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Lack of association between diabetic nephropathy and human leukocyte antigen type 2 (HLA II-DQ1) in patients with type 2 diabetes mellitus in west of Iran

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ABSTRACT

Introduction: Diabetic nephropathy (diabetic kidney disease) is one of the microvascular complications of diabetes mellitus. The human leukocyte antigen (HLA) is a group of genes that is related to autoimmune diseases, infections and inflammation. Studies regarding the association of type 2diabetes and HLA-II are negligible.
Objectives: The aim of this study is to determinate association between diabetic nephropathy and HLA II-DQ1 in diabetes type 2 patients.
Patients and Methods: In this study, 120 diabetes type 2 patients were divided into two groups of diabetic nephropathy (case group) and without diabetic nephropathy (control group). Blood samples were taken and DNA was isolated. Asymmetric polymerase chain reaction (PCR) was used to amplify the HLA II-DQ1 exon 2 and exon 3. PCR products were hybridized and labeled with probes on the chip. Determination of HLAII-DQ1 gene typing was conducted by scanning hybrid products and analyzed with PerkinElmer ScanArray software.
Results: The results of chi-square test showed no significant difference between expression levels of HLA in the two groups ($P<0.05$).
Conclusion: There was no significant difference between expression levels of HLA in two groups of patients. Various factors such as demographic characteristics, lifestyle, geographic region, and race are the factors influencing the relationship between diabetic nephropathy and DQ1-HLA II. Since this study is conducted in one region and one race and with limited population, it is suggested that future studies should be considered and the association between the mentioned variables with HLA should be considered.

Implication for health policy/practice/research/medical education:
The association between diabetic nephropathy and human leukocyte antigen type 2 (HLA II-DQ1) in patients with type 2 diabetes mellitus can be a risk factor for diabetic kidney disease.
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Introduction

Diabetes mellitus is a distinct group of metabolic disorders identified with chronic hyperglycemia and disorder of carbohydrates, lipids, and protein metabolism due to insufficiency of the secretion or function of the insulin, which ultimately leads to long-term complications in various systems of the body (1). The prevalence of diabetes has increased dramatically over the past two decades, from around 30 million in 1985 to 382 million in 2013, and according to the reports, by 2035, the global

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prevalence of this disease will reach 592 million (2).

Complications associated with diabetes can be divided into two vascular and non-vascular categories that are similar in type 1 and type 2 diabetes (T2DM). Vascular complications of diabetes are classified into macro-vascular groups (including cerebrovascular disease, coronary artery disease and peripheral vascular disease) and micro-vascular (including diabetic nephropathy, diabetic retinopathy and diabetic neuropathy) (3,4). The most common cause of renal failure in the United States and Europe and in many developing countries is diabetic nephropathy (5,6). Asian people with type 2 diabetes have a higher incidence of nephropathy (7,8). About 43% of type 2 diabetes patients suffer from chronic renal disease, of which the prevalence of chronic renal disease is 61% among patients aged 65 years and older (9). Several causes have been reported for diabetic nephropathy(diabetic kidney disease), including hyperglycemia, hypertension, inflammation, smoking, and dyslipidemia (10,11). Additionally, familial clustering indicates the role of genetic in pathogenesis of diabetic nephropathy (12).

The human leukocyte antigen (HLA) is a group of genes, which has been mostly studied with regard to its association with autoimmune diseases, infections and inflammation. The association of type 1 diabetes and HLA class 2 has been reported in various studies (13,14). However, the number of studies regarding the association of type 2 diabetes and HLA class 2 are scarce. Studies have reported various results on the association between type 1 diabetes and HLA class II. For example, in the study of Chowdhury et al in England, no relationship was reported between diabetic nephropathy and HLA class II (15). Additionally in the study by Ražanskaitė-Virbickienė et al in Lithuania, HLA-DRB1*03 was reported as a risk factor for diabetic nephropathy ($P = 0.021$) (13) and in the study of Cordovado et al in the United States, HLA-DRB1*04 was introduced as a protective agent against diabetic nephropathy ($P = 0.001$) (14). Accordingly, in a study conducted by Ma et al in China, the relationship between type 2 diabetes and HLA-DQA1 and HLA-DQB1 was investigated, which showed a significant relationship was reported compared to the healthy subjects (control group) ($P < 0.01$) (16).

Considering the high prevalence of type 2 diabetes and also the risk of diabetic nephropathy as an important complication and an effective factor on the morbidity and mortality of this disease, conducting studies is necessary to better understanding the pathogenesis of the disease. Since HLA II-DQ1 has been shown to be effective in various diseases and has contributed to its role in diabetic nephropathy in type 2 diabetes, as well as the racial differences in the genetics of patients, we therefore aimed to determine the relationship between HLA II-DQ1 and diabetic nephropathy in type 2 diabetes patients in Kurdistan province, west of Iran.

