

The Role of Inflammation and Endothelial Dysfunction in the Pathogenesis of Diabetic Retinopathy

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ABSTRACT

The pathogenesis of diabetic retinopathy (DR) is insufficiently understood and presumed to possibly involve inflammation and endothelial dysfunction. The aim of the study was to investigate the relationship between inflammation markers, other markers of endothelial dysfunction and anthropometric parameters and their association with DR in patients with type 2 diabetes, divided into three groups: no retinopathy (N=65), mild / moderate nonproliferative diabetic retinopathy (NPDR; N=19) and severe NPDR / proliferative diabetic retinopathy (PDR; N=23). The groups did not differ in the levels of inflammation markers, other markers of endothelial dysfunction and anthropometric parameters. C-reactive protein was correlated with fibrinogen, HbA_{1c}, LDL-cholesterol, BMI, WC, WHR and C index. HbA_{1c} was correlated with cholesterol, LDL-cholesterol, BMI and WC. Logistic regression analysis showed that diabetes duration and HbA_{1c median} were the main predictors of retinopathy. The study demonstrated that the association between obesity, inflammation and other risk factors plays an important role in endothelial impairment involved in the pathogenesis of DR.

Key words: diabetic retinopathy, endothelial dysfunction, inflammation, obesity

Introduction

Diabetes mellitus is the most frequent endocrine disease in developed countries, estimated to have affected 284.6 million people worldwide in 2010 and projected to affect 438.4 million by 2030¹. It was the 5th leading cause of death in 2000, and its complications account for a significant portion of morbidity and mortality². Diabetic retinopathy (DR), a long-term microvascular and visually devastating diabetic complication, is estimated to be the most frequent cause of new blindness among working-aged adults (20–74 years) in developed countries^{3,4}. Many epidemiological studies and clinical trials have proven the impact of diabetes duration, poor glycemic control, hypertension, hyperlipidemia and obesity on the prevalence, incidence and progression of diabetic retinopathy^{5–8}. However, these factors explain a small proportion of the presence and progression of retinopathy, and of the incidence of proliferative retinopathy⁹, whereas

exact pathogenesis of diabetic retinopathy is insufficiently understood. Dysfunction of retinal endothelium is thought to be a possible mechanism as it plays a crucial role in all stages of diabetic retinopathy^{10,11}. Strategically located between blood and tissue, healthy endothelium actively regulates vascular tone and permeability, the balance between coagulation and fibrinolysis, the composition of the subendothelial matrix, the extravasation of leukocytes, and the proliferation of vascular smooth muscle. To perform these functions, endothelium produces components of the extracellular matrix and a variety of regulatory mediators. Functional impairment of endothelial activity precedes the development of morphological alterations during the progression of diabetes and its vascular complications. This endothelial dysfunction results from reduced bioavailability of the vascular nitric oxide (NO), mainly due to accelerated NO degrada-

tion by reactive oxygen species (ROS). Although hyperglycemia, insulin resistance, hyperinsulinemia and hyperlipidemia independently and/or simultaneously contribute to endothelial dysfunction via several different mechanisms¹², hemorheological alterations and systemic inflammation found in obese diabetic patients may play an essential role in the endothelial dysfunction and the aetiology of diabetic retinopathy^{13,14}.

Many studies have documented the association of inflammation markers and endothelial dysfunction with macroangiopathy in obese non-diabetic individuals and type 2 diabetic patients^{15,16}, but only some of them have investigated the association of inflammation and endothelial dysfunction with the prevalence and progression of diabetic microangiopathy^{17,18}.

The aim of the present study was to investigate the relationship between inflammation markers, other markers of endothelial dysfunction and anthropometric parameters, and their association with diabetic retinopathy in patients with type 2 diabetes.

