The ABO Blood Groups are Related to Diabetic Nephropathy

ABO Kan Grupları Diyabetik Nefropati ile İlişkilidir

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ABSTRACT

OBJECTIVE: In this study, we aimed to evaluate any possible relationship between DN and ABO-Rh blood groups.

MATERIAL and METHODS: The study included 743 patients with DN and 25253 healthy donors that presented at the Erciyes University Blood Bank in the year 2012.

RESULTS: There was a significant difference between patients with DN and the control group in terms of distribution of ABO blood groups and Rh factor (p: 0.002). A Rh positive blood group was remarkably frequent in patients with DN compared to control subjects (43.3% vs. 38.5%, respectively) whereas frequency of the O Rh positive blood group was remarkably lower in patients with DN compared to control subjects (26.1% vs. 29.5%, respectively). There was a significant difference between patients with DN and the control group in terms of the distribution of the ABO blood groups (p: 0.001). The A blood group was remarkably frequent in patients with DN compared to control subjects (48.3% vs. 43.6%, respectively) whereas frequency of the O blood group was remarkably lower in patients with DN compared to control subjects (28.5% vs. 34.1%, respectively).

CONCLUSION: DN is closely related to the ABO-Rh blood groups, especially the A Rh positive blood group. Possible genetic or other mechanisms of this relationship may be revealed in future studies.

KEY WORDS: ABO blood groups, Diabetic nephropathy, Rh factor

ÖZ

AMAÇ: Bu çalışmada, diyabetik nefropati (DN) ve ABO-Rh kan grupları arasında olası herhangi bir ilişkiyi değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER: Bu çalışmaya 743 DN'li hasta ile 2012 yılında Erciyes Üniversitesi Kan Bankası'na bağışta bulunan 25253 sağlıklı donör dahil edildi.

BULGULAR: DN'li hastalar ile kontrol grubu arasında ABO kan grupları ve Rh faktörün dağılımı açısından anlamlı fark vardı (p: 0,002). A Rh pozitif kan grubu kontrol grubu ile karşılaştırıldığında DN'li hastalarda kayda değer şekilde daha sıktı (sırasıyla %43,3'e karşın %38,5). Buna karşılık 0 Rh pozitif kan grubu sıklığı kontrol grubu ile kıyaslandığında DN'li hastalarda dikkat çekici olarak daha düşüktü (sırasıyla %26,1'e karşın %29,5). DN'li hastalar ile kontrol grubu arasında ABO kan grupları dağılımı açısından anlamlı fark vardı (p: 0,001). A kan grubu kontrol grubu ile karşılaştırıldığında DN'li hastalarda kayda değer şekilde daha sıktı (sırasıyla %48,3'e karşın %43,6). Buna karşılık 0 kan grubu sıklığı kontrol grubu ile kıyaslandığında DN'li hastalarda dikkat çekici olarak daha düşüktü (sırasıyla %28,5'a karşın %34,1).

SONUÇ: DN, özellikle A Rh pozitif kan grubu olmak üzere, ABO-Rh kan grupları ile yakından ilişkilidir. Bu ilişkinin olası genetik veya diğer mekanizmaları gelecek çalışmalarda ortaya konabilir.

ANAHTAR SÖZCÜKLER: ABO kan grupları, Diyabetik nefropati, Rh faktörü

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INTRODUCTION

The most problematic issue in clinical nephrology is the relentless and progressive increase in patients with end-stage renal disease (ESRD) worldwide. Diabetic nephropathy has become the leading cause of ESRD (1). Only 30% to 40% of patients with type 1 diabetes mellitus and 10% to 20% of those with type diabetes mellitus develop nephropathy. Diabetic nephropathy may develop in some patients despite very good glycemic control. On the other hand, it may not develop even when high glucose levels are maintained for long periods of time. These observations suggest that factors other than hyperglycemia such as hereditary and environmental factors also contribute to the development of diabetic nephropathy (2).

