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Original Scientific Paper

BLOOD PRESSURE IS ASSOCIATED WITH DIABETIC RETINOPATHY IN TYPE 1 BUT NOT IN TYPE 2 DIABETES

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SUMMARY – The aim of this study was to investigate the role of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the development of diabetic retinopathy (DR) in type 1 and type 2 diabetes and to determine the differences between these two types of diabetes. This cross-sectional study included 84 patients with type 1 diabetes (T1DM) and 107 patients with type 2 diabetes (T2DM). Ophthalmologic retinal examination included indirect slit-lamp fundoscopy, color fundus photography according to EURODIAB (EUROpe and DIABetes) protocol and optical coherence tomography. Blood pressure was measured with a mercury sphygmomanometer after a 10-minute rest period. In T1DM, DR was positively associated with SBP ($p = 0.035$), $HbA1c_{median}$ ($p < 0.001$) and hypertensive retinopathy ($p < 0.001$), while in T2DM DR was positively related only to $HbA1c_{median}$ ($p = 0.021$). Binary logistic regression analysis (no DR/DR) showed that diabetes duration and $HbA1c_{median}$ were the main predictors of DR in both types of diabetes. In contrast, SBP (OR = 1.05, $p = 0.045$) and hypertensive retinopathy (OR = 3.75, $p < 0.001$) were the main predictors/indicators of DR only in T1DM. In conclusion, blood pressure is associated with DR in type 1 but not in type 2 diabetes.

Keywords: blood *pressure, type 1 and type 2 diabetes, retinopathy, risk factors*

Introduction

The prevalence of diabetes mellitus is rapidly increasing and is now the most common non-communicable disease, globally projected to affect over 700 million people by 2045.[1]

Diabetic retinopathy (DR), a microvascular complication of diabetes, is one of the leading causes of visual impairment and blindness in patients with type 1 (T1DM) and type 2 (T2DM) diabetes.[2] T1DM is an autoimmune disease that result from autoimmune β-cell destruction with absolute insulin deficiency and accounts for 5-10% of diabetes, while T2DM occurs more frequently, comprising more than 90% of all diabetes cases. It is associated with insulin resistance and metabolic syndrome components (obesity, hypertension, and dyslipidemia)[3]. Prospective studies identified hyperglycemia, diabetes duration and blood pressure as the most important risk factors for development of DR in T1DM and T2DM[4-7]. Besides diabetes duration, hyperglycemia and hypertension are modifiable risk factors.[8]

In patients with diabetes, high blood pressure increases blood flow and hypothetically damages the retinal capillary endothelial cells.[9] The results from the large and prospective United Kingdom Prospective Diabetes Study (UKPDS) showed that the incidence

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of DR was associated with systolic blood pressure (SBP) in T2DM.[10] T2DM in the highest tertile range with SBP over 140 mmHg had almost a three times higher risk of development of DR compared to subjects in the lowest tertile range with SBP below <125 mmHg. In contrast, results from the 25-year follow-up of the WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy) study, which included T1DM, found that diastolic blood pressure (DBP) was a significant predictor of the progression of DR.[11] However, in the same study neither SBP nor DBP at baseline were associated with the incidence and progression of DR in T2DM.[12] We previously observed that SBP is a risk factor for the development and progression of DR in T1DM, but in patients with normal renal function and normoalbuminura.[13] In contrast, we previously observed that DBP is a risk factor and predictor for cataract development in T2DM[14].

The aim of this study was to investigate the role of SBP and DBP in the development of DR in T1DM and T2DM.

Subjects, materials and methods

This cross-sectional study included 84 T1DM and 107 T2DM patients at the Department of Ophthalmology and the Department of Diabetes of the Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases in Zagreb over a six-month period. The study was performed in accordance with the Helsinki Declaration and approved by the hospital's ethics committee. The patients included in the study received both written and oral information about the study and signed a consent form. T1DM and T2DM were defined according to the ADA classification.[3] We excluded from the study all illnesses that may affect eye function and blood pressure, such as therapy with corticosteroids or cytostatics, immunological and acute infectious inflammatory diseases, pregnant women and patients with other eye diseases. At the inclusion visit, consent forms were signed, blood samples were collected for laboratory analyses, and complete clinical and ophthalmologic retinal examinations were performed.