Materials and Methods

This cross-sectional study was conducted in collaboration between the Department of Endocrinology and Metabolic Diseases and the Department of Diabetic Complications, Division of Ophthalmology of the Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital in Zagreb. A total of 107 patients with type 2 diabetes consecutively attending both Departments over a six-month period were included. Their age ranged from 50 to 80 years, and diabetes duration from 5 to 25 years. They were on either oral hypoglycemic agent (OHA) therapy or insulin therapy. Patients with malignancies, immunologic, infectious inflammatory diseases, patients receiving corticosteroids or cytostatics, pregnant women and patients with other eye diseases (mature cataract, uveitis, age-related macular degeneration) were not included in the study. The study protocol was approved by the Vuk Vrhovac University Clinic Ethics Committee. The patients received both written and oral information about the study and signed a written informed consent.

Markers of inflammation

C-reactive protein (CRP) was determined by an automated immunoturbidimetric assay on an Olympus AU600 analyzer (Olympus Optical Co., Tokyo, Japan) (reference value <5.0 mg/L)¹⁹. Fibrinogen was measured by the Clauss method (reference values 1.8–4.1 g/L)²⁰.

Other markers of endothelial dysfunction

Glycated hemoglobin value (HbA_{1c}), total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were measured. HbA_{1c} was determined at the beginning of the study from a single venous blood sample, and HbA_{1c}_{median} was obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet). The statistical

analysis included HbA_{1c} values from venous blood samples taken from each individual patient at 3–4 month intervals over the past three years. HbA_{1c} was determined by an automated immunoturbidimetric assay (reference values 3.5–5.7%)²¹. Total cholesterol was measured by an enzymatic colorimetric test (reference value <5.00 mmol/L)²², HDL cholesterol by an enzymatic immunoinhibition test (reference value >1.00 mmol/L)²³, and LDL cholesterol by Friedwald's method (reference value <3.00 mmol/L)²⁴. Triglycerides were determined by an enzymatic colorimetric test (reference value <1.70 mmol/L)²⁵.

Anthropometric parameters

Body mass index (BMI) as a common index of obesity was calculated by dividing weight and height squared (kg/m²). Weight was measured using a balance-beam scale and height was measured using a wall-mounted stadiometer with patients in their underwear and without shoes. Recommended value among men was considered <23 and among women <22 kg/m² with a normal range between 18.5 and 24.9 kg/m^{2,26}. Waist circumference (WC), a direct indicator of abdominal obesity, was measured in the middle distance between the last floating rib and the iliac crest (cm). Recommended values were considered <94 cm (men) and <80 cm (women)²⁷. The waist-to-hip ratio (WHR) as an index of body fat distribution was determined by dividing waist and hip circumference. The hip circumference was measured with a measuring tape passing on femoral trochanters (cm). Suggested values of WHR were considered as <1.0 (men) and <0.8 (women)²⁷. The conicity index (C index), another index of body fat distribution, was determined by measuring weight, height and waist circumference and a density constant 0.109 by using mathematical equation: WC (m) / 0.109 x $\sqrt{\text{weight (kg) / height (m)}}$. The value of the C index varies between 1.00 (a perfect cylinder – an »ideal« body fat distribution) and 1.73 (a perfect biconical shape – huge abdominal obesity)²⁸.

Clinical parameters

Blood pressure was measured with an ambulatory sphygmomanometric device after a 5-min rest, and a mean of three measurements was used. Hypertension was defined as blood pressure >130/80 mm Hg.

Ophthalmologic examination

Complete eye examination included best corrected visual acuity (BCVA), Goldmann applanation tonometry, slit lamp biomicroscopy of the anterior eye segment, binocular indirect slit lamp funduscopy and fundus photography after mydriasis with eye drops containing 0.5% tropicamide and 5% phenylephrine. Color fundus photographs of two fields (macular field, disc/nasal field) of both eyes were taken with a suitable 45° fundus camera (VISUCAM, Zeiss) according to the EURODIAB retinal photography methodology²⁹. Macular field: positioned in such a way that the exact center of the optic disc laid at the nasal end of the horizontal meridian of the field view. Disc/nasal field: such that the optic disc was positioned

one disc-diameter in from the temporal edge of the field, on the horizontal meridian. EURODIAB classification scheme was used because it uses two-field 45° fundus photography and standard photographs to grade retinal lesions²⁹. In each patient the »worse« eye was graded for retinopathy using fundus photographs.