The ABO blood group system was first discovered by Karl Landsteiner, who found three different blood types (A, B, and O) in 1900 (3). Blood group antigens are chemical components on membrane of the red blood cells but they are also expressed on a variety of epithelial cells including the urothelium, gastrointestinal system, mucosa and lung as well as saliva and body fluids (4,5). The ABO blood group genes are mapped at chromosome 9q and consist of 7 exons, in which a genetic alteration is common in many cancers (6). Blood group antigens have an important role in identifying matched blood products for transfusion. It has been reported that some of these molecules have varied and important functions in cell physiology and human pathology (7). The relationships between ABO blood groups and benign or malignant diseases have been observed for a long time. Deficiency of these membrane components is related to certain erythrocyte disorders (7). Aird et al. reported such a relationship with gastric cancer. They found that blood group A was significantly more frequent, while blood group O was less frequent in patients with gastric cancer when compared with the normal population in England (8). Some recent studies have reported a significant association between the ABO blood groups and pancreas cancer (9,10). There are a few studies in which the relationship between ABO blood groups and diabetes mellitus has been investigated. In 1957, Zeytinoglu reported predominance of group A in the Kimmelstiel-Wilson syndrome (11). Pontiroli et al. did not find an association between ABO and Rh blood groups and the development of diabetic late complications in both patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus (12,13).

In this study, we aimed to investigate any possible relationship between diabetic nephropathy and the ABO and Rh blood groups.

MATERIAL and METHODS

This study included 743 patients with diabetic nephropathy and 25253 healthy donors that presented to the Erciyes University Blood Bank in the year 2012. The blood group and Rh factor were determined serologically. Patients and control subjects were classified according to blood groups (A, B, AB, O) and Rh status (+, -). The distribution of the blood groups of patients with diabetic nephropathy was compared with the distribution of the blood groups of healthy donors. Diabetic nephropathy was defined as overt proteinuria (i.e. protein excretion above 300 mg/day) or otherwise unexplained renal dysfunction (i.e. serum creatinine above 1.4 mg/dL) in diabetic patients.

Statistical Analysis

SPSS 16.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Qualitative variables were given as percent and the correlation between diabetic nephropathy and blood groups was investigated using the chi-square test. A p value of <0.05 was considered significant. *Post hoc* power analysis was used to evaluate the power of statistical analysis.

RESULTS

Table I shows comparison of ABO blood groups and Rh factor between patients with diabetic nephropathy and the control group. There was a significant difference between patients with diabetic nephropathy and the control group in terms of distribution of ABO blood groups and Rh factor (p: 0.002; 0.959 of the power of statistical analysis). The A Rh positive blood group was remarkably frequent in patients with diabetic nephropathy whereas frequency of the O Rh positive blood group was remarkably lower.

Table II shows comparison of the ABO blood groups between patients with diabetic nephropathy and the control group. There was a significant difference between patients with diabetic nephropathy and the control group with regard to distribution of ABO blood groups (p: 0.001; statistical analysis power 0.942). The A blood group was remarkably frequent in patients with diabetic nephropathy whereas frequency of the O blood group was remarkably lower.

Table I: Comparison of ABO blood groups and Rh factor between patients with diabetic nephropathy and the control group.

Blood group	Diabetic nephropathy group n (%)	Control group n (%)
A Rh (+)	322 (43.3)	9720 (38.5)
A Rh (-)	37 (5.0)	1284 (5.1)
B Rh (+)	115 (15.5)	3331 (13.2)
B Rh (-)	15 (2.0)	464 (1.8)
AB Rh (+)	39 (5.2)	1590 (6.3)
AB Rh (-)	3 (0.4)	247 (1.0)
O Rh (+)	194 (26.1)	7410 (29.5)
O Rh (-)	18 (2.4)	1207 (4.8)
Total	743 (100)	25253 (100)

Table II: Comparison of ABO blood groups between patients with diabetic nephropathy and the control group.

Blood group	Diabetic nephropathy group n (%)	Control group n (%)
A	359 (48.3)	11104 (43.6)
B	130 (17.5)	3795 (15.0)
AB	42 (5.7)	1837 (7.3)
O	212 (28.5)	8617 (34.1)
Total	743 (100)	25253 (100)

DISCUSSION

Diabetic nephropathy may not develop even when high glucose levels are maintained for long periods of time. This observation suggests that factors other than hyperglycemia such as hereditary and environmental factors also contribute to development of diabetic nephropathy. The prevalence of nephropathy among diabetic nephropathy varies between different racial and ethnic groups; for example, it is relatively increased in Native Americans, African Americans, Hispanics, and Polynesians (2).

Familial clustering of diabetic nephropathy has been reported in both type 1 and type 2 diabetes mellitus and both in Caucasian and non-Caucasian populations (2). Gene polymorphisms, including a polymorphism in the carnosinase gene and the double deletion polymorphism of the angiotensin converting enzyme, may also contribute to familial clustering (2,14,15). In addition to genetic factors, environmental factors also contribute to the familial and racial clustering of diabetic nephropathy (2).

