Coll. Antropol. **37** (2013) Suppl. 1: 65–70
Original scientific paper

The Association between the HLA System and Retinopathy Development in Patients with Type 1 Diabetes Mellitus

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A B S T R A C T

*Duration of diabetes and chronic hyperglycemia are the most important risk factors in the pathogenesis of diabetic retinopathy (DR). However, there is increasing evidence suggesting that genetic factors may also contribute to its development. The aim of this study was to determine the role of the HLA system in the development of DR in patients with type 1 diabetes mellitus. Class II genes (DRB1, DQB1) were typed using the PCR-SSP method. Based on the fundus examination the patients were divided into two groups: one group with no or mild nonproliferative diabetic retinopathy (NPDR) and the other group with severe/very severe NPDR or proliferative diabetic retinopathy (PDR). The study confirms the influence of HLA genes in the development of DR in Croatian type 1 diabetic patients. In our patients, susceptibility to PDR appears to be primarily associated to DQB1*0201 with the relative risk, RR=5.29 and DQB1*0302 (RR=2.84). However, a strong positive correlation between DR and alles DRB1*0301 (RR=2.12) and DRB1*0402 (RR=3.01) was also found.*

***Key words**: diabetic retinopathy, pathogenesis, HLA system, type 1 diabetes mellitus*

Introduction

Diabetic retinopathy is a common and progressive complication of diabetes mellitus. It is a leading cause of acquired blindness in working-age adults and it has been estimated that it causes 12% of blindness in developed countries[1]. Diabetic retinopathy is characterized by the loss of pericytes, hypertrophy of the basement membrane, microaneurysms formation, increased vascular permeability, capillary occlusions, neovascularisation and fibrovascular proliferation. The predominant cause of visual loss in diabetic patients results primarily from intraocular angiogenesis (proliferative diabetic retinopathy, PDR) and leakage of the retinal vessels (diabetic macular edema, DME)[1,2]. According to the Wisconsin epidemiologic study of diabetic retinopathy (WESDR) in patients with type 1 diabetes mellitus the prevalence of any grade of retinopathy after more than 15 years of duration of diabetes was 99.5% and after 35 years 67% of them had proliferative diabetic retinopathy (PDR)[3]. Chronic hyperglycemia and the duration of diabetes are the most important risk factors in the development of retinopathy, with strict control of the blood glucose level preventing and delaying its onset and progression[4,5]. However, in some patients retinopathy progresses in a short period of time despite good glycemic control, whilst others do not develop retinopathy even in the absence of adequate glycemic control suggesting that certain genetic predisposition may exist. In some families the risk of PDR development is increased with the familial clustering of this form of DR which could not be accounted for with the conventional risk factors[6]. The genetic component is further confirmed by twin and population studies[7–10]. It is presumed that genetic influence may explain 50% of the risk of PDR[6].

Received for publication July 15, 2012

Although extensively studied, the pathogenesis of diabetic retinopathy is still insufficiently understood, and the mechanisms leading to blood-retinal barrier disruption, capillary occlusion and subsequent retinal neovascularisation have still not been completely determined. There is undeniable evidence however that the immune system has an active role in its development with a marked affect of autoimmune mechanisms in its initial and particularly in its proliferative phases with increasing data suggesting that genetic factors may also play an important role[11–16].

Human leukocyte antigen (HLA) system plays a significant role in immune responses and immunologic tolerance, and its association to diabetes type 1 is well recognized[17]. Hence, the search for markers of a genetic predisposition for diabetic retinopathy has focused on genes encoded by the HLA region. There are several studies investigating the role of different HLA antigens in development and progression of diabetic retinopathy. A small number of accomplished studies have revealed controversial results and have not completely succeeded to explain the relationship between retinopathy and hereditary factors[18–30]. Development of modern molecular biology techniques and accessibility of high resolution HLA gene typing has advanced research addressing the relationship of the HLA system and different particularly autoimmune diseases. This in turn has also enabled more precise identification of HLA genes susceptible to diabetic retinopathy development. More recent studies have demonstrated that the relationship of HLA complex and diabetic retinopathy could in fact be determined on the DNA level[31–34].