Statistical analyses

Results are presented as means ± SD and percentages. Differences in distributions of continuous data were determined by ANOVA or Kruskal-Wallis test. Scheffe's post-hoc test was used. Differences in distributions of categorical data were evaluated by Chi-square test or Fisher exact test. The normality of distribution was tested by Shapiro-Wilks W test and homogeneity of variance by Leven test. The Spearman rank correlation test was used. Univariate and multiple logistic regression analyses were used to assess the strength and independence of associations. All analyses were performed using SAS 9.1.3 and STATA/IC ver.11.1. p value of less than 0.05 was considered statistically significant.

Results

This study included 107 patients with type 2 diabetes (67 male, 40 female) with a mean age 66.74 ± 8.01 years

and a mean diabetes duration of 15.05 ± 5.69 years. Forty (37%) patients were on oral hypoglycemic agents (OHA) and 67 (63%) on insulin therapy.

The average best corrected visual acuity (BCVA) of our patients was 0.91 ± 0.22, and the average intraocular pressure (IOP) was 13.55 ± 1.33 mmHg. Nine (8%) patients were suffering from primary open angle glaucoma (POAG) and were treated with topical antiglaucomatous therapy. 16 (15%) patients had clear crystalline lenses, 74 (69%) an initial cataract and 17 (16%) patients had the condition after cataract surgery (an artificial IOL implanted). Hypertensive retinopathy was detected in 40 (37%) patients.

According to the two-field 45° color fundus photography (EURODIAB standards) patients were divided into three groups: Group 1 – patients with no retinopathy (N=65), Group 2 – patients with mild / moderate non-proliferative diabetic retinopathy (NPDR; N=19), and Group 3 – patients with severe / very severe NPDR or proliferative diabetic retinopathy (PDR; N=23).

Descriptive statistics of basic characteristics, markers of inflammation, other markers of endothelial dysfunction, anthropometric and clinical parameters according to the diabetic retinopathy status are presented in Table 1. There were no differences in age and sex between the groups. Group 3 had significantly longer diabetes dura-

TABLE 1
BASIC CHARACTERISTICS, MARKERS OF INFLAMMATION, OTHER MARKERS OF ENDOTHELIAL DYSFUNCTION, ANTHROPOMETRIC AND CLINICAL PARAMETERS OF TYPE 2 DIABETIC PATIENTS (N=107) DIVIDED INTO THREE GROUPS ACCORDING TO THE DIABETIC RETINOPATHY STATUS

	Group 1 (N=65)	Group 2 (N=19)	Group 3 (N=23)	F ^a χ^2 ^c	p
Age (years)*	66.31 ± 8.31	68.47 ± 7.11	66.52 ± 7.98	0.543 ^a	0.583 ^a
Sex (m/f)**	65/35	42/58	74/26	0.280 ^c	0.595 ^c
Diabetes duration (years)*	13.22 ± 5.08	16.11 ± 6.01	19.35 ± 4.60	12.498 ^a	<0.001 ^a
Therapy (OHA/insulin)**	48/52	32/68	13/87	7.520 ^c	0.009 ^c
C-reactive protein (CRP) (mg/L)*	3.37 ± 4.14	4.05 ± 3.34	5.36 ± 5.77	1.721 ^a	0.184 ^a
Fibrinogen (g/L)*	4.73 ± 1.23	4.75 ± 1.48	4.75 ± 1.09	0.002 ^a	0.998 ^a
HbA _{1c} (%)*	6.42 ± 1.06	6.53 ± 1.06	6.70 ± 1.29	0.551 ^a	0.578 ^a
HbA _{1c} median (%)*	6.77 ± 0.76	7.18 ± 0.81	7.31 ± 0.85	2.976 ^a	0.055 ^a
Total cholesterol (mmol/L)*	4.96 ± 0.85	4.87 ± 1.27	5.05 ± 1.05	0.178 ^a	0.838 ^a
HDL cholesterol (mmol/L)*	1.31 ± 0.33	1.38 ± 0.28	1.45 ± 0.35	1.472 ^a	0.234 ^a
LDL cholesterol (mmol/L)*	2.71 ± 0.84	2.61 ± 0.99	2.73 ± 0.94	0.111 ^a	0.895 ^a
Triglycerides (mmol/L)*	2.14 ± 1.19	2.48 ± 2.41	1.50 ± 0.61	1.230 ^a	0.066 ^a
Body mass index (BMI) (kg/m ²)*	30.77 ± 6.06	30.91 ± 5.28	30.12 ± 5.33	0.129 ^a	0.879 ^a
Waist circumference (WC) (cm)*	107.52 ± 14.96	108.21 ± 12.09	107.91 ± 12.28	0.020 ^a	0.980 ^a
Waist to hip ratio (WHR)*	0.96 ± 0.08	0.96 ± 0.07	0.97 ± 0.07	0.162 ^a	0.851 ^a
Conicity index (C index)*	1.36 ± 0.09	1.39 ± 0.07	1.39 ± 0.11	0.824 ^a	0.441 ^a
Systolic blood pressure (mmHg)*	139.00 ± 22.97	151.32 ± 23.85	144.35 ± 21.18	2.267 ^a	0.109 ^a
Diastolic blood pressure (mmHg)*	82.15 ± 12.90	80.26 ± 15.50	78.70 ± 8.15	0.691 ^a	0.503 ^a