All subjects were examined the morning after an overnight fast to determine HbA1c, serum lipids and serum creatinine. Basic anthropometric measurements were performed on all study subjects, including body mass index (BMI). HbA1c was determined at the beginning of the study from a single venous blood sample. $HbA1c_{median}$ was obtained by a statistical analysis of data from the National Registry for Diabetes (CroDiabNet) and used as a marker of long-term glycemic control. The statistical analysis included HbA1c values from venous blood samples taken from each patient at 3-4-month intervals over the past three years. SBP and DBP were measured with an ambulatory mercury sphygmomanometer after a 10-min rest period, and a mean of three measurements was used.

The ophthalmologic retinal examination included indirect slit-lamp fundoscopy, color fundus photography, and optical coherence tomography (OCT) of the macula after mydriasis with eye drops containing 0.5 % tropicamide. Color fundus photographs of two fields (macular field, disc/nasal field) of both eyes were taken with the standard 45° fundus camera (Visucam NM/FA, Carl Zeiss Meditec) according to the EURODIAB retinal photography methodology[15]. Two medical retina specialists independently graded the photographs and assigned a DR level. The final diagnosis for each patient was determined from the level of DR of the worse eye using EURODIAB criteria.[15] OCT of the macula of both eyes was performed by Spectral Domain OCT (SD-OCT Copernicus REVO NX, Optopol Technology), and diabetic macular edema (DME) was defined by the proposed international clinical DR and diabetic macular edema disease severity scales.[16] Hypertensive retinopathy was defined and graduated using the Keith-Wagner-Barker classification.[17] Patients with active proliferative DR and active DME were not included in the study.

Statistical analysis was performed with the Statistica software package, version 14.0 (TIBCO Inc., USA). The normality of data distribution was evaluated by the Kolmogorov-Smirnov test and the homogeneity of variance by the Leven test. The results of the descriptive analyses were expressed as means ± SD or medians (min-max) for continuous variables and as numbers and percentages for categorical variables. Differences between continuous data were determined by t-test or a Mann-Whitney test. A nonparametric test was used when the assumption of homogeneity of variance for tested variables was not met. Differences among categorical data were evaluated by the Chi-square test. The Pearson's and Spearman rank correlation tests were used. ANOVA with two main factors

Table 1. Basic characteristics and clinical parameters of type 1 and type 2 diabetic patients included in the study.

	T1DM (n=84)	**T2DM** (n=107)	**t[a] Chi[b] Z[c]**	**p**
Age (years)*	41.54±7.58	66.74±8.01	-14.976[a]	**<0.001**
Gender (m/f)**	36/48	40/67	0.281[b]	0.596
Diabetes duration (year)†	15.5 (8-35)	15 (7-25)	1.289[c]	0.159
SBP (mmHg)*	123.75±21.15	142.34±23.03	-3.864[a]	**<0.001**
DBP (mmHg)*	78.39±11.39	81.07±12.53	-1.026[a]	0.307
HbA_1c (%)*	6.77±1.37	6.50±1.11	1.111[a]	0.268
HbA_1c_{median} (%)*	7.25±1.11	6.80±0.84	2.124[a]	**0.038**
Diabetic retinopathy**	33 (39.3)	42 (39.2)	0.000[b]	0.997
Hypertensive retinopathy**	27 (32.1)	40 (37.4)	0.264[b]	0.608

* mean ± SD ** number (percentage) † median (min-max) [a] t-test [b] Chi-square test [c] Mann-Whitney test
T1DM = type 1 diabetic patients; T2DM = type 2 diabetic patients; SBP = systolic blood pressure; DBP = diastolic blood pressure; 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).

and their interaction was used to compare the analyzed variables according to the type of diabetes and the DR status. Binary logistic regression analysis was used to assess the strength and independence of the associations between DR and the risk factors. In all analyses, $p < 0.05$ was considered statistically significant.