Accordingly, the aim of this study was to investigate the immunogenetic profile with high-resolution genotyping in Croatian type 1 diabetic patients in order to evaluate the association between the HLA system and retinopathy development and consequently identify the high-risk population.

Patients and Methods

Patients

The study included 87 unrelated adults of both sexes with type 1 diabetes mellitus. The main characteristics of the patients are shown in Table 1. Based on the fundus examination they were divided into two groups. The first group (DR–) consisted of 44 patients who have had diabetes for more than 12 years and showed none or mild signs of nonproliferative diabetic retinopathy (NPDR) on both eyes. The second group, also named the severe retinopathy group (PDR+), comprised of 43 patients with severe/very severe NPDR or proliferative diabetic retinopathy (PDR) in one or both eyes. All patients went through a complete medical and ophthalmologic examination and their medical history was noted.

Fundus examination

Each patient partaking in the study underwent a full ophthalmologic examination. After pupil dilatation with topical 1% tropicamide detailed fundus examination for presence of diabetic retinopathy was performed by binocular indirect ophthalmoscopy using the Goldman three mirror lens. Assessment was carried out on seven fields and the diagnosis and pathological retinal findings were carefully recorded. Fluorescein angiography was performed on all patients exhibiting signs of diabetic retinopathy and retinopathy was graded using the scale modified from Airlie House grading system, according to ETDRS (Early Treatment Diabetic Retinopathy Study) criteria[35]. The first DR– group (N=44) consisted of patients who despite a duration of diabetes for more than 12 years had none or only mild signs of nonproliferative diabetic retinopathy (NPDR) on both eyes. Patients in the second PDR+ group (N=43) had severe/very severe nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) in one or both eyes. Severe/very severe NPDR was defined by the presence of severe retinal hemorrhages in four quadrants, and/or ve-

TABLE 1
BASELINE CHARACTERISTICS OF TYPE 1 DIABETIC PATIENTS WITHOUT SIGNS OF DIABETIC RETINOPATHY (DR– Group) AND PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY (PDR+ Group)

	DR– Group (N=44)	PDR+ Group (N=43)	p
Women N (%)	24 (54.55)	20 (46.51)	NS
Men N (%)	20 (45.45)	23 (53.49)	NS
Age (years)*	47.95±13.35	35.49±7.76	<0.0001
Onset of diabetes (years)*	24.41±3.02	18.37±8.96	0.0138
Duration of diabetes (years)*	23.57±9.44	17.37±5.64	0.0004
Insulin dosage (IU/kg)*	0.76±0.18	0.74±0.20	NS
HbA_1c (%)*	8.49±1.32	8.26±1.61	NS
BMI (kg/m^2)*	24.77±3,80	23.26±2.69	0.0359
Systolic blood pressure (mmHg)*	134.66±17.96	129.30±13.61	NS
Diastolic blood pressure (mmHg)*	82.50±9.37	84.42±10.19	NS
Antihypertensive treatment N (%)	27 (61.36)	22 (51.16)	NS

Abbreviations: HbA_1c – glycated hemoglobin value, BMI – body mass index, NS – not significant

nous beading in two quadrants, and/or extensive intraretinal microvascular abnormalities (IRMA) in one quadrant. PDR was defined by the presence of new vessels on the disc and/or within 1 disc diameter from the optic disc (NVD), and/or new vessels elsewhere in the retina (NVE), and/or preretinal or vitreous hemorrhage.

HLA typing

DNA was extracted from peripheral blood using the salting out method. The determination of HLA-DRB1 and -DQB1 specificities was performed using the PCR--SSP (Polymerase Chain Reaction – Sequence Specific Primers) method as described by Olerup[36]. This method is based on a PCR reaction which contains 50 μg/μL genomic DNA, 10xPCR buffer, dNTPs, Taq polymerase and specific primers, and a subsequent electrophoresis on a 2% agarose gel. Gels were examined under UV illumination and based on the positive reactions pattern, the HLA specificity was determined. The method allows the determination of theerteen HLA-DRB1 and seven HLA--DQB1 specificities.