statistically significant p < 0.05; * $\bar{X} \pm SD$; ** percentage; ^aANOVA, df=2; ^cChi-square test, df=1

Abbreviations: OHA – oral hypoglycemic agent, HbA_{1c} – glycated hemoglobin value determined at the beginning of the study from a single venous blood sample, HbA_{1c} median – glycated hemoglobin value obtained by statistical analysis of data from the National Register for Diabetes (CroDiabNet)

TABLE 2
OPHTHALMOLOGIC PARAMETERS OF TYPE 2 DIABETIC PATIENTS (N=107) DIVIDED INTO THREE GROUPS ACCORDING TO THE DIABETIC RETINOPATHY STATUS

	Group 1 (N=65)	Group 2 (N=19)	Group 3 (N=23)	H ^b χ^2 ^c	p
BCVA (decimal)*	0.97±0.08	0.92±0.15	0.72±0.37	13.86 ^b	0.001 ^b
Glaucoma**	11	5	4	0.54 ^c	0.461 ^c
IOP (mmHg)*	13.66±1.50	13.58±1.07	13.22±0.95	0.49 ^b	0.487 ^b
Lens**	20/71/9	5/69/26	9/65/26	7.50 ^c	0.023 ^c
Hypertensive retinopathy **	31	47	48	3.09 ^c	0.079 ^c

statistically significant $p < 0.05$; * $\bar{X} \pm SD$; ** percentage; ^b Kruskal-Wallis $df=1$; ^c Chi-square test $df=2$
Abbreviations: BCVA – best corrected visual acuity, IOP – intraocular pressure, Lens – clear crystalline lens/initial cataract/condition after cataract surgery (an artificial IOL implanted)

tion (19.35±4.60 years vs. 13.22±5.08 years; $p < 0.001$) and more often insulin than OHA therapy (87/13 % vs. 52/48 %; $p = 0.009$) than Group 1. The three groups did not significantly differ in the levels of inflammation markers, other markers of endothelial dysfunction, anthropometric and clinical parameters.

Table 2 presents ophthalmologic parameters according to the diabetic retinopathy status. Group 3 was found to have significantly lower best corrected visual acuity (BCVA) than Group 1 (0.72±0.37 vs. 0.97±0.08; $p = 0.001$). The presence of cataract as well as the condition after cataract surgery (an artificial IOL implanted) were observed significantly more often in Groups 2 and 3 than in Group 1 ($p = 0.023$). There were no differences in the average intraocular pressure (IOP), presence of glaucoma and hypertensive retinopathy between the studied groups.