Objectives

The aim of this study is to determinate relationship between diabetic nephropathy and human leukocyte antigen type 2 (HLA II-DQ1) in type 2 diabetes mellitus patients.

Patients and Methods

Patients

In this study, patients with type 2 diabetes who referred to the Tohid hospital of Sanandaj (affiliated to Kurdistan University of Medical Sciences) based on the 2017 American Diabetic Association diagnostic criteria (17) were selected as the study population. These patients entered the study based on the inclusion and exclusion criteria. In this study, exclusion criteria were; 1) secondary diabetes due to specific cause (e.g, Cushing's syndrome or chronic pancreatitis) 2) type 1 diabetes, 3) patient dissatisfaction. Finally, 120 patients were enrolled in the study. Patients were divided into 2 groups of type 2 diabetes mellitus with diabetic nephropathy as the case group and the type 2 diabetic group without diabetic nephropathy (based on protein excretion in 24-hour urine) as the control group. The non-diabetic nephropathy group included patients with a history of at least 10 years of type 2 diabetes mellitus without albuminuria (24-hour urinary albumin <30 mg). Patients with diabetic nephropathy included type 2 diabetes patients with microalbuminuria (24-hour urinary albumin of 30-299 mg) or macroalbuminuria (24-hour urinary albumin ≥300 mg). Albuminuria was confirmed after rule out of other causes such as urinary tract infection, hematuria, nephritis, and other causes of transient proteinuria and in at least two trials with intervals of 3 to 6 months. Finally, 60 patients in the case group and 60 patients in the control group were placed. Matching for age and duration was performed in the form of group matching. In this way, mean age and mean duration in the two groups of case and control were approximately equal. For gender, individual matching was performed.

Intervention and biochemical measurements

After explaining all of the stages of the study for the patients and getting informed written consent from them, 2 cc peripheral blood containing ethylenediaminetetraacetic acid (EDTA) anticoagulant was collected from each individual and DNA was extracted based on column method using blood genomic DNA extraction kit of Favorgen company (China) with catalog number FABGK001 and the quality and the quantity of DNA was determined using DeNovix DS-11 FX spectrophotometer.

Then, using the DQ low-resolution kit of Olerup Company, the DQA1 and DQB1 alleles were reproduced in the presence of Master Mix and Taq DNA polymerase in the T100 thermal cycler (Bio-Rad, USA). The polymerase chain reaction (PCR) products were electrophoresed on

2% agarose gels, stained with Ethidium bromide and visualized under UV light by gel documentation system. Finally, the obtained image was analyzed using SCORE™ software (Olerup SSP company) version 5.00.80.02T and the presence and absence of alleles were investigated.

Data analysis

Data analysis was performed using Stata version 13 software. To analyze the data, descriptive statistics including mean and standard deviation were used to describe the quantitative variables and frequency and percentage were used to describe the qualitative variables. To compare the clinical and biochemical variables in both groups, independent *t* test and chi-square test were used. The level of significance was $P < 0.05$.

Results

The mean and standard deviation of biochemical and clinical features of the patients are presented in Table 1. In addition, the frequency and percentage of biochemical and clinical features of the patients are reported in Table 2. This table compares the mean quantitative parameters and the frequency distribution of qualitative parameters evaluated in diabetic nephropathy patients and patients without nephropathy. Independent t-test showed that systolic blood pressure, diastolic blood pressure and low-density lipoprotein (LDL-C) mean values were appreciably different in both groups ($P<0.05$). The mean of systolic blood pressure, diastolic blood pressure and LDL-C in patients with nephropathy was appreciably higher than in patients without retinopathy. Additionally, the frequency distribution of hypertension in the two groups was appreciably different ($P<0.05$). While 52 (86.7%) of patients with hypertension were in the group of patients with nephropathy. Table 3 and Figure 1 show the frequency of different levels of HLA in the two patient groups. According to the results of this study, alleles of HLA-DQA1*0401 and HLA-DQA1*0301 and HLA-DQB1*0201 were 15%, 13.3% and 13.3% respectively in type 2 diabetes patients and diabetic nephropathy since in the non-diabetic nephropathy group, the highest rates were 13.3%, 11.7% and 11.7%, for alleles of HLA-DQA1*0301 and HLA-DQB1*0201 and HLA-DQB1*0501 respectively. The findings of this study showed no significant difference between different levels of HLA in the two groups ($P<0.05$).