Statistical methods

The patients characteristics were compared by using the Student's t-test. The obtained p values less than 0.05 were considered significant. Frequencies were compared by the chi-square test of independence or alternatively the Fisher exact probability test where appropriate. The level of significance was set at $p<0.05$[37]. Severity of the correlation of diabetic retinopathy and each antigen (allele, genotype) of HLA was determined by calculating the relative risk using the Woolf's method[38].

Results

Patient characteristics

The baseline characteristics of the patients with type 1 diabetes without DR (DR-) and patients with severe diabetic retinopathy (PDR+) are shown in Table 1. The mean page in the DR– group was 47.95±13.35 years and in the PDR+ group 35.49±7.76 years ($p<0.0001$). The mean diabetes duration in the DR- group was 23.57± 9.44 years and in the PDR+ group 17.37±5.64 years ($p=0.0004$). There were no statistically significant differences in the blood sugar level control expressed by HbA_1c value (8.26±1.61 IU/kg vs. 8.49±1.32 IU/kg), insulin dose per kilogram of body weight (0.74±0.20 IU/kg vs. 0.76±0.18 IU/kg) as well as systolic blood pressure (129.30±13.61 mmHg vs. 134.66±17.96 mmHg) and diastolic blood pressure (84.42±10.19 mmHg vs. 82.50± 9.37 mmHg) between the study groups. There were also no statistically significant differences in the use of antihypertensive treatment.

HLA typing

The HLA association with diabetic retinopathy was determined by analyzing the results of low resolution typing of HLA class II alleles (Table 2 and Table 4) and subtyping / high resolution typing of DRB1*03 and DRB1*04 (Table 3) as well as DQB1*02 and DQB1*03 (Table 5) allele frequencies.

The results of low resolution typing of DRB1 alleles in patients with proliferative diabetic retinopathy compared with diabetics without signs of retinopathy are shown in Table 2. In both groups, the most common allele was HLA-DRB1*03 with a frequency of 38.37% in patients with PDR and 22.73% in patients without retinopathy. This difference was statistically significant ($p= 0.0378$) with a relative risk of 2.12. The frequency of DRB1*04 allele was significantly more common in the group of diabetic patients with proliferative retinopathy (15.91% in DR- and 34.88% in PDR+ group, $p=0.0068$) with the relative risk of 2.83.

The DRB1*0301 was the only DRB1*03 allele found in both groups after high resolution typing/subtyping and it was significantly more frequent in PDR+ than DR– patients with an incidence of 38.37% and 22.73% respectively ($p =0.0378$ and RR=2.12). Comparing the results of DRB1*04 allele subtyping five distinct subtypes namely *0401, *0402, *0404 *0405 and *0408 were detected. The most prevalent in both groups, and also significantly more frequent in patients with PDR+ was allele *0401 (22.09% in the PDR+ and 9.09% in the DR–, $p=0.0309$). The relative risk was 2.84 (Table 3).

TABLE 2
FREQUENCY AND STATISTICAL SIGNIFICANCE OF ALLELES HLA-DRB1*03 AND *04 IN TYPE 1 DIABETIC PATIENTS WITHOUT SIGNS OF DIABETIC RETINOPATHY (DR– Group) AND PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY (PDR+ Group)

HLA-DRB1*	DR– Group (N=44)		PDR+ Group (N=43)		p
	N	%	N	%	
03	20	22.73	33	38.37	0.0378
04	14	15.93	30	34.88	0.0068

TABLE 3
FREQUENCY AND STATISTICAL SIGNIFICANCE OF ALLELES SUBTYPES HLA-DRB1*03 AND *04 IN TYPE 1 DIABETIC PATIENTS WITHOUT SIGNS OF DIABETIC RETINOPATHY (DR– Group) AND PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY (PDR+ Group)

HLA-DRB1*	DR– Group (N=44)		PDR+ Group (N=43)		p
	N	%	N	%	
0301	20	22.73	33	38.37	0.0378
0401	8	9.09	19	22.09	0.0309
0401	8	9.09	19	22.09	0.0309
0402	1	1.14	7	8.14	NS
0404	1	1.14	3	3.49	NS
0405	2	2.27	1	1.16	NS

Analysis of DQB1 allele frequencies is shown in Table 4. In both groups of patients the most common allele was DQB1*03, with significantly higher frequency (p=0.0474) in patients with proliferative diabetic retinopathy (47.67%) as opposed to patients without retinopathy (31.82%) with a relative risk of 1.95. Alternatively DQB1*02 allele (45.35% in the PDR+, to 31.82% in the DR-) showed no statistically significant differences.

