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INCREASED ATHEROGENIC RISK INDICES IN HEALTHY MALES WITH AB BLOOD GROUP PHENOTYPE

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ABSTRACT

Objective: *Although the relationship between ABO blood phenotype and atherosclerosis has been investigated; to our knowledge, new atherogenic indices, including the atherogenic index (AI), atherogenic plasma index (AIP), lipoprotein combined index (LCI), and Castelli's risk indices, have not been extensively discussed. The aim of this study is to investigate the effects of new atherogenic indices in determining atherogenic risk in men who appear healthy according to ABO blood phenotypes.*

Material and Method: *The study included 188 apparently healthy male medical staff (≥18 years); the participants were grouped according to their ABO blood group phenotype (A, B, AB, O or non-O blood). Laboratory tests included assessment of ABO blood types and measurements of the levels of total cholesterol (TC), high- and low-density lipoprotein cholesterol (HDL–C and LDL–C), and triglycerides (TGs). Also novel atherogenic risk indices were calculated.*

Results: *Although smoking was significantly higher in the AB blood phenotype group among the study groups, there was no significant difference in terms of TC, TGs, LDL-C and HDL-C levels. However, the new atherogenic risk indices AI, AIP, LCI and non-HDL, TG/HDL-C values were significantly higher in AB blood group phenotype ($p<0.05$ for each).*

Conclusion: *The statistically significant relationship between AB blood phenotype and new atherogenic indices (AI, AIP, LCI and TG/HDL-C ratio) found in this study supports the potential role of new atherogenic risk indices in the pathogenesis of atherosclerosis .*

Keywords: *ABO phenotypes, atherosclerosis, atherogenic indices, cholesterol.*

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AB KAN GRUBU FENOTİPLİ SAĞLIKLI ERKEKLERDE ARTMIŞ ATEROJENİK RİSK İNDEKSLERİ

ÖZET

Amaç: ABO kan fenotipi ile ateroskleroz arasındaki ilişki araştırılsa da; bildiğimiz kadarıyla, aterojenik indeks (AI), aterojenik plazma indeksi (AIP), lipoprotein kombine indeksi (LCI) ve Castelli'nin risk indeksleri dahil olmak üzere yeni aterojenik indeksler kapsamlı bir şekilde tartışılmamıştır. Bu çalışmanın amacı, ABO kan fenotiplerine göre sağlıklı görünen erkeklerde yeni aterojenik indekslerin aterojenik riski belirlemedeki etkilerini araştırmaktır.

Materyal ve Metot: Çalışmaya görünüşte sağlıklı 188 erkek sağlık çalışanı (≥18 yaş) dahil edildi. Katılımcılar ABO kan grubu fenotiplerine (A, B, AB, O veya non-O) göre gruplandırıldı. Laboratuvar testleri olarak, kan grubu tayini, toplam kolesterol (TK), yüksek ve düşük yoğunluklu kolesterol (YYK, DYK) ve trigliserid (TG) ölçümleri yapıldı. Yeni aterojenik risk indeksleri hesaplandı.

Bulgular: Çalışma grupları arasında AB kan fenotip grubunda sigara kullanımı anlamlı derecede yüksek olmasına rağmen, TK, TG, YY ve DYK düzeyleri açısından anlamlı fark yoktu. Ancak yeni aterojenik risk indeksleri AI, AIP, LCI ve non-HDL, TG/HDL-C değerleri AB kan grubu fenotipinde anlamlı olarak daha yüksekti (her biri için $p<0,05$).

Sonuç: Bu çalışmada saptanan AB kan fenotipi ile yeni atereojenik indeksler (AI, API, LKI ve TG/YYL-K oranı) arasındaki istatistiksel olarak anlamlı ilişki, atereoskleroz patogenezinde yeni aterojenik risk indekslerinin potansiyel rolünü destekledi.