Results

This study included 84 (48 male/36 female) T1DM and 107 (67 male/40 female) T2DM. Their basic characteristics and clinical parameters are presented in Table 1. T2DM were significantly older ($p < 0.001$) and had significantly higher SBP ($p < 0.001$), while T1DM had significantly higher $HbA1c_{median}$ ($p = 0.038$). No significant differences in gender, diabetes duration, DBP, HbA1c, and number (percentage) of patients with diabetes and hypertensive retinopathy were found between the patients with different types of diabetes.

According to the DR status, patients were divided into two groups: Gr 1 (patients without DR; type 1 n=51, type 2 n=65) and Gr 2 (patients with DR; type 1 n=33, type 2 n=42). Table 2 presents the clinical parameters of T1DM and T2DM divided into two DR groups. T1DM with DR had significantly higher SBP than patients without DR ($p = 0.035$), while no significant difference in SBP in T2DM with and without DR was observed ($p = 0.062$). Also, the two DR groups in both types of diabetes did not significantly differ in DBP, and HbA1c determined at the beginning of the study, but $HbA1c_{median}$ was significantly higher in patients with DR than those without DR in T1DM ($p < 0.001$) and T2DM ($p = 0.021$). T1DM with DR had significantly more frequent signs of hypertensive retinopathy than those test subjects without DR ($p < 0.001$), although no significant difference in the number (percentage) of patients with and without DR and concomitant hypertensive retinopathy was found in T2DM ($p = 0.079$) (Table 2, Figure 1). Figure 2 presents the macular field of the left and right eye of one T1DM with non-proliferative DR and concomitant hypertensive retinopathy Gr. 3/2.

In T1DM DR was positively associated with SBP ($p = 0.035$), $HbA1c_{median}$ ($p < 0.001$) and hypertensive retinopathy ($p < 0.001$), while in T2DM it was positively related only to $HbA1c_{median}$ ($p = 0.021$) (Table 3).

The differences in SBP and DBP according to the type of diabetes and DR status were evaluated by ANOVA with two main factors and their interaction (Table 4, Figure 3). The among-group differences in SBP were observed according to the type of diabetes ($p < 0.001$) and DR status ($p = 0.009$), but no significant difference in SBP was found in the interaction between the type of diabetes and DR status ($p = 0.378$). For DBP, no differences were observed among-group according to the type of diabetes ($p = 0.451$) and DR status ($p = 0.904$) or in the interaction of the type of diabetes and DR status ($p = 0.253$).

Table 2. Clinical parameters of type 1 and type 2 diabetic patients divided into two groups according to the diabetic retinopathy status.

	T1DM (n=84)				T2DM (n=107)			
	DR		t[a] Chi[b]	p	DR		t[a] Chi[b]	p
SBP (mmHg)*	Gr 1 Gr 2	117.06±18.12 134.09±22.12	-2.228[a]	**0.035**	Gr 1 Gr 2	139.00±22.97 147.50±22.42	-1.887[a]	0.062
DBP (mmHg)*	Gr 1 Gr 2	77.06±12.75 80.45±9.07	-0.765[a]	0.451	Gr 1 Gr 2	82.15±12.89 79.40±11.90	1.109[a]	0.269
HbA_1c (%)*	Gr 1 Gr 2	6.57±1.49 7.07±1.16	-0.933[a]	0.359	Gr 1 Gr 2	6.42±1.06 6.62±1.18	-0.939[a]	0.349
HbA_1c_{median} (%)*	Gr 1 Gr 2	6.57±0.93 8.03±0.73	-4.384[a]	**<0.001**	Gr 1 Gr 2	6.65±0.81 7.03±0.83	-2.350[a]	**0.021**
Hypertensive retinopathy**	Gr 1 Gr 2	0 (0) 27 (81.8)	20.498[b]	**<0.001**	Gr 1 Gr 2	20 (30.8) 20 (46.6)	3.095[b]	0.079

* mean ± SD ** number (percentage) [a] t-test [b] Chi-square test
T1DM = type 1 diabetic patients; T2DM = type 2 diabetic patients; DR = diabetic retinopathy; Gr 1 = patients without DR (type 1 n=51; type 2 n=65); Gr 2 = patients with DR (type 1 n=33; type 2 n=42); SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA_1c = glycated hemoglobin value determined at the beginning of the study from a single venous blood sample; $HbA_{1cmedian}$ = glycated hemoglobin value obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet).

