocity in the retino-choroidal circulation with a tendency for more pronounced differences in the aforementioned parameters in the lens opacity group. Similar results have been documented by other authors [10–13,26].

The obtained results show that the increased RI in the narrowest arterioles may be an early compensational response to poor blood perfusion in diabetic patients, especially with incipient cataract. Most authors consider HbA_{1c} of 7.0% as a threshold, above which a rapid increase in the incidence of eye vascular lesions and diabetic complications in the lens is highly probable, particularly with an

additional factor, which is dyslipidemia [3,11,13,20]. This is signalled by significant but not very intensive correlations of PSV and RI with HbA_{1c} and ApoB in the CRA as well as PSV and RI with HbA_{1c} in the TPCA in the adolescents with lens opacity, and no such relationships in the remaining diabetic patients (Tables 4 and 5). This study showed that diabetes might influence vasoconstriction and decrease in chorio-retinal blood flow velocity. Additionally, it seems significant that, in isolated vessels, chronic hyperlipidaemia moderately reduces endothelin-dependent relaxations in the coronary circulation in diabetes and vasospastic syndromes. In atherosclerosis, circulating and vascular endothelin levels are increased [27].

Considerable *in vitro* and *in vivo* evidence indicates a close correlation between a high resistance index and a low systolic velocity [3,8,10–13,19]. The presence of abnormal response in the CRA and PCA in the diabetic patients with and without lens opacity, suggests that even subtle changes in vascular resistance might occur primarily to lens cloudiness, confirming their limited vascular reactivity to metabolic fluctuation, which could presumably accentuate the diminished autoregulatory capacity of retrobulbar vessels.

Table 5. Correlations between blood flow parameters measured in selected retrobulbar arteries and biochemical blood parameters in diabetic patients without lens opacity (DM-0, n₀=18).

	HbA _{1c} % ¹	TCH ¹	HDL	LDL ¹	TG	ApoB ¹
OA						
PSV	-0.38	-0.36	-0.36	-0.32	-0.27	-0.26
EDV	-0.42	-0.23	-0.21	-0.31	-0.34	-0.34
MV	-0.27	-0.16	-0.13	-0.30	-0.41	-0.37
PI	0.17	0.17	0.26	0.19	0.31	0.38
RI	0.27	0.05	0.35	0.41	0.36	0.31
CRA						
PSV	-0.37	-0.22	0.05	0.13	-0.20	-0.29
EDV ¹	-0.24	-0.20	0.22	0.39	0.08	-0.30
MV ¹	-0.31	-0.33	0.18	0.13	-0.21	-0.37
PI	0.10	0.25	0.18	0.07	0.09	0.17
RI	0.38	0.38	0.16	0.01	0.12	0.27
TPCA						
PSV	-0.33	-0.18	-0.22	-0.17	0.16	-0.33
EDV ¹	-0.15	-0.17	-0.28	-0.29	0.38	-0.21
MV ¹	-0.25	-0.16	0.15	0.11	-0.24	-0.20
PI ¹	0.22	0.19	0.41	0.14	0.18	0.23
RI	0.39	0.20	0.37	0.12	-0.20	0.32

¹ Variables strongly deviated from normality, using Spearman rank correlation; OA – ophthalmic artery; CRA – central retinal artery; TPCA – temporal posterior ciliary artery; HbA_{1c} – glycated haemoglobin; TCH – total cholesterol; HDL – high density lipoprotein fraction cholesterol; LDL – low density lipoprotein fraction cholesterol; TG – triglycerides; ApoB – apolipoprotein B; PSV – peak systolic velocity (cm/s); EDV – end-diastolic (cm/s); velocity; MV – mean velocity (cm/s); PI – pulsatility index; RI – resistance index.

In conclusion, it can be stated that a significant increase and the observed fluctuations in HbA_{1c}, TCH and TG in type-1 diabetic adolescents, especially with lens cloudiness, might suggest their influence not only on the development of diabetic angiopathy but also on lens transparency abnormalities. Additionally, slight correlations of blood flow velocities with HbA_{1c} in the chorio-retinal vessels and with ApoB in the CRA only might suggest their significant role in retrobulbar endotheliopathy in diabetes. Our observation remains in agreement with other reports, in which perturbations in the lipids and glucose concentrations are well-known risk factors for the disturbances of ocular microcirculation in chorio-retinal vessels in other diseases of vascular origin [28]. This can be associated with the fact that the branches of PCAs supply nutrients not only to the choroid but also to the anterior segment of the eye.

These preliminary results may suggest the participation of the above-mentioned factors in the initial diabetic complications of the lens through the higher risk of vasoconstriction and vascular dysregulation in the retinal arteries and choroidal arterioles. It cannot be excluded that especially ocular ischaemia, leading to altered blood flow velocities and resistance indices in the ocular nutrient branches, might increase the risk of incipient cataract [29].

Conclusions

Further experimental studies, clinical observations, and laboratory data are necessary to continue the research on a larger group of subjects in order to verify these observations.

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