Anahtar kelimeler: ABO fenotip, ateroskleroz, aterojenik indeksler, kolesterol

INTRODUCTION

The ABO blood group system, which is the first discovered and remains the major clinically significant blood group system, is used to classify human blood, an individual's complete and unchangeable identity, according to the presence of A and B antigens found on the surface of the red blood cells (RBC).[1] The ABO blood group antigens are encoded by the ABO locus comprises of three main alleles (A, B, O); the A and B alleles encode A and B glycosyltransferases that transform precursor H antigen into either A or B determinant and the O allele encode non-functional enzyme and thus neither A or B antigen is produced and the underlying precursor (the H antigen) remains unchanged.[1]

Nearly 2 million ABO blood group antigens are expressed by each human RBC and accordingly the ABO blood group antigens are considered RBC antigens; however, ABO blood group antigens are also expressed on a broad variety of human tissues; they are found on epithelial and endothelial cells, other blood cells (such as T cells, B cells, and platelets), plasma proteins, certain tissues, and various cell surface enzymes and exist in soluble form in body secretions such as breast milk, seminal fluid, saliva, sweat, gastric secretions, urine, and amniotic fluid.[1-4] Yet, the certain functions of the ABO blood group antigens are not known as the individuals who were deficient of A and B antigens are healthy.[5] It seems thus biologically plausible that the clinical significance of ABO blood type would not be limited to transfusion medicine and solid organ/hematopoietic transplantation but that these antigens may also participate in the pathogenesis of various systemic diseases.[4]

Many scientific reports now support the relation of ABO blood groups with various systemic diseases including cancer, diabetes mellitus (DM), and infectious and cardiovascular disorders.[4,6-10] Among these diseases, the strong clinical evidence supporting this relation emerged from the association between ABO blood antigens and atherosclerosis.[4]

Individuals with non-O blood-type have been reported to have a significantly increased risk for cardiovascular, peripheral vascular and venous thromboembolic events and ischemic heart disease.[4] Moreover, it has been demonstrated that individuals of AB blood group phenotype are more susceptible to cardiovascular diseases.[9]

There are some mechanisms that are considered responsible for the association between ABO blood group and atherosclerotic diseases; the most likely mechanism have been suggested as the non-O related increased levels of von Willebrand factor (VWF) and coagulation factor VIII (FVIII), in addition with those of some inflammatory cytokines and cholesterol levels.[11] Another mechanism might be the genetic

variants at the ABO locus, which independently affect serum E-selectin levels and thereby alter the levels of main actors in atherosclerosis pathogenesis that is triglycerides (TGs) and high-density lipoprotein cholesterol (HDL-C), in ethnic populations.[2,7,12] Some populations are known to have low levels of HDL-C relative to other populations but the reason is still unclear.[13] Moreover, the relation of ABO blood groups with total cholesterol (TC) and low-density lipoprotein (LDL) levels has also been noticed for a long time. Accordingly, subjects with non-O blood phenotypes, who may have an increased risk of coronary artery disease (CAD), are associated with increased TC and LDL-cholesterol (LDL-C) levels.[5] Most importantly, these findings demonstrate the potential importance of ABO blood groups in altering atherogenic risk.[14-16] It has been also demonstrated that individuals with non-O-type phenotype have higher cholesterol enteric absorption rates, which is positively associated with atherosclerotic risk and are at an increased risk of atherosclerosis.[16,17] Thus, it is considered that the effect of ABO blood groups has a role on susceptibility to atherosclerosis partly through their effects on blood lipid levels.

Despite their obvious clinical importance, the atherogenicity of ABO blood group antigens remains unknown. Recently, studies have suggested that novel atherogenic indices have quite strong positive predictively in determining plasma atherogenicity and that they could be used as simple and readily calculated parameters for determining plasma atherogenicity of plasma lipoproteins.[18-20] The novel non-traditional atherogenic indices include the atherogenic index (AI), atherogenic index of plasma (AIP), lipoprotein combine index (LCI), Castelli's risk index–I (CRI–I) and Castelli's risk index–II (CRI–II), and to the best of our knowledge, these indices in the ABO blood groups of apparently healthy subjects has not been broadly discussed in the literature.[20-22] Thus, the present study aimed to investigate the effects of novel atherogenic indices in determining atherogenic risk in apparently healthy males according to their ABO blood phenotypes.