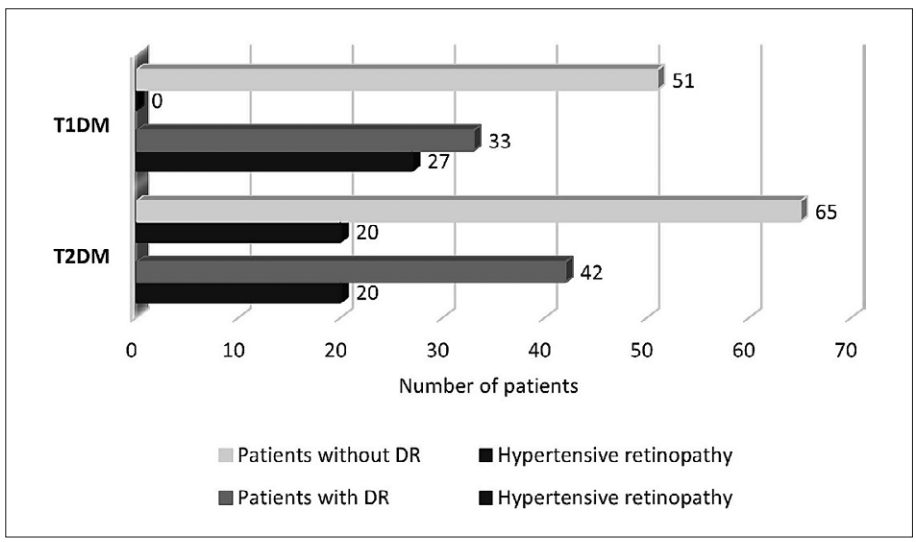

Fig. 1. Proportion of type 1 and type 2 diabetic patients with and without diabetic retinopathy and concomitant hypertensive retinopathy.

Binary logistic regression analysis (no DR/DR) showed that diabetes duration and long-term poor glycemic control, presented by $HbA1c_{median}$, were the main predictors of DR in both types of diabetes (Table 5). In contrast, SBP (OR = 1.05, p = 0.045) and hypertensive retinopathy (OR = 3.75, p < 0.001) were the main predictors/indicators of DR only in T1DM. Using the same logistic regression analysis, no significant association between DR and other analyzed variables were observed.

Discussion

The results of our study showed that in T1DM DR is positively associated with SBP, $HbA1c_{median}$ and hypertensive retinopathy, while in T2DM DR is posi-