In patients with proliferative diabetic retinopathy implementation /use of subtyping DQB1*02 allel only the DQB1*0201 allele was found. Conversely in the group of DR– patients two subtypes DQB1*0201 and *0202 were detected. The frequency of DQB1*0201 allele in PDR patients was statistically higher than in the group of patients with no signs of retinopathy (45.35% vs. 21.59%, p=0.0016) with a relative risk of 3.01. Allele DQB1*0202 was discovered only in the DR– group (10.23%). Subtyping of the DQB1*03 allele identified four distinct subtypes (*0301–*0304). In diabetic patients with proliferative retinopathy the most common allele was DQB1*0302 with a frequency of 43.02% and was found to be statistically significantly higher than in patients without diabetic retinopathy with a frequency of 12.5% (p<0.0001). The relative risk was 5.29. Conversely the frequency of DQB1*0301 allele in patients with proliferative diabetic retinopathy was statistically significantly lower compared to patients without retinopathy (3.49%, *vs*. 14.77%, p=0.0207) with a relative risk of 0.21 (Table 5).

TABLE 4
FREQUENCY AND STATISTICAL SIGNIFICANCE OF ALLELES HLA-DRB1*02 AND *03 IN TYPE 1 DIABETIC PATIENTS WITHOUT SIGNS OF DIABETIC RETINOPATHY (DR– Group) AND PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY (PDR+ Group)

HLA-DRB1*	DR– Group (N=44)		PDR+ Group (N=43)		p
	N	%	N	%	
02	28	31.82	39	45.35	NS
03	28	31.82	41	47.67	0.0474

TABLE 5
FREQUENCY AND STATISTICAL SIGNIFICANCE OF ALLELES SUBTYPES HLA-DQB1*02 AND *03 IN TYPE 1 DIABETIC PATIENTS WITHOUT SIGNS OF DIABETIC RETINOPATHY (DR– Group) AND PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY (PDR+ Group)

HLA-DRB1*	DR– Group (N=44)		PDR+ Group (N=43)		p
	N	%	N	%	
0201	19	21.59	39	45.35	0.0016
0202	9	10.23	0	0.00	0.0069
0301	13	14.77	3	3.49	0.0207
0302	11	12.50	37	43.02	<0.0001
0303	2	2.27	1	1.16	NS
0304	2	2.27	0	0.00	NS

Discussion

Diabetic retinopathy (DR) is a common and progressive microvascular complication of diabetes and despite the availability of effective treatment it remains one of the leading causes of vision impairment and blindness in working-age adults[3]. No distinct predisposing factor has yet been identified and risk factors such as hypertension, poor metabolic control, nephropathy and triglycerides level cannot fully explain the development and progression of this complication of diabetes mellitus[39]. It has been established that strict control of glycemia is the best approach to preventing this complication[18]. However, there are certain diabetic patients who develop retinopathy despite good glycemic control and conversely others irrespective of poor glucose control do not develop signs of retinopathy. It is regarded that these differences could be due to genetic predisposition[40–42].

Although the etiopathogenesis of diabetic retinopathy is still not fully understood, there is undoubtedly an impact of the immune system on its origin and development. It is proven that certain autoimmune mechanisms exist particularly in the occurrence of retinal capillary occlusions 1and the development of neovascularization. The presence of antipericite and antiendothelial antibodies in the blood of patients with diabetes indicate a possible role of autoimmune reactions in the early stages of diabetic retinopathy. Infiltration of monocytes, T and B lymphocytes, fibroblasts, deposits of immunoglobulins, activated complement components and lymphokines in retinal neovascular membranes are evidence of autoimmune activity in its proliferative phase[11–16].