MATERIAL AND METHOD

Subjects

The present study included apparently healthy male (n=188) medical staff aged ≥18 years who were blood donors and underwent laboratory testing at the time of blood donation in the Transfusion Centre of the University of Health Sciences Antalya Training and Research Hospital between January 2018 and January 2019. Subjects who had any sign/symptom suggestive of dyslipidaemia, DM, heart or kidney failure and those with an acute/chronic illness were excluded. In addition, non-fasting subjects at the time of blood donation were also excluded. All subjects voluntarily participated in the study and provided informed consent for their participation. The present study was approved by the Clinical Research Ethics Committee of University of Health Sciences Antalya Training and Research Hospital (approval number: 2/14 date: January 25, 2018).

In all subjects, the diastolic and systolic blood pressures (BPs) were measured by a physician with a sphygmomanometer and a stethoscope while the subjects were in a resting state; their body mass index (BMI) and waist circumference values were also measured. Data regarding clinical and demographic characteristics including age, history of hypertension (HT) and DM, and smoking status were also obtained from medical records.

Blood Sampling and ABO Blood Tests

Venous blood samples were obtained from all subjects after an overnight fasting and were used to determine ABO blood groups by hemagglutination principle and to measure routine laboratory parameters. Microcolon method was used to determine ABO blood groups. For this purpose, gel cards with A, B, AB, D^{VI-}, D^{VI+}, Ctl, $N_{/A1}$, $N_{/B}$ profiles (Across Gel® Forward and Reverse ABO with D^{VI-}/D^{VI+}; Across Gel, Diapro Medical Products, Turkey) were studied in accordance with the manufacturer's instructions. The subjects were grouped according to their ABO-Rh blood type. The venous blood samples were allowed to clot and then centrifuged at 3000 rpm for 5 min. The collected serums were then stored frozen at -20 °C. All analyses were carried out within 1 week of sample collection. Blood lipid analyses were also performed using the collected serum samples and routine biochemical parameters were determined using commercially available reagents.

Routine Biochemical Tests

For routine biochemical tests including the measurements of creatinine, fasting blood glucose (FBG), uric acid (UA), TC, LDL–C, HDL–C, and TGs levels were performed using an autoanalyzer (Beckman AU5800®; Beckman Coulter Diagnostics, CA, USA) and its commercial diagnostic reagent kits. While enzymatic methods were used for the measurements

of TC, LDL–C, and TG levels, a direct method was used to measure HDL–C level. All lipid parameters were double measured in all subjects. Non-HDL-C levels were calculated using the following formula: non–HDL–C = (TC level) - (HDL level).

Novel Non-Traditional Atherogenic Indices

The following novel non-traditional atherogenic indices were calculated in the present study: AI, AIP, LCI, CRI–I and CRI–II. The AI is defined as the ratio of non–HDL–C level to HDL–C level and calculated using the formula: AI=non–HDL–C/HDL–C.[22] LCI is calculated using the formula LCI=(TC × TG × LDL)/HDL-C.[23] AIP is calculated as the logarithmic transformation of the ratio of the TG level to HDL–C level, the formula is shown as AIP=$\log_{10}$ (TG/HDL–C).[20,22]

The AIP indicates the risk of atherosclerosis according to the values obtained an AIP of -0.3 to 0.1 indicates low risk, an AIP of 0.1 to 0.24 indicates medium risk, and >0.24 indicates high risk. The CRI–I and CRI–II are calculated using the following formulas where each lipid concentration is expressed in mmol L^{-1}: CRI–I = TC / HDL-C and CRI–II = LDL–C / HDL–C.[22]

Statistical Analyses

Data analyses were performed using the MedCalc© Statistical Software version 15.8 (MedCalc Software®, Ostend, Belgium; https://www.medcalc.org; 2018). The Kolmogorov-Smirnov test was used to test the distribution of variables. The results of descriptive statistics were used for categorical variables such as HT, known disease, number (frequency) and percentage. Kolmogorov-Simirnov test was used for countable data with normal distribution, One-way analysis of variance (ANOVA) was used to identify the differences between the A, B, AB, and O blood groups. MedCalc© was a post hoc test using Tukey-Kramer for pairwise comparison of subgroups and Kruskal-Wallis test was used for countable data without normal distribution.