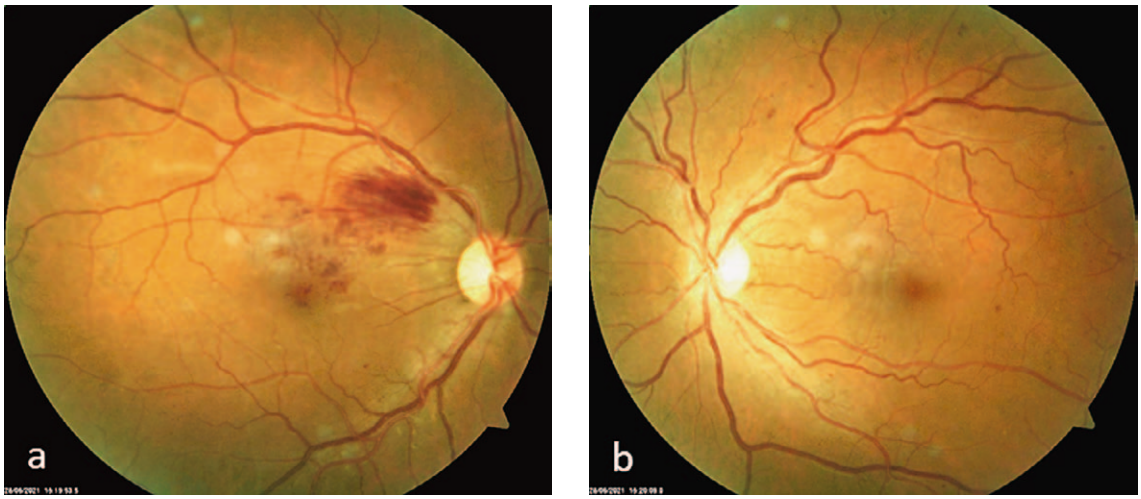

Fig. 2. Macular field of right (a) and left (b) eye of type 1 diabetic patient with nonproliferative diabetic retinopathy and concomitant hypertensive retinopathy Gr 3/2.

Table 3. Correlation between diabetic retinopathy and clinical parameters in type 1 and type 2 diabetic patients included in the study.

	Diabetic retinopathy					
	T1DM			**T2DM**		
	r^2	**t**	**p**	**r^2**	**t**	**p**
SBP	0.160	2.228	**0.035**	0.033	1.887	0.062
DBP	0.022	0.765	0.451	0.012	-1.109	0.269
HbA_1c	0.032	0.933	0.359	0.008	0.939	0.349
HbA_1c_{median}	0.425	4.384	**<0.001**	0.049	2.350	**0.021**
	Spearman R	t(N-2)	p	Spearman R	t(N-2)	p
Hypertensive retinopathy	0.856	8.428	**<0.001**	0.170	1.768	0.079

T1DM = type 1 diabetic patients; T2DM = type 2 diabetic patients; SBP = systolic blood pressure; DBP = diastolic blood pressure; 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).

tively related only to $HbA1c_{median}$. Binary logistic regression analysis (no DR/DR) showed that diabetes duration and $HbA1c_{median}$ were the main predictors of DR in both types of diabetes (Table 5). In contrast, SBP (OR = 1.05, p = 0.045) and hypertensive retinopathy (OR = 3.75, p < 0.001) were the main predictors/indicators of DR only in T1DM. Using the same logistic regression analysis, no significant association between DR and other analyzed variables was observed. Elevated blood glucose is a well-established risk factor for macrovascular and microvascular complications in patients with diabetes. The large prospective DCCT (Diabetes Control and Complications Trial) that included T1DM, as well as a UKPDS trial that included T2DM, showed that tight glycemic control significantly reduces the risk of the development and progression of DR and blindness.[18,19]

SBP and DBP are additional important modifiable risk factors for DR that have been documented in many trials. The ABCD (Appropriate Blood Pressure Control in Diabetes) and UKPDS are large, prospective trials that included T2DM and observed that strict blood pressure control can prevent and/or limit DR and visual dysfunction.[20,21] In ABCD study there were no significant differences in SBP and DBP between DR groups in T2DM. Similar to our results, blood pressure was similar in normotensive normoalbuminuric T2DM patients with and without DR[22].

Table 4. Results of two-way ANOVA for the differences in systolic and diastolic blood pressure according to the type of diabetes, diabetic retinopathy status, and their interaction.

		SBP		DBP	
	df	F	p	F	p
DM type	1	13.431	**<0.001**	0.571	0.451
DR	2	7.006	**0.009**	0.015	0.904
DM type & DR	3	0.782	0.378	1.317	0.253

DM type = type of diabetes mellitus; DR = diabetic retinopathy status; SBP = systolic blood pressure; DBP = diastolic blood pressure.