In view of the role of HLA system in immune activity and tolerance as well as its association with type 1 diabetes, the search for indicators of genetic predisposition for the development of diabetic retinopathy is focused on the HLA gene. It is known that patients with type 1 diabetes are more prone to develop severe diabetic retinopathy than patients with type 2 diabetes. The cause is not entirely known, but it could at least partially be connected to the HLA system[3]. This may therefore indicate that the genetic factors may influence the susceptibility for developing severe retinopathy and thus that risk could additionally be linked to HLA genes[6–10].

Studies on the subject of the association of the HLA system and different autoimmune diseases have been advanced using the methods of molecular biology and typing of HLA genes on the DNA level. This has enabled investigation of the role of certain alleles in the pathogenesis of specific autoimmune diseases. In contrast to serological methods, methods of molecular genetics are more precise whereby the number of undetected alleles is significantly lower, and the obtained results provide direct insight into the genetic basis of the disease. To our best knowledge this is the first report addressing the association between diabetic retinopathy and the HLA system in Croatian patients with type 1 diabetes. This form of investigation is also rare in other populations[21–23,25, 26,31,32,34].

It is known that the duration of diabetes and glycemic control are the most important risk factors in the devel-

opment of diabetic retinopathy. To avoid the influence of the duration of diabetes on the study's results we compared a group of patients with pronounced signs of diabetic retinopathy at an early age with a group consisting of patients without retinopathy or with initial signs of nonproliferative retinopathy in which the diabetes lasted significantly longer. In addition to the duration of diabetes, glucose level is another significant risk factor for developing diabetic retinopathy and thus improvement of glycemic control can slow down or even prevent its progression[2–5]. The level of glucose control in both groups of our patients showed no statistically significant differences, which means that there were no statistical differences in mean HbA_1c values or in the average dose of insulin per kilogram of body weight. Arterial hypertension is also a well-known risk factor for developing diabetic retinopathy. In our study, there was no statistically significant difference in blood pressure control in view of systolic and diastolic pressure or antihypertensive treatment[2–5].

There are several studies investigating the role of different HLA antigens in development and progression of diabetic retinopathy with conflicting results[18–34].

Barbosa et al.[18] found that patients with proliferative retinopathy had lower incidence of HLA-B7 and higher incidence of HLA-B15. Likewise Gray et al.[43] found a lower incidence of HLA-B7 in diabetic patients with proliferative retinopathy. Furthermore, Dornan et al.[19] established that patients with the same mean blood glucose level with retinopathy had a higher incidence of HLA-DR4 and lower incidence of HLA-DR2 than those without retinopathy. Cruickhanks et al.[23] found that diabetics with HLA-DR4 who were negative for HLA-DR3 were five times more likely to have severe retinopathy than those negative for both antigens. Falck et al.[23] studied 105 Finnish adolescents with type 1 diabetes mellitus and found a significantly higher prevalence of HLA-DR1 in patients with retinopathy. In patients with type 2 diabetes mellitus Birinci et al.[24] establish that HLA-DR4 and DQ8 frequencies were higher in patients with nonproliferative retinopathy than in those with proliferative retinopathy and HLA-DR7 frequency was higher in patients with proliferative retinopathy than in nonproliferative cases. Mimura et al.[25] in a study of type 1 diabetic patient found that the frequencies of alleles HLA-B62, Cw4 and DQ4 as well as haplotype Cw4-DR4-DQ4, were significantly higher in the patients with proliferative retinopathy.