C-reactive protein was significantly positively correlated with another inflammation marker fibrinogen ($p = 0.022$), other markers of endothelial dysfunction HbA_{1c} ($p = 0.050$) and LDL cholesterol ($p = 0.043$), and anthropo-

metric parameters BMI ($p = 0.038$), WC ($p = 0.000$), WHR ($p = 0.030$) and C index ($p = 0.008$) (Table 3).

HbA_{1c} was significantly positively correlated with other markers of endothelial dysfunction total cholesterol ($p = 0.022$) and LDL cholesterol ($p = 0.010$), and anthropometric parameters BMI ($p = 0.009$) and WC ($p = 0.047$) (Table 4).

Univariate and multiple logistic regression analyses showed that diabetes duration, insulin therapy and prolonged poor glycemic control (HbA_{1c median}) were the main predictors of retinopathy in patients with type 2 diabetes (Table 5). The increasing prevalence of retinopathy was significantly associated with longer duration of diabetes (OR=1.17, 95%CI 1.08–1.27), even after adjustment for age and sex (AOR=1.2, 95%CI 1.1–1.32). Insulin therapy, not mandatory in type 2 diabetes but often used in patients with prolonged diabetes duration and poor glycemic control, increased the prevalence of retinopathy to a significant extent (OR=3.34, 95%CI 1.38–8.09), even after adjustment for age and sex (AOR=3.28, 95%CI 1.34–8.02). The increasing prevalence of retinopathy was significantly related to prolonged poor glycemic control (HbA_{1c median}) (OR=1.76, 95%CI 1.08–2.86), the association also remaining significant after adjustment for age and sex (AOR=1.84, 95%CI 1.10–3.06).

TABLE 3
CORRELATION BETWEEN CRP AND OTHER MARKERS OF INFLAMMATION, MARKERS OF ENDOTHELIAL DYSFUNCTION AND ANTHROPOMETRIC PARAMETERS IN TYPE 2 DIABETIC PATIENTS (N=107)

	C-reactive protein (CRP)		
	Spearman R	t(N-2)	p
Fibrinogen	0.221	2.323	0.022
HbA _{1c}	0.188	1.964	0.050
LDL cholesterol	0.196	2.053	0.043
Body mass index (BMI)	0.201	2.102	0.038
Waist circumference (WC)	0.331	3.595	0.000
Waist to hip ratio (WHR)	0.210	2.205	0.030
Conicity index (C index)	0.254	2.686	0.008

statistically significant $p < 0.05$
Abbreviations: HbA_{1c} – glycated hemoglobin value determined at the beginning of the study from a single venous blood sample

TABLE 4
CORRELATION BETWEEN HbA_{1c} AND OTHER MARKERS OF INFLAMMATION MARKERS OF ENDOTHELIAL DYSFUNCTION AND ANTHROPOMETRIC PARAMETERS IN TYPE 2 DIABETIC PATIENTS (N=107)

	HbA _{1c}		
	Spearman R	t(N-2)	p
Total cholesterol	0.221	2.327	0.022
LDL cholesterol	0.248	2.625	0.010
Body mass index (BMI)	0.252	2.669	0.009
Waist circumference (WC)	0.193	2.014	0.047

statistically significant $p < 0.05$
Abbreviations: HbA_{1c} – glycated hemoglobin value determined at the beginning of the study from a single venous blood sample

TABLE 5
ODDS RATIOS (95% CIs) FOR DIABETIC RETINOPATHY ASSOCIATED WITH BASIC CHARACTERISTICS, INFLAMMATION MARKERS, OTHER MARKERS OF ENDOTHELIAL DYSFUNCTION, ANTHROPOMETRIC AND CLINICAL PARAMETERS OF TYPE 2 DIABETIC PATIENTS (N=107)