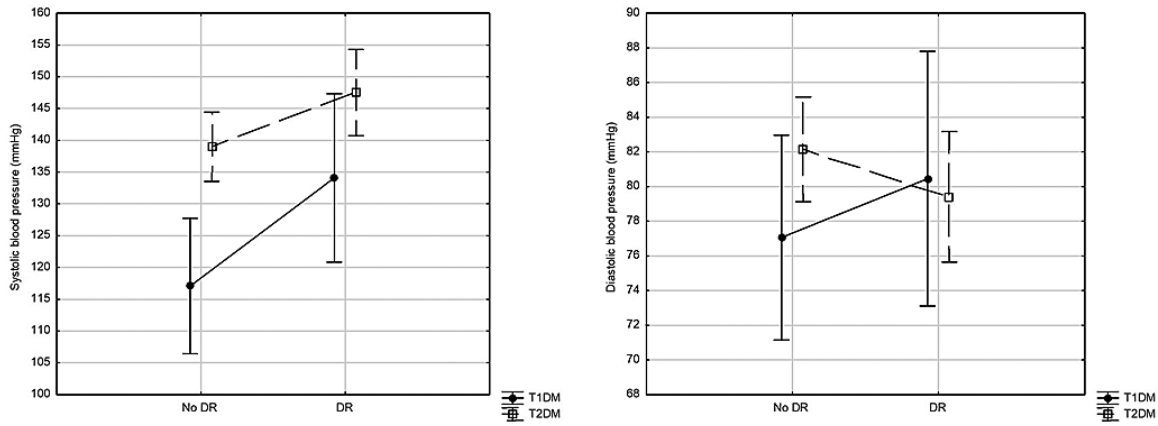

Fig. 3. Differences in systolic and diastolic blood pressure according to the type of diabetes and diabetic retinopathy status

Table 5. Predictors and indicators of diabetic retinopathy in type 1 and type 2 diabetes using binary logistic regression analysis.

	T1DM		T2DM	
	OR (95% CI)	p	OR (95% CI)	p
Diabetes duration	1.20 (1.05-1.38)	**0.005**	1.17 (1.08-1.27)	**<0.001**
SBP	1.05 (0.99-1.10)	**0.045**	1.02 (0.99-1.04)	0.065
DBP	1.03 (0.95-1.10)	0.438	0.98 (0.95-1.01)	0.269
HbA_1c	1.32 (0.72-2.41)	0.351	1.18 (0.83-1.68)	0.348
HbA_1c_{median}	6.92 (1.58-30.17)	**0.007**	1.75 (1.07-2.87)	**0.024**
Hypertensive retinopathy	3.75 (1.78-7.89)	**<0.001**	2.05 (0.91-4.61)	0.081

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; 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).

High blood pressure in T1DM has been shown to significantly increase the risk of proliferative DR in the Wisconsin Epidemiology Study.[23] Another study that also included T1DM indicated that each increment of 5 mmHg in night-time SBP and DBP increase the risk of DR up to 40% even in T1DM without hypertension.[24] In contrast, it has been documented that normoalbuminuric T1DM with hypertension had no higher prevalence of DR compared to normoalbuminuric normotensive patients[25]. Another study that in-

cluded normoalbuminuric T1DM found higher only night blood pressure in patients with DR compared to those without retinopathy.[26] The results from the EURODIAB Prospective Complications Study, which included T1DM, found that DBP is a significant risk factor for DR after adjusting for nephropathy, while nighttime 24-hour ambulatory SBP was associated with the presence and severity of DR in T1DM without nephropathy and hypertension.[6,27] In our study, only SBP was associated with DR, which is in line with our previous study in which we observed that SBP is a risk factor for the development and progression of DR in T1DM with normal renal function and normoalbuminuria, and with the prospective UKPDS study, which also found higher relative risk for the incidence of DR with higher SBP in T2DM.[13,28] However, the methods used for diagnosis of blood pressure in our study (single standard sphygmomanometer not 24-hour ambulatory blood pressure) may influence the final results of our investigation and make a comparison between studies difficult.

In T1DM treatment with the ACE-inhibitor lisinopril resulted in a statistically significant 50% reduction in the progression of DR and an 82% reduction in the progression to proliferative DR even after an adjustment for glycemic control.[29] In the Diabetes Remission Clinical Trial (DIRECT) 5 years of ACE-inhibitor candesartan treatment in T1DM reduced the incidence of DR in severity by 18% and reduced the incidence of DR progression by 35%.[30] ACE-inhibitors have a beneficial hemodynamic effect, reduce endothelial dysfunction via enhancement of nitric oxide and blocking vascular endothelial growth factor receptors, and improve the blood-retinal barrier.[31] The beneficial effect on DR is observed even in T1DM with blood pressure in the "normal range," which is also observed in UKPDS, where researchers reported that there was no evidence of a threshold effect of SBP for the incidence of microvascular complications in T2DM.[28] It should be stressed that the majority of our T1DM were not on antihypertensive therapy and that the mean SBP and DBP was within the normal range for patients with diabetes (mean blood pressure 123/78 mmHg).