Possible relationship between the Spearman correlation coefficient and the clinical characteristics of individuals with different blood phenotypes on pro-atherogenic lipid levels was evaluated. Graph distributions in some of the parameters were shown using multiple comparison graphics. The significance level (α) was set at a p value of <0.05.

RESULTS

The present study included 188 healthy males (age range, 18–58 years), who were grouped according to their ABO blood group phenotypes (A, B, AB, O or non-O blood groups). The baseline characteristics and laboratory findings of the ABO blood type groups are presented in Table 1. The rate of smoking in the AB blood group was significantly higher than in the other blood groups (p<0.05; Table 1). The mean values of age, FBG, and BMI as well as the rate of presence of hypertension were observed to be higher in the subjects with AB blood phenotype as compared with those with A, B, and O blood phenotype; however, the difference was not statistically significant (p>0.05). On the other hand, the mean plasma UA level was significantly higher in the subjects with A blood phenotype than in those with B, AB, O, and non-O blood phenotype (p<0.05; Table 1).

Evaluation of the traditional routine lipid parameters revealed that the study groups did not significantly differ in terms of the mean levels of TC, TGs, LDL–C, and HDL–C (Table 1). Evaluation of novel non-traditional atherogenic indices revealed that the values of non-HDL, AIP, AI, LCI, and TG/HDL–C were the highest in the AB blood group phenotype and the difference was significant (p<0.05 for each; Table 2). It was also observed that the values of AIP, AI, and TG/HDL–C were significantly higher in the blood group non–O healthy males than in those with A, B and O blood phenotypes (Table 2). On the other hand, the healthy males with O blood phenotype had significantly lower AI as compared with those with A, B, AB and non-O blood group phenotypes (Table 2).

Although smokers had a higher AB blood phenotype rate, there was no statistically significant difference between the groups in TC, TG, HDL-C and LDL-C measurements (Table 1). In addition, there was no significant difference between age, FBG and HT rates and blood phenotypes.

DISCUSSION

The most important findings of the present study were that the healthy male subjects with AB blood group phenotype were demonstrated to have a higher atherogenic risk than that of those with non-AB blood group phenotypes and that this difference could only be established by comparing calculable novel atherogenic indices rather than traditional lipid parameters between the blood groups A, B, O, AB and non-O healthy male subjects. Accordingly, it could

be suggested that these novel calculable atherogenic indices may be superior to traditional serum lipid parameters for identifying the risk of atherogenesis. To the best of our knowledge, there is no study in the literature showing the relationship between novel calculable atherogenic risk indices and ABO blood groups in apparently healthy male individuals.

Atherosclerosis is a multifactorial disorder. The aetiology of atherosclerotic diseases is complex and appears to involve interactions between genetic and environmental factors.[13] There is no doubt that atherogenic lipoproteins of plasma are important risk factors for atherosclerotic diseases such as CAD. CAD is characterized by a high ratio of LDL-C to HDL-C and increased levels of TGs.[8]

On the other hand, significant associations of A and B alleles of the ABO locus with CAD have also been reported.[4,10] The mechanism underlying the relationship between blood phenotypes and higher plasma atherogenesis has not been clarified.[7] Relationships between ABO blood phenotypes and dyslipidaemia have been investigated for several decades in patients.[7] However, the results are conflicting, particularly for prospective cohort studies.[23] It has been reported that as compared with blood group O individuals, blood group non-O individuals had significantly higher risk of myocardial infarction.[23] In the studies conducted in general populations, having a non-O blood group has been identified as potential risk factor for the development of CAD. Moreover, the risk of CAD has been reported to be less common among individuals with O blood group phenotype.[23] In the present study, the AI was found to be significantly lower in the blood group O healthy male subjects than in blood groups A, B, AB and non-O male subjects; accordingly, it can be suggested that O blood group phenotype may have the lowest risk of atherogenicity.[17,24,25]

Although most studies in the literature have been principally focused on non-O blood phenotypes and O blood phenotype; recently, there are few studies showing that blood group AB individuals have more CAD.[7,8] In their study investigating the associations between ABO blood group and CAD risk through a meta-analysis of two large prospective cohort studies, reported that blood group AB individuals had a 23% greater risk of developing CAD as compared with other blood group individuals.[7] In the present study, we also found that the values of all calculable atherogenic indices, except for CRI-I and CRI-II, were significantly higher in the blood group AB healthy males.