Table 1. Demographic findings of the studied patients

Variable	Studied population (120 cases)
Age (year)	62.73 ± 9.60
Gender	
Female	60 (50%)
Male	60 (50%)
Age of onset (year)	50.56 ± 6.4
Duration of the disease (year)	12.25 ± 5.12
Body mass index (kg/m$^{2)}$	29.26 ± 2.49
Hypertension	87 (72.5%)
Insulin therapy	90 (75%)
Oral agent therapy	19 (16%)
Combination therapy (Insulin and Oral agent)	11 (9%)

Discussion

In this study, findings showed that the mean body mass index (BMI) in the patients was 29.26 ± 2.49 kg/m^2 and indicates overweight, which was consistent with the studied by Wei et al (18), Zhou et al (19) and Saleem et al (20). Obesity is very common in type 2 diabetes (≥80% of patients are obese), also it is thought to be part of the pathogenic process. Therefore, if obese patients lose weight, they will reduce the complications of diabetes, while in other studies (21,22) weight loss up to 5-10% in overweight patients reduces the risk of diabetes and improves glucose control.

The results showed that hypertension was appreciably different between the two groups and the number of people with hypertension was higher in the group of patients with nephropathy, which was consistent with the study by Aghamohammadzadeh et al (23). In this study, less than 50% of patients were hypertensive which was consistent with the study by Safaei et al (24). There are various reasons for high blood pressure in patients of this study, which for example, age and gender can be mentioned; therefore, blood pressure is lower in younger people. Studies such as Duggirala et al reported that for every 10 years increase in age, blood pressure increases for 0.83 times (25).

Our findings did not show significant association between HbA1c (glycated haemoglobin) in diabetic nephropathy and non-diabetic nephropathy patients, which is similar to the study of Farahandi et al (26). As well, in the present study, the mean of HbA1c was 9.94 ± 1.28 % which was higher than the mean reported in the study of Rahimi et al (8.7 ± 1.9 %) (27). Higher mentioned mean for HbA1c in the present study can be due to the type of diet and lifestyle, as in Glasgow et al, HbA1c was attributed to factors such as diet and exercise (28).

The findings of this study showed that there was no significant difference between different levels of HLA in the two groups. In the study of Quiroz-Mercado et al in Mexico, a significant association was found between diabetic retinopathy and HLA-DRB1*1406 in type 2 diabetic patients (29). The study by Marzban et al showed a significant relationship between diabetic peripheral neuropathy and HLA-DRB1*10 and HLA-DRB1*12 in type 2 diabetes patients (30). In a study conducted by Ma et al in China with the aim of determining the association between type 2 diabetes mellitus and HLA-DQA1 and HLA-DQB1, a significant correlation with the control

Table 2. Clinical and biochemical parameters of the two groups

Variables	Groups		*P* value
	Patients with T2DM without diabetic nephropathy (60 cases)	Patients with T2DM and diabetic nephropathy (60 cases)	
Age (y)	62.41±9.67	63.05±9.61	0.72
Gender			
Female	30 (50%)	30 (50%)	0.57
Male	30 (50%)	30 (50%)	
Age of Onset (y)	51.08±6.03	50.05±6.77	0.38
Duration of disease (y)	11.53±5.6	12.98±4.51	0.12
BMI (kg/m^2)	28.98±2.56	29.55±2.41	0.21
Hypertension	35 (58.33%)	53 (86.66%)	0.001*
Systolic BP (mm Hg)	126.5±8.82	131.28±11.39	0.01*
Diastolic BP (mm Hg)	81.06±7.61	84.4±9.63	0.03*
Insulin therapy	46 (76.66%)	44 (73.33%)	0.6
Oral agent therapy	10 (16.66%)	9 (15%)	0.8
Combination therapy (Insulin and oral agent)	6 (10%)	5 (8.33%)	0.5
HbA1c (%)	9.77±1.25	10.11±1.3	0.14
FPG (mg/dL)	186.2±34.52	189.45±34.23	0.6
TG (mg/dL)	280.61±81.4	263.85±84.27	0.27
HDL (mg/dL)	38±5.06	38.26±5.46	0.78
LDL (mg/dL)	124.86±31.01	151±29.41	0.001*
GFR (mL/min)	46.3±14.28	42.9±14.96	0.2

BMI: Body mass index, BP: blood pressure, FPG: fasting plasma glucose, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, GFR: glomerular filtration rate.
* *P* value < 0.05 is statistically significant.