In diabetic mouse models, hypertension significantly increases the thickness of the basement membrane and permeability to albumin.[32] The frequency of acellular capillaries, the morphological gold-standard marker for DR, is doubled in diabetic rats with hypertension compared to those without hypertensionin.[33] Depositions of advanced glycation end products-proteins in the retinal vasculature activated with hypertension induced development of DR in that study. Othe studies also suggested that hypertension could induce oxidative stress and inflammation, risk factors strongly implicated in the pathogenesis of DR, and contributed to the development of DR.[34] In animal models with diabetes and genetic susceptibility to hypertension, inflammation processes in the retina are present before the establishment of full hypertension.[35] It seems that the coincidence of hyperglycemia and hypertension can accelerate inflammation and oxidative stress, which are pathological processes involved in DR development and progression.

The present study has a number of potential limitations. First, its design was cross-sectional and sample size in subgroups was small, which limited our ability to infer a causal relation between DR and blood pressure. Second, ambulatory blood pressure measurement is more useful than causal or office blood pressure measurement, and the methods used for diagnosis of DR and blood pressure may have an influence on the final results, making comparisons of the findings between studies difficult.[36] Third, our analyses were based on a single measurement of blood pressure that may not reflect the relation over time. Fourth, this cohort had little racial/ethnic diversity and our data would be primarily relevant to a white European population.

In conclusion, our results suggest that diabetes duration and $HbA1c_{median}$ are the main predictors of DR in both types of diabetes. However, SBP and hypertensive retinopathy were the predictors/indicators of DR only in T1DM, indicating that blood pressure is associated with tDR in Type 1 but not in type 2 diabetes. This points to the need for close monitoring of blood pressure in T1DM aimed at preventing or limiting the progression of DR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the Acta Clinica Croatica. The authors did not receive any

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Sažetak

KRVNI TLAK JE POVEZAN S DIJABETIČKOM RETINOPATIJOM KOD BOLESNIKA SA TIPOM 1 ALI NE I KOD TIPA 2 ŠEĆERNE BOLESTI

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Cilj ovog istraživanja bio je istražiti povezanost sistoličkog krvnog tlaka (SKT) i dijastoličkog krvnog tlaka (DKT) te dijabetičke retinopatije (DR) kod šećerne bolesti tipa 1 i tipa 2 te utvrditi razlike između ova dva tipa šećerne bolesti. Ova presječna studija uključila je 84 bolesnika sa šećernom bolešću tipa 1 (ŠB1) i 107 bolesnika sa šećernom bolešću tipa 2 (ŠB2). Oftalmološki pregled uključivao je neizravnu fundoskopiju, fotografiju fundusa u boji prema EURODIAB (EUROpe and DIABetes) protokolu i optičku koherentnu tomografiju. Krvni tlak izmjeren je živinim tlakomjerom nakon 10-minutnog mirovanja. Kod ŠB1 DR je bila pozitivno povezana sa SKT ($p = 0,035$), $HbA1c_{medijanom}$ ($p < 0,001$) i hipertenzivnom retinopatijom ($p < 0,001$), dok je u ŠB2 DR bila pozitivno povezana samo s $HbA1c_{medijanom}$ ($p = 0,021$). Analiza binarne logističke regresije (bez i sa DR) pokazala je da su trajanje šećerne bolesti i $HbA1c_{medijan}$ glavni prediktori DR u oba tipa šećerne bolesti. Međutim, SKT ($OR = 1,05$, $p = 0,045$) i hipertenzivna retinopatija ($OR = 3,75$, $p < 0,001$) bili su glavni prediktori/indikatori DR samo u ŠB1. Zaključno, krvni tlak je povezan s DR kod tipa 1, ali ne i kod tipa 2 šećerne bolesti.

Ključne riječi: *sistolički krvni tlak, šećerna bolest tip 1 i tip 2, retinopatija, čimbenici rizika*