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The Relationship Between ABO and Rh Blood Groups and Microvascular Complications of Diabetes in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Aim: This study aimed to investigate the possible relationships between ABO and Rh blood groups and microvascular complications of diabetes in type 2 diabetes mellitus (DM) patients.

Material and Methods: This study included Type 2 DM patients who were hospitalized and followed in our clinic between February 2019 and April 2022. The patients' data files were retrospectively reviewed in order to record demographic characteristics, antidiabetic medications, comorbid diseases, fasting plasma glucose, HbA1c values, ABO/Rh blood groups, and microvascular complication status (nephropathy, retinopathy, and neuropathy).

Results: A total of 348 patients were included in the study. In the sample group, male patients constituted 40.9% (142) and female patients 59.1% (206) of the sample, and the mean age was 59.3±12.8 years. Diabetic nephropathy, retinopathy, and neuropathy rates were 31.3%, 41.0%, and 52.0%, respectively. The blood group was A in 151 (43.4%), B in 51 (14.6%), 0 in 127 (36.5%), and AB in 19 (5.5%) patients. Patients with different blood types did not show any significant differences in the microvascular complications of diabetes. The frequency of nephropathy and retinopathy were lower in Rh-negative patients than in Rh-positive patients (p=0.044 and p=0.041, respectively).

Conclusion: ABO blood groups are not correlated with the microvascular complications of diabetes in patients with type 2 DM. However, Rh positivity may pose certain risks for nephropathy and retinopathy.

Keywords: *ABO and Rh blood groups, Type 2 diabetes mellitus, Microvascular complications of diabetes*

Tip 2 Diabetes Mellituslu Hastalarda ABO ve Rh Kan Grupları ile Diyabetin Mikrovasküler Komplikasyonları Arasındaki İlişki

ÖZ

Amaç: Bu çalışma tip 2 diyabetes mellitus (DM) hastalarında ABO ve Rh kan grupları ile diyabetin mikrovasküler komplikasyonları arasındaki olası ilişkiyi araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Çalışmaya Şubat 2019-Nisan 2022 tarihleri arasında tip 2 DM nedeniyle yatırılan hastalar dahil edildi. Hastaların demografik özellikleri, kullanmış oldukları antidiyabetik ilaçlar, komorbid hastalıkları, açlık glukoz, HbA1c değerleri, ABO/Rh kan grupları ile mikrovasküler komplikasyon durumu (nefropati, retinopati ve nöropati) her bir hasta için retrospektif olarak kayıt edildi.

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Bulgular: Çalışmaya toplam 348 hasta dahil edildi. Hastaların 142'si erkek (%40,9), 206'sı kadındı (%59,1). Ortalama yaş 59,3 ± 12,8'di. Hastalarda diyabetik nefropati, retinopati ve nöropati sırasıyla %31,3, %35,20 ve %52,0 olarak saptandı. Hastaların 151'i (%43,4) A kan grubu, 14 hasta (%14,7) B kan grubu, 127 (%36,7) hasta 0 kan grubu ve 19 hasta (%5,5) AB kan grubuna sahipti. Rh kan grubu 318 hastada pozitif, 30 hastada negatifti. Kan grupları ile mikrovasküler komplikasyon arasında anlamlı bir ilişki saptanmadı. Rh kan gurubu negative olan hastalarda nefropati ve retinopati anlamlı daha az saptandı (sırasıyla p=0.044 ve p=0.041).

Sonuç: Kan grupları ile mikrovasküler komplikasyon arasında anlamlı bir ilişki saptanmadı ancak Rh pozitifliği diyabetik nefropati ve retinopati gelişimi için risk faktörü olabilir.

Anahtar Sözcükler: *ABO ve Rh kan grupları, Tip 2 diyabetes melitus, Diyabetin mikrovasküler komplikasyonları*

INTRODUCTION

There has been a significant rise in the prevalence of diabetes all over the world, particularly in developing countries. This increase leads to increasing rates of nephropathy, retinopathy, and neuropathy, which are among the microvascular complications of diabetes (1). Although hyperglycemia is the major systemic risk factor (2), it is not sufficient alone for the development of diabetic microvascular complications. Only 20-40% of diabetic patients develop renal failure, which suggests that genetic or endogenous protective factors that have not yet been identified may play a role (1). Although many studies have associated microvascular complications with factors such as age, gender, marital status, hypertension, obesity, and duration of diabetes, this issue has not been fully clarified yet (2).