Table 1. Baseline characteristics and laboratory findings of the study groups

	ABO Blood Group Phenotypes				
	A n=52	**B n=52**	**AB n=32**	**O n=52**	**Non-O n=136**
Baseline characteristics					
Age, years, mean±SD	34.9±11	33.9±8.4	37.03±8.	34.05±10	36.2±9.6
BMI, kg/m^2, mean±SD	26.3±3	25.8±2.9	26.8±2.61	25.4±2.77	26.3±2.92
Smoking rate, n (%)	16 (30)	19 (36)	13 (40)*	10 (19)	48 (35)
Presence of HT, n (%)	3(6)	4(7)	2(6)	4(7)	10(7)
Laboratory findings, mean±SD					
FBG, mg dL^{-1}	103±11	99±9	102±12	100±13	101.3±9
UA, mg dL^{-1}	5.72±1.3*	5.6±1.4	5.6±1.46	5.46±1.24	5.64±1.5
TC, mmol L^{-1}[a]	4.54±1.4	4.50±1.2	4.9±1.3	4.78±1.1	4.81±1.2
TG, mmol L^{-1}[a]	1.97±1.4	1.98±1.4	2.61±1.5	2.16±1.3	2.11±1.2
LDL-C, mmol L^{-1}	2.67±0.8	2.74±0.9	2.7±0.75	2.69±0.06	2.7±0.7
HDL-C, mmol L^{-1}	1.03±0.29	1.04±0.29	1.05±0.28	1.14±0.31	1.04±0.24

One-way ANOVA test (post hoc test,Tukey-Kramer's) were used to identify the difference among the A, B, AB, and O blood type groups. **BMI:** Body mass index, **HT:** hypertension, **FBG:** fasting blood glucose, **UA:** uric acid, **TC:** total cholesterol, **TG:** triglycerides, **LDL-C:** low-density lipoprotein cholesterol, **HDL-C:** high-density lipoprotein cholesterol, **SD:** standard deviation, ***:** significant difference as compared with other groups at $p<0.05$, **[a]:** Kruskal-Wallis test (H-test) was used for TC and TG frequencies. Pearson's chi-square test was used for frequencies.

Table 2. Comparison of the values of novel non-traditional atherogenic indices in the study groups.

	ABO Blood Group Phenotypes				
	A n=52	**B n=52**	**AB n=32**	**O n=52**	**Non-O n=136**
Non-HDL-C (mmol L^{-1}) [a]	3.6±1.3	3.49±1.28	3.86±1.36*	3.47±1.28	3.62±13
AIP [a]	0.278±0.27	0.288±0.27	0.398±0.34**	0.279±0.26	0.31±0.29¶
LCI [a]	24.23±24.38	23.85±25.82	33.80±27.96**	24.36±23.68	27.23±27.46
AI [a]	3.59±1.62	3.41±1.48	3.72±1.8**	3.13±1.14*	3.59±1.6¶
CRI-I [a]	4.59±1.9	4.45±1.6	4.67±2.1	4.78±1.9	4.54±2.0
CRI-II	2.56±0.9	2.63±0.97	2.57±0.88	2.56±0.89	2.59±0.97
TG/HDL-C	2.09±0.93	1.98±0.91	2.57±0.87*	1.99±0.9	2.11±0.99¶

One-way ANOVA test(mean±SD) was used to identify the differences between the A, B, AB, and O blood type groups. **HDL-C:** High-density lipoprotein-cholesterol, **AIP:** atherogenic index of plasma, **LCI:** lipoprotein combine index, **AI:** atherogenic index, **CRI-I:** Castelli's risk index-I, **CRI-II:** Castelli's risk index-II, **SD:** standard deviation, **[a]:** Kruskal-Wallis test (H-test)was used for non-HDL-C,AIP,LCI,AI and CRI frequencies(median±SD), ***:** significant difference as compared with other groups at $p<0.05$; ****:** significant difference as compared with other groups at $p<0.01$, **¶:** significant difference as compared with A, B, O blood groups at $p<0.05$.