Erythrocyte blood group antigens are polymorphic, inherited structures on the surface of membrane of the cells. Many novel functions associated with blood group antigens have recently been identified. These include contributing to erythrocyte membrane integrity, transport of molecules though the membrane, and complement regulation as well as acting as adhesion molecules, receptors, extracellular ligands and enzymes (7). In addition, the relationships between blood groups and benign or malignant diseases have been observed for a long time.

ABO antigens are expressed on the surface of many cells other than erythrocytes, such as epithelial cells including urothelium, gastrointestinal system, mucosa and the lung. Alterations on the cell surface structures as blood group antigens can lead to changes in the interactions in between cells or cells and extracellular matrix. These changes have been thought to be important for tumor development (16). Possible associations between the ABO blood group and risk of some epithelial malignancies such as gastric and pancreatic cancer have been reported previously. Aird et al. reported such a relationship with gastric cancer. They found that blood group A was significantly more frequent, while blood group O was less frequent in patients with gastric cancer when compared with the normal population in England (8). Similarly, Edgren et al have performed a cohort study on 1,089,022 healthy blood donors using the Scandinavian Donations and Transfusions database. The donors were followed for up to 35 years, during which 688 gastric cancer cases and 5667 peptic ulcer cases accrued. They concluded that blood group A was associated with a higher risk of gastric cancer with an incidence of 1.20 (95% CI: 1.02-1.42) and conversely that peptic ulcer risk was highest among subjects with blood group O (17). Recently in some studies, a significant association between ABO blood groups and pancreas cancer was reported (9,10). Wolpin and coworkers have observed that those with blood group A, AB, or B were more likely to develop pancreatic cancer compared to subjects with the O blood group (9).

In addition to the development of malignancy, possible associations between the ABO blood group and survival in patients with cancer have been reported. Graziano et al. investigated the prognostic significance of blood group antigen A loss in a large cohort of patients with non-small cell lung cancer (NSCLC). They observed that the median survival time of the patients with primary tumors negative for blood group antigen A was significantly higher compared with those with antigen A-positive tumors (38 months vs. 98 months, respectively). Multivariate analysis showed that the loss of antigen A was a predictor for poorer disease-free and overall survival (5).

Recently, Karamatic Crew et al. published a very interesting study (18). They showed that CD151, a tetraspanin protein, expresses the MER2 blood group antigen of RAPH blood group system and is located on erythrocytes. They examined CD151 in 3 MER2-negative patients with ESRD and observed that the 3 patients were homozygous for a single nucleotide insertion (G383) in exon 5 of CD151, causing a frameshift and premature stop signal at codon 140 and the resultant truncated protein would lack its integrin-binding domain. Finally, they concluded that CD151 is essential for the proper assembly of the glomerular and tubular basement membrane in kidney (18).

The ABO blood group is determined by the presence of A and B antigens on surface of the erythrocytes, and of anti-A or anti-B antibodies in the serum. Anti-A and anti-B antibodies are usually the IgM type, and not present in newborns but appear in the first year of life. It is possible that they are produced against food and environmental antigens (bacterial, viral or plant antigens), which are similar in structure to A and B antigens on red blood cells (6). In the present study, we observed that the A blood group was remarkably frequent in patients with diabetic nephropathy whereas frequency of the O blood group was remarkably lower. These observations suggest that the environmental factors triggering formation of antibodies against blood group antigens may also contribute to the familial and racial clustering of diabetic nephropathy.

Studies on the relationship of ABO blood group and DM have reported different results (19-23). Kamil et al. reported that there was a negative association between the A and O blood groups and DM, with the A and O groups having less risk of diabetes (19). Qureshi and Bhatti found that the frequency of the blood groups B and O was significantly higher and lower respectively in diabetic patients than in the general population (20). Sidhu et al. observed a strong association of DM with blood groups and especially with the A, AB and Rh-positive blood groups (21). Macafee examined in relation between DM and ABO blood group distribution in 865 diabetic patients and 11,327 controls and found that there was no significant difference between the observed and expected distributions (22). Qi et al reported that the genetic variants at ABO locus affect plasma sE-selectin levels and diabetes risk. They found that the genetic-inferred blood group B was associated with a decreased risk of type 2 diabetes compared with blood group O (23).

In conclusion, diabetic nephropathy is closely related to the ABO-Rh blood groups and especially the A Rh positive blood group. Further studies are necessary to define the mechanisms by which ABO blood group or closely linked genetic variants may influence the development of nephropathy in patients with diabetes mellitus. Physicians may consider this observation for treatment and prevention in patients with diabetes mellitus.

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