The primary human blood group system is ABO. Since the blood groups were discovered in 1900, the possible relationship of ABO and Rh blood groups with various health conditions has been the subject of curiosity and research (3). Apart from erythrocytes, ABO antigens are expressed in a number of tissues, such as sensory neurons, vascular endothelium, epithelium, and platelets (4). Various studies have revealed a relationship between ABO or Rh blood groups and coronary artery disease, salivary gland cancer, duodenal ulcer, gastric cancer, thyroid disorders, colorectal cancer, and ovarian tumors (5). Although the relationship is not fully understood, there are also studies investigating the role of ABO blood group phenotypes in the pathophysiology of type 2 diabetes mellitus (DM). However, in the literature, a few studies have examined possible relationships between different blood types and the microvascular complications of DM.

The incidence of DM and its natural complications are increasing day by day. Knowing the risk factors for the microvascular complications of DM will help to screen and prevent the complications early, thus providing better care and treatment. In this study, we aimed to investigate possible relationships between ABO and Rh blood groups and the microvascular complications in type 2 DM patients.

MATERIALS and METHODS

Type 2 DM Patients hospitalized in our clinic between February 2019 and April 2022 were included in the study. We excluded from the study those with type 1 DM, pregnant women, and patients with a history of pancreatic surgery and temporary problems (including uncontrolled hypertension, urinary infection, hypovolemia, intense exercise in the last 24 hours, high fever, significant hyperglycemia, decompensated heart failure) that may cause albuminuria or low GFR and patients with a nondiabetic neuropathy. The patients' files were retrospectively reviewed, and their demographic characteristics, antidiabetic medications, comorbid diseases, fasting plasma glucose mg/dL and HbA1c values, ABO/Rh blood groups, and microvascular complication status (nephropathy, retinopathy, and neuropathy) were recorded.

The presence of retinopathy was evaluated through ocular examination using an ophthalmoscope by an eye specialist. The patients with proliferative or/and non-proliferative retinopathy were recorded as having diabetic retinopathy. A nephropathy examination was performed with urinary albumin excretion as specified by the ADA. Accordingly, our study recorded urine albumin/creatinine ratio <30 mg/gr as no nephropathy, and ≥30 mg/gr was recorded as high urinary albumin excretion and diabetic nephropathy.

For neuropathy evaluation, the pinprick test, vibration threshold using a 128 Hz tuning fork, light touch perception using 10 g monofilament, and ankle reflexes were evaluated. The patients who were found to have symmetrical, asymmetrical, or focal diabetic neuropathy and who used drugs for neuropathic pain were recorded as having diabetic neuropathy.

The ABO/Rh blood group was determined in all the patients. The frequency of microvascular complications was compared in those who had different ABO blood groups and Rh-positive and negative patients.

Statistical Method

Data analysis was performed via SPSS 22.0 software. Categorical variables were given as numbers and percentages. The mean±standard deviation or median and the first and third quartiles (IQR) were given for continuous variables. Whether the variables showed a normal distribution or not was tested by the Kolmogorov-Smirnov test. Three or more independent groups were compared using the Kruskal-Wallis test since the normal distribution condition was not met. Categorical data were compared with the chi-square test. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The study was carried out on a total of 348 patients. Male patients constituted 142 (40.9%) and female patients 206 (59.2%) of the sample. The mean age was 59.3±12.8 years, and the mean duration of DM was 12.7±8.8 years. The mean plasma glucose and HbA1c levels were 176.4±84.49 mg/dL and 9.96%±2.18, respectively. The blood group was A in 151 (43.4%), B in 51 (14.6%), O in 127 (36.5%), and AB in 19 (5.5%) patients. While the Rh blood group was positive in 318 (91.4%) patients, it was negative in 30 (8.6%).

Nephropathy was detected in 109 (31.3%), and neuropathy was detected in 181 (52.0%) patients (Table 1). Eye examination was performed in 300 patients, and 123 (41.0%) had diabetic retinopathy. There was no significant difference in the presence of any diabetic microvascular complications in different blood groups (Table 1). The proportions of the patients with two or all three complications were similar in the groups.

The rates of microvascular complications in the Rh-positive and negative patients are presented in Figure 1A,B. Nephropathy was detected in 13.3% of the Rh-negative and 33.0% of the Rh-positive patients (p=0.044). The neuropathy rate was similar in the Rh- negative and positive patients. The rate of retinopathy was significantly lower in the Rh-negative patients than in the positive patients (20% vs 42.9%, p=0.041). Also, the proportions of the patients with three complications were significantly lower in the Rh-negative patients (40/318 (12.58%) of the Rh-positive patients and 0 (0%) of the Rh-negative patients (p=0.035)).