	OR	95%CI (OR)	AOR*	95%CI (AOR)
Diabetes duration (years)	1.17	1.08–1.27	1.20	1.10–1.32
Therapy (insulin)	3.34	1.38–8.09	3.28	1.34–8.02
C reactive protein (CRP)	1.07	0.98–1.18	1.08	0.99–1.18
Fibrinogen	1.01	0.74–1.38	0.99	0.71–1.37
HbA _{1c}	1.18	0.83–1.68	1.23	0.85–1.77
HbA _{1c} median	1.76	1.08–2.86	1.84	1.10–3.06
Total cholesterol	1.01	0.68–1.51	1.03	0.68–1.57
HDL cholesterol	2.65	0.79–8.85	2.51	0.69–9.06
LDL cholesterol	1.01	1.00–1.02	1.01	1.00–1.02
Triglycerides	0.89	0.69–1.13	0.90	0.70–1.15
Body mass index (BMI)	0.99	0.93–1.06	0.99	0.92–1.07
Waist circumference (WC)	1.00	0.97–1.03	1.01	0.98–1.04
Waist to hip ratio (WHR)	1.34	0.01–185.05	7.42	0.14–3806.64
Conicity index (C index)	15.02	0.23–965.31	21.22	0.29–1544.61
Systolic blood pressure	1.02	1.00–1.03	1.02	1.00–1.04
Diastolic blood pressure	0.98	0.95–1.01	0.98	0.95–1.02

statistically significant $p < 0.05$; *OR adjusted for age and sex

Abbreviations: HbA_{1c} – glycated hemoglobin value determined at the beginning of the study from a single venous blood sample, HbA_{1c} median – glycated hemoglobin value obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet)

Discussion

Type 2 diabetes is nowadays, because of its high incidence and risk of macrovascular and microvascular diabetic complications, one of the potentially most damaging diseases and biggest public health problems. Diabetic eye disease with its complications, especially diabetic retinopathy which leads to macular edema and retinal neovascularization, is the leading cause of blindness and visual dysfunction in working-aged adults in economically developed societies.

As expected, we found a significantly lower visual function, expressed by best corrected visual acuity (BCVA), in the group of patients with severe NPDR and PDR than in the group of patients with no retinopathy. Also, a significantly more frequent cataract and the condition after cataract surgery (an artificial IOL implanted) was observed in the groups of patients with diabetic retinopathy (NPDR and PDR) as compared with the group of patients with no retinopathy. Last result is similar to other study³⁰, and may be explained by the activation of the polyol pathway by intracellular hyperglycemia, which leads to the sorbitol-induced osmotic stress and occurrence of a typical snowflake diabetic cataract or earlier senile cataract.

The results of our study are consistent with the literature, suggesting that diabetes duration and poor glycaemic control are the main predictors of the prevalence and progression of retinopathy in patients with type 2 diabetes^{31–33}. We also found insulin therapy to be among the main predictors of retinopathy in this type of diabetes. It

is common knowledge that insulin therapy is not mandatory for patients with type 2 diabetes, but in these patients it is often necessary in progressive insulinopenia, prolonged duration of diabetes and very poor glycaemic control. Our results are analogous to those of the Wisconsin Epidemiologic Study of Diabetic Retinopathy, which reported an increased 4- and 10-year cumulative incidence and significantly increased prevalence of diabetic retinopathy in older patients on insulin therapy than those on OHA therapy (70% vs. 39%)⁵.

Hypertension is another risk factor for diabetic retinopathy documented in many epidemiological studies and clinical trials. United Kingdom Prospective Diabetes Study (UKPDS) and Appropriate Blood Pressure Control in Diabetes (ABCD) Study have observed that strict blood pressure control can prevent and/or limit the development and progression of diabetic retinopathy and visual dysfunction^{34,35}. In our study there was no significant difference in the level of systolic and diastolic blood pressure between the groups according to their diabetic retinopathy status. It is worth noting that the average systolic blood pressure among our patients was 142.34 ± 23.03 mmHg and the average diastolic blood pressure 81.07 ± 12.53 mmHg, these values being very near to those recommended by the American and European Societies of Cardiology^{36,37}.