Newer and more advanced methods of HLA typing on the DNA level used in recent studies even enable a more precise determination of the relationship between diabetic retinopathy and HLA. In our study DRB1*0301 was the only DRB1*03 allele found in all patients. On the basis of its frequency, we can conclude that the DRB1*0301 allele could be a risk carrier for the development of diabetic retinopathy, especially in its proliferative form. The role of subtypes of DRB1*04 allele was determined by comparison of the relative frequency of certain DRB1*04 alleles in both patient groups. A comparison of these groups in respect to DRB1*0401 allele frequency implies that the DRB1*0401 allele determines susceptibility to the development of proliferative diabetic retinopathy in Croatian diabetic patients with type 1 diabetes. Our results indicate a susceptibility for diabetic retinopathy development in allele DQB1*03 carriers whilst a comparison of patients with proliferative diabetic retinopathy and patients without signs of retinopathy, we find no significant differences in allele DQB1*02 frequency. The specific role of distinct DQB1 alleles becomes clearer after the suptyping (when high resolution typing) of DQB1*02 and *03 alleles is conducted. Analysis of DQB1*02 and *03 allele subtyping results revealed a significant difference in the distribution of certain subtypes in the two study groups. A few of the investigated alleles exhibited a protective role whilst others susceptibility to the development of diabetic retinopathy. Accordingly a carrier of the DQB1*0201 allele showed susceptibility to the development of proliferative diabetic retinopathy whilst the DQB1*0202 allele exhibited a protective role (RR=0.05). Examination of DQB1*03 allele subtypes in both groups of patients showed a correlation between DQB1*0302 allele and the development of an advanced form of diabetic retinopathy (RR=5.29).

The HLA alleles associated with diabetic retinopathy in our research were to some extent consistent with those found in other studies. To our best knowledge, Agardh et al.[32] conducted one of the few studies addressing the association of HLA and diabetic retinopathy in patients with type 1 diabetes using molecular genetics (PCR-SSOP). They found a difference in the DRB1*0301 allele frequency between the groups of patients with advanced diabetic retinopathy and patients without retinopathy. Further their results confirmed a link between the DQB1*0201 allele and proliferative diabetic retinopathy. However, in contradiction to the results of our study they found no relationship between DRB1*0401 allele and proliferative diabetic retinopathy development.

Conclusion

Since HLA status established in our patients with proliferative diabetic retinopathy are generally different from those related to the onset of type 1 diabetes, we can conclude that the HLA status may play a certain role in the development and progression of diabetic retinopathy. Further, larger prospective studies need to be conducted to confirm this premise. Our results, in accordance to the results of some previous studies in other populations indicate a genetic component in the etiology of diabetic retinopathy. In addition to the importance of glycemic control, immunological factors may also play a notable role in the pathogenesis of this serious diabetic complication. Our research suggests that the genetic factors and genetic investigations may be useful in predicting the prognosis of retinopathy in patients with type 1 diabetes mellitus.

Finally, in view of our results it should be emphasized that high resolution typing is necessary required in order to ensure more precise findings which in turn enable greater accuracy in determining the connection of a particular allele and retinopathy development.

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POVEZANOST SUSTAVA HLA I RAZVOJA RETINOPATIJE U BOLESNIKA S TIPOM 1 ŠEĆERNE BOLESTI

SAŽETAK

Trajanje šećerne bolesti i kronična hiperglikemija najvažniji su rizični čimbenici u razvoju dijabetičke retinopatije (DR). Međutim, sve je više dokaza da bi u njenom nastanku važnu ulogu mogla imati i genetska predispozicija. Cilj ovog istraživanja bio je odrediti ulogu HLA sustava u nastanku i razvoju DR u bolesnika s tipom 1 šećerne bolesti. Geni razreda II sustava HLA (DRB1, DQB1) određeni su metodom lančane reakcije polimerazom PCR-SSP. Na osnovu nalaza na očnoj pozadini bolesnici su bili podijeljeni u dvije skupine: skupinu bolesnika bez znakova dijabetičke retinopatije odnosno minimalnim neproliferativnim promjenama (NPDR) te skupinu bolesnika s proliferativnom dijabetičkom retinopatijom (PDR), odnosno uznapredovalim neproliferativnim promjenama. Ovo istraživanje potvrdilo je postojanje utjecaja gena HLA na razvoj DR u hrvatskih dijabetičara s tipom 1 šećerne bolesti. U ispitivanih bolesnika podložnost za razvoj dijabetičke retinopatije prvenstveno je povezana s alelima DQB1*0201 (relativni rizik, RR=5,29) i DQB1*0302 (RR=2,84), dok su visoko podložni, ali uz manje izražen relativni rizik, aleli DRB1*0301 (RR=2,12) and DRB1*0402 (RR=3,01).