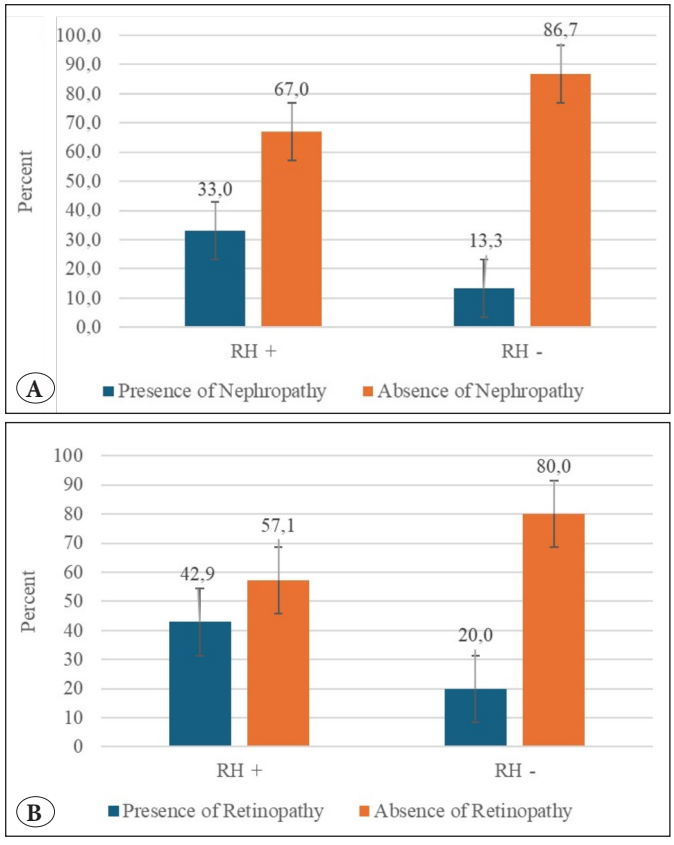

Figure 1: Presence of nephropathy in Rh-positive and negative patients **(A)**, Presence of retinopathy in Rh-positive and negative patients **(B).**

Table 1: Presence of microvascular diabetic complications in different blood groups.

	A (n=151)	B (n=51)	O (n=127)	AB (n=19)	p-value
Age, year(min.-max.)	59 (20–91)	59 (21–88)	62(29–86)	59(21–88)	0.932
Female/Male (n)	85/66	27/24	84/43	10/9	0.238
Fasting plasma glucose (mg/dL±SD)	173.30±87.34	190±68.83	171.1±85.78	196 ± 90.52	0.223
HbA1c (%±SD)	9.91±2.22	10.23±2.15	9.90±2.16	10.16 ± 2.04	0.048
Nephropathy, n(%)*	45/151 (29.80)	16/51 (31.37)	42/127 (33.07)	6/19 (31.57)	0.952
Neuropathy, n(%)*	76/151 (50.33)	26/51 (50.98)	69/127 (54.33)	10 / 19 (52.63)	0.926
Retinopathy, n(%)**	54/129 (41.86)	16/45 (35.55)	46/109 (42.20)	7/10 (70.0)	0.935
Any complication, n(%)	104/151 (68.87)	34/51 (66.66)	93/127 (73.23)	15/19 (78.95)	0.646
Two complications, n(%)	60/151 (39.74)	18/51 (35.29)	52/127 (40.94)	7/19 (36.84)	0.909
Three complications, n(%)	16/151 (10.60)	7/51 (13.73)	15/127 (11.81)	2/19 (10.0)	0.940

* n =A total of 348 cases of DM , **n=A total of 300 cases of DM were studied for presence of Retinopathy

Table 2: Comparison of blood groups in terms of microvascular diabetic complications.

	Nephropathy (n=348)	p	Retinopathy (n=300)	p	Neuropathy (n=348)	p
A	45/151 (29.80%)	0.592	54/129 (41.86%)	0.851	76/151 (50.33%)	0.851
Non-A	64/197 (32.49%)		69/171 (40.35%)		105/197 (53.30%)	
B	16/51 (31.37%)	1.000	16/45 (35.5%)	0.510	26/51 (50.98%)	0.881
Non-B	93/297 (31.31%)		107/255 (41.96%)		155/297 (52.18%)	
O	42/127 (33.07%)	0.594	46/109 (42.2%)	0.819	69/127 (54.33%)	0.817
Non-O	67/122 (54.91%)		77/281 (27.4%)		112/221 (50.67%)	
AB	6/19 (31.58%)	1.000	7/17 (41.17%)	1.000	10/19 (52.63%)	1.000
Non-AB	103/329 (31.30%)		116/283 (40.98%)		171/348 (49.13%)	

When the A blood group and other blood groups (non-A) were compared, complications did not show significant differences. The same results were found for the B and non-B, O and non-O, and AB and non-AB blood groups (Table 2).