Besides these notorious risk factors, overweight and obesity are very frequently found in patients with type 2 diabetes. Obesity is a chronic, stigmatized disease whose

prevalence has risen progressively over the last 20 years³⁸. It increases the risk of type 2 diabetes and is connected with insulin resistance, hyperinsulinemia and hyperlipidemia³⁹. Many studies support the correlation between obesity expressed by BMI and deterioration of HbA_{1c}, decrease in HDL cholesterol, increase in triglycerides and a higher prevalence of hypertension and cardiovascular disease^{40,41}. Some other studies have found a correlation between obesity and diabetic microvascular complications in patients with type 2 diabetes^{8,33}. New data suggest that adipose tissue is an important determinant of a low-level, chronic inflammatory state reflected by the production of various proinflammatory cytokines, which induce insulin resistance and endothelial dysfunction, consequently linking the later phenomenon with obesity and diabetic angiopathy⁴². Several authors have shown that elevated plasma levels of fibrinogen, C-reactive protein and interleukin-6 are associated with the risk of cardiovascular disease and the severity of atherosclerosis^{43,44}. The Hoorn Study found a positive association between the levels of C-reactive protein and soluble intracellular adhesion molecule-1 (sICAM-1) and the prevalence of diabetic retinopathy¹⁷.

In our study there was no significant difference in the levels of inflammation markers, other markers of endothelial dysfunction and anthropometric parameters between the groups according to the diabetic retinopathy status. The lack of difference in the levels of inflammation markers and other markers of endothelial dysfunction in our study could be due to the sample size and to

the fact that the majority of our patients had near normal values of these markers. However, we observed a positive correlation of the inflammation marker C-reactive protein with another inflammation marker fibrinogen, other markers of endothelial dysfunction HbA_{1c} and LDL cholesterol, and the anthropometric parameters BMI, WC, WHR and C index. We also found a positive correlation of the endothelial dysfunction marker HbA_{1c} with other markers of endothelial dysfunction total cholesterol and LDL cholesterol, and with the anthropometric parameters BMI and WC.

Conclusion

Diabetes duration, prolonged poor glycemic control and the resulting need for insulin therapy are the main predictors of retinopathy in patients with type 2 diabetes. The positive correlation of C-reactive protein with fibrinogen, HbA_{1c}, LDL cholesterol and anthropometric parameters BMI, WC, WHR and C index, as well as the positive correlation of HbA_{1c} with total cholesterol, LDL cholesterol and anthropometric parameters BMI and WC suggests that the association between obesity, inflammation and other risk factors plays an important role in endothelial impairment involved in the pathogenesis of diabetic retinopathy. These findings point to the need for testing the effects of treatment aimed at decreasing inflammatory activity and improving endothelial function as a means of preventing or limiting the progression of retinopathy.

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ULOGA UPALNIH ČIMBENIKA I ENDOTELNE DISFUNKCIJE U RAZVOJU DIJABETIČKE RETINOPATIJE

S A Ž E T A K

Etiopatogeneza dijabetičke retinopatije (DR) je nedovoljno razjašnjena, no pretpostavlja se da u njoj važnu ulogu imaju upalni čimbenici i endotelna disfunkcija. Cilj istraživanja bio je ispitati povezanost upalnih čimbenika s ostalim čimbenicima endotelnog oštećenja i antropometrijskim parametrima, te njihovu povezanost sa stupnjem DR kod bolesnika sa šećernom bolešću tipa 2 podijeljenih u tri skupine: bez retinopatije (N=65), s blagom / umjereno teškom neproliferativnom dijabetičkom retinopatijom (NPDR; N=19) i teškom NPDR / proliferativnom dijabetičkom retinopatijom (PDR; N=23). Među skupinama nije bilo značajne razlike u razini upalnih i ostalih čimbenika endotelnog oštećenja, te vrijednostima antropometrijskih parametara. C-reaktivni protein bio je pozitivno povezan s fibrinogenom, HbA_{1c}, LDL-kolesterolom, BMI, WC, WHR i C indeksom, a HbA_{1c} s kolesterolom, LDL-kolesterolom, BMI i WC. Logistička regresija je trajanje dijabetesa i HbA_{1c}_{median} izdvojila kao glavne pretkazatelje razvoja retinopatije. Ovo istraživanje ukazalo je na važnost povezanosti pretilosti, upalnih i ostalih čimbenika endotelne disfunkcije u razvoju dijabetičke retinopatije.