Table 3. Comparison of the frequency of HLA in the patients with diabetic nephropathy and the control group

HLA	Groups		*P* value*
	Patients with T2DM without diabetic nephropathy (60 cases)	Patients with T2DM and diabetic nephropathy (60 cases)	
A0201	5 (8.3 %)	6 (10 %)	0.75
A0301	8 (13.3 %)	8 (13.3 %)	0.9
A0401	3 (5 %)	9 (15 %)	0.07
A0501	5 (8.3 %)	4 (4.7 %)	0.73
B0201	7 (11.7 %)	8 (13.3 %)	0.78
B0301	5 (8.3 %)	5 (8.3 %)	0.9
B0401	3 (5 %)	3 (5 %)	0.9
B0501	7 (11.7 %)	6 (10 %)	0.77

* *P* value < 0.05 is statistically significant.

group (healthy subjects) was reported (16). The reason for the lack of association between different levels of HLA in the two groups of the studied patients in this study can be due to differences in the characteristics of the two groups, such as demographic characteristics and lifestyle and even the geographical area, as in Laadhar et al (31), and Todd et al (32), demographic characteristics have been introduced as effective factors for different levels of HLA.

According to the results of this study, alleles of HLA-DQA1*0401 and HLA-DQA1*0301 and HLA-DQB1*0201 were 15%, 13.3% and 13.3% respectively in type 2 diabetes patients and diabetic nephropathy and in the non-diabetic nephropathy group, the highest rates were 13.3%, 11.7% and 11.7%, for alleles of HLA-DQA1*0301 and HLA-DQB1*0201 and HLA-DQB1*0501 respectively which is consistent with the study of Ma et al (16). In their study HLADQA1*0301, in diabetic nephropathy and the control group was 15.5% versus 8% ($P<0.01$), HLA-DQA1*0501 was 16.6% versus 8.5% ($P<0.01$), HLA-DQA1*0302 was 6.5% versus 13.5% ($P<0.01$) and HLA-DQB1*0501 was 5.8% versus 14.5% ($P<0.01$). Since there was no significant relationship between different alleles in the present study, which is not consistent with the study of Ma et al (16), it seems that the rate of HLA alleles and the association between them in the two groups of patients depends on racial and ethnic characteristics of

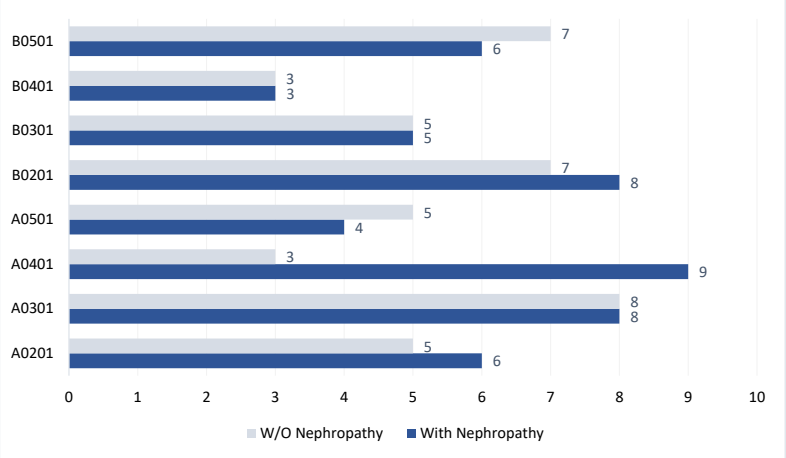

Figure 1. Comparison of the frequency of HLA in the patients with diabetic nephropathy and the control group.

each population. Few studies have been conducted on the relationship between T2DM and HLA, therefore this relationship is remaining unclear. However, in a study in Punjab, no relationship was reported between HLA-DQ and HLA-DR with type 2 diabetes (33), on the other hand type 2 diabetes was appreciably associated with HLA-DQA in Belgians (34). In Bahrain, relationship between type 2 diabetes with HLA-DQB1 and HLA-DRB1 was statistically significant (35). Differences in the results of this section, which have been reported in various studies, can be attributed to potential factors such as study design and sample size.

Conclusion

In this study, there was no statistically difference between the two groups regarding HbA1c, fasting plasma glucose and body mass index. However, there was a significant difference between the groups in systolic and diastolic blood pressures, though no significant difference between different levels of HLA in the two groups of patients was detected. Researchers of this study consider the various factors such as demographic characteristics, lifestyle, geographic region, and race as factors influencing the relationship between diabetic nephropathy and type 2 human leukocyte antigen (DQ1-HLA II). Since this study is conducted in one region and one race and with limited population, it is suggested that future studies should be considered and the association between the mentioned variables with type 2 HLA should be considered.

Limitation of the study

Limited statistical population and the cost of the experiments studied were limitation of this study.

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Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. MM, MB and MSF conducted the research. MM and MR wrote the primary draft. MM and MB prepared the final paper. MSF and MR conducted the final check of the paper. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical issues

The study was in accordance with the Declaration of Helsinki and all participants gave their informed consent to enter the study. The study was approved by the Research Committee and the Ethical Committee of the Kurdistan University of Medical Sciences (Ethics code# IR.MUK.REC.1397.111). This study was extracted from the residential thesis by Mahsa Mohammadi at the department of internal medicine of this university. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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