DISCUSSION

Controversial results have been found so far in studies conducted to investigate the relationships between type 2 DM and the ABO and Rh blood groups. Legese et al. evaluated the risk of type 2 DM in 424 patients and reported an increased risk in the B blood group and a lower risk in the O blood group; however, the Rh blood group and type 2 DM were not significantly related (5). Increased factor VIII-VWF complex, intercellular adhesion molecule-1(ICAM-1), and tumor necrosis factor-2 (TNF-2) levels in those with B blood group have been associated with a higher risk of DM development in these patients (6,7). Aggarwal et al. also found a reduced risk of DM in the O blood group. However, this relationship was not statistically significant (8). It was considered that this protective effect against DM in the O blood group was linked with the decrease in inflammatory mediators (TNF-2, ICAM-1, and factor VIII-VWF complex). On the other hand, in a study conducted in India, an increased risk of DM development was reported in those with the O blood type (9). In another study, 75 patients were examined, and diabetes mellitus risk was higher in those with the A blood group than the other blood groups. According to the authors of this study, blood group A should be evaluated as a risk factor in DM screening (10). A meta-analysis of 47 studies evaluating the DM risk in different blood types revealed that blood group O had the least association with diabetes, and blood group B had the highest association; however, all diabetes types, including gestational DM, were included in this meta-analysis (11).

Compared to the studies that investigated the association of DM and blood types, a limited number of studies examined how the blood type and complications of DM are associated. Ünal et al. studied 743 patients with diabetic nephropathy and 25,253 healthy donors who donated to the blood bank in Turkey. The distribution of the ABO blood groups was significantly different among diabetic nephropathy patients and in the control group. While the rate of the A Rh-positive blood group was significantly higher (43.3% vs 38.5%), the rate of the O Rh-positive group was significantly lower (26.1% vs. 29.5%) in patients with diabetic nephropathy (12). In contrast, although not statistically significant, Gupta et al. evaluated 319 patients and reported that the complications, particularly nephropathy, were seen more frequently in the B blood group (13). In a study carried out in Ethiopia, no significant relationships were found between the ABO blood groups and the microvascular complications of DM (1). Another study compared 276 type 2 DM patients and 117 healthy controls. Although neuropathy was found at a lower rate in group AB and A than in group O, no significant relationship was found between the microvascular complications of DM and blood groups (14). Similarly, in our study, we found no relationships between the ABO blood groups and the microvascular complications of DM. Varying results in different studies may be due to differences in the designs, such as size, methods, and patient selection, as well as geographical, environmental, and genetic differences (15). Genome-wide related studies have shown that ABO gene locus variants, especially A and B antigens, were related to an increase in well-known risk factors for DM, such as blood lipid levels and inflammatory markers (P-selectin, E-selectin, TNF-2, and ICAM-1). These molecules are inflammatory regulators that might contribute to the development of DM and affect insulin and insulin receptors (16, 17). However, the pathophysiology of the association between microvascular complications and blood groups is not clearly understood.

A limited number of studies investigated the association between the Rh factor system and diseases. Rasmussen et al. revealed that the RhD blood group was associated with diseases including malignant neoplasm (other), tongue cancer, HIV, tuberculosis, hereditary hemolytic anemias, hep-

atitis B infection, major puerperal infection, contracture of the tendon, anxiety disorders, and type 2 DM (18). A recent meta-analysis, which included 26 studies, found no connections between the Rh blood group and type 2 DM (19). To our knowledge, the association between microvascular complications of DM and the Rh blood group has not been evaluated in the literature before. Our study also examined how the Rh blood group and microvascular complications were related. Diabetic nephropathy and retinopathy were lower in Rh-negative patients than in Rh-positive patients (Figure 1A,B).

The present study was mainly limited by its retrospective design. Secondly, an ophthalmologic examination was not performed by the same clinician. Additionally, we evaluated only the presence of microalbuminuria for nephropathy. The lack of a healthy control group can be considered another limitation; however, our primary aim was to determine the possible effect of blood group status on microvascular complications in diabetic patients. Lastly, our study group included hospitalized patients who generally had poorly regulated DM. A more extensive prospective study, including outpatients with relatively better glucose control, may provide more accurate information.

In conclusion, no relationship was found between the ABO blood groups and microvascular complications of DM in type 2 DM patients. However, Rh positivity might pose a risk for nephropathy and retinopathy. Further studies with larger sample sizes are required to elucidate the possible role of blood groups on the development of DM and complications.

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Author Contributions
Abbas Ali Tam contributed to the conception and design of the study. **Sevgül Fakı, Nurcan İnce, Feride Pınar Altay, Gülsüm Karaahmetli, Neslihan Çuhacı Seyrek, Beril Turan Erdoğan** manuscript and analyzed the data. **Oya Topaloğlu, Reyhan Ersoy, Bekir Çakır** contributed to writing–review & editing supervision. All authors contributed to the article and approved the submitted version.

Conflict of Interest
The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethical Considerations
Local ethics committee approval was obtained for the study as per the Declaration of Helsinki (Number: E.Kurul-E1-22-2681, Date: 15/06/2022).

Peer Review
Extremely and externally peer-reviewed and accepted.

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