Besides, those with non-O blood group phenotypes had also significantly higher AIP, AI, and TG/HDL-C values as compared with those with A, B, and O blood group phenotypes.

According to our results, healthy men with O blood type may have the lowest atherogenic risk when compared to healthy men with non-AB blood types.

It has been known for a long time that ABO blood phenotype might affect the risk factors of dyslipidaemia.[4,10,23,26]

ABO blood groups have been associated with plasma lipid levels; in particular, the AB blood phenotype has been reported to have higher levels of serum TC and LDL-C.[23,26]

This suggests greater susceptibility of individuals with AB blood phenotype to myocardial infarction, atherosclerotic peripheral vascular occlusive disease, and other forms of CAD as compared with those with non-AB blood phenotypes.[27] Nevertheless, the uncertainty about the mechanisms related to the associations between AB blood group and atherogenesis risk remains unclear.[10,23] Although numerous criteria are considered the indicators of atherosclerosis; the novel atherogenic indices have recently become commonly used laboratory parameters as they are easy to use. For instance, the high predictive value of AIP may be explained by its strong correlation with the size of pre and anti-atherogenic lipoprotein particles.[18]

Previous studies have demonstrated that the positive predictively of novel atherogenic indices in determining plasma atherogenicity is quite strong.[18,19]

Researchers have speculated that novel atherogenic indices (such as AIP) indicate a balance between the actual concentration of plasma TC, TGs, LDL and HDL-C, which may predetermine the direction of cholesterol transport in the intravascular pool, for example the flux of cholesteryl esters newly produced by lecithin cholesterol acyltransferase toward atherogenic LDLs or beneficial HDLs.[20]

Cholesterol esterification rate and HDL particle size are functionality indicators at which TGs interact with HDL-related cholesteryl ester transfer protein.[20,27] In the present study, significantly lower TG/HDL-C rates were determined in the blood group A healthy males, as opposed to our expectations. On the other hand, the highest TG/HDL-C ratio was found in the healthy males with AB blood group phenotype, with a statistically significant difference as compared with other blood group phenotypes.

Smoking status was previously reported risk factor for pro-atherogenic risk factors. The existence of a relationship between atherogenic risk indices and smoking is still controversial in the literature.[28-33] Undoubtedly, smoking is a serious risk factor for atherosclerosis and cardiovascular risk in a dose-dependent manner.[28-30]

Thus, the limitation of the study is that there are many factors which can affect atherogenic risk indices and lipid metabolism independent of ABO blood groups, so, multicentred long-term studies involving more patients are needed. The fact that AB blood phenotype was at lowest frequency (6.5%) in the region where the study was conducted, resulted in the lower number of subjects with AB blood phenotype than other blood groups in the study.[34] The small number of cases in this study and the heterogeneity of smoking makes it difficult to make a decision.

In our study, statistically significantly higher atherogenic risk indices were found in smokers with AB blood group. However, there was no statistically significant correlation between pro-atherogenic lipid values, smoking status and other basic characteristics in individuals with different blood phenotypes.

However, the research is a preliminary study that draws attention to the possible relationship between individuals with AB blood group and diseases. Since atherogenic risk indices are a cost-effective and easy-to-calculate method, they can facilitate the evaluation of atherosclerosis and cardiovascular risk factors. Possible effects of risks such as smoking on lipid values and the role of blood groups in smoking addiction, which is the most important modifiable risk factor, should be investigated. Considering that, the rate of smoking is significantly higher in our subjects with AB blood group phenotype, it can be thought that smoking and AB blood group phenotype may indicate an atherogenic risk.

Also it has been reported that individuals with AB blood group can increase the risk of death due to COVID-19 disease.[35] Moreover, the relationship between the risk of death due to COVID-19 disease and atherogenicity has been demonstrated.[36]

In conclusion, the results of the present study demonstrated the existence of an association between AB blood group and plasma atherogenic risk using novel atherogenic indices in a small population of apparently healthy male subjects. Our results suggested that novel atherogenic indices might reflect the delicate metabolic interactions within the whole lipoprotein complex. Taking the small sample size as a limitation of the present study, prospective broad clinical trials are needed to confirm the practical utility of these novel atherogenic indices in apparently healthy subjects.

*The authors declare that there are no conflicts of interest.

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