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High-density lipoprotein functionality and AB blood phenotype

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Abstract:

BACKGROUND: The impact of the different ABO blood phenotypes has not been extensively investigated on high-density lipoprotein (HDL) functionality. Therefore, the aim of this study was to assess HDL-related serum paraoxonase 1 (PON1), ApolipoproteinA-1 (ApoA-I) and also oxidized low-density lipoprotein (OxLDL) in relation to ABO blood groups.

SUBJECTS AND METHODS: ABO blood types represent part of the genetic phenotype. Therefore, we assume that ABO blood phenotypes are associated with many diseases. This cross-sectional study involved 169 apparently healthy male medical staff with different ABO blood phenotypes.

RESULTS: The most important of the findings in this study is that the amount of PON1, which is one of the valuable markers of HDL function, was statistically significantly lower in people with AB blood group than in other blood groups. Furthermore, one notable important findings of this study are the lowest serum ApoA-I levels of individuals in AB blood phenotype. On the contrary, serum OxLDL levels in the subjects with AB blood phenotype are increased.

CONCLUSION: There is no doubt that it is necessary to examine in more detail the molecular changes in HDL metabolism linked to the ABO blood group phenotype. What is really interesting is that the AB blood phenotype in many Mediterranean countries has the lowest rate of distribution. According to the findings from this study, the A and B blood group phenotypes may be more effective than expected in disease susceptibility.

Keywords:

AB phenotype, ABO blood groups, apolipoproteinA-1, high-density lipoprotein, oxidized low-density lipoprotein

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Introduction

Scientists still do not understand the purpose of blood types. Whereas the ABO blood group system was discovered in the last century. What is the function of ABO blood groups in the evolutionary process? ABO blood phenotypes are inherited from parents and ancestors, which, to some extent, illustrate genetic characteristics. The distribution of ABO blood phenotypes differs greatly by area and ethnicity. What scientists have found in the last century, however, are some interesting associations between blood phenotypes and diseases.[1]

ABO blood system categorizes the blood group into three main alleles; A and B that are co-dominant and O that is recessive. The combination of these three alleles produces the four known major genotypes: A, B, AB, and O. Even the certain functions of the ABO blood group antigens are not known. Because individuals who deficiency the A and B antigens are healthy. However, many scientific reports now support the association between ABO blood phenotypes and cancer, diabetes, as well as with infectious disorders and cardiovascular diseases.[2,3]

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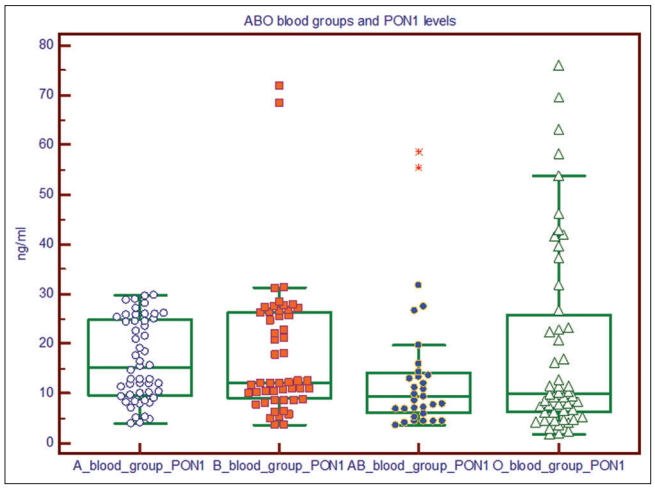

Figure 1: Paraoxonase enzyme distribution by blood phenotypes. In the box-and-whisker plot, the central box represents the values from the lower to upper quartile (25–75 percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding outside and far out values which are displayed as separate points

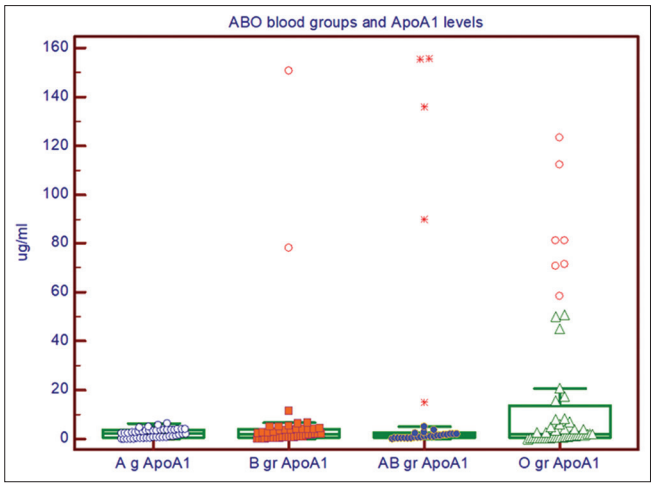

Figure 2: ApolipoproteinA-1 protein distribution by blood phenotypes. In the Box-and-whisker plot, the central box represents the values from the lower to upper quartile (25–75 percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding outside and far out values which are displayed as separate points

Whereas in many studies, non-O blood groups have been identified as a potential risk factor for the development of atherosclerotic diseases. Furthermore, a few recent studies have reported a significant relationship between the A and B alleles and cardiovascular disease.[4] Finally, scientists in an epidemiological study, individuals with AB blood phenotype had reported a 23% higher risk of developing coronary heart disease than the O blood group.[5]

Increased levels of some blood clotting factors, many inflammatory cytokines and cholesterol levels, have been proposed as the most likely mechanisms for explaining the association between diseases and ABO blood system.[6-8] However, there is no study in the literature showing the interaction of ABO blood groups with high-density lipoprotein (HDL)-related proteins and enzymes. Furthermore, it is well established that dysfunctional HDL plays an essential role in the pathogenesis of a lot of diseases.

ApolipoproteinA-1 (ApoA-I), the major protein component of HDL, well known for regulating cholesterol metabolism, may also modulate inflammatory and immune responses.[9,10] Furthermore, HDL-related paraoxonase 1 (PON1) has been found to be directly involved in the pathogenesis of atherosclerosis. On the other hand, "dysfunctional HDL" reduces PON1 activity, which potentially results in increased the formation of oxidized end products, which in turn, oxidized LDL. Hence, PON1 and oxidized low-density lipoprotein (OxLDL) have been implicated in endothelial dysfunction and atherosclerosis.[10]

We aimed to show the possible relationship between changes in HDL-related protein and enzymes of the healthy individuals participating in our study with the ABO blood phenotyping system. Therefore, in the present study, we were identified whether the distribution of the ABO phenotype influences the PON1, ApoA-I, and OxLDL levels in apparently healthy subjects.

Subjects and Methods

Sampling and ABO blood tests

This cross-sectional study was conducted in the AEAH Hospital, Health and Science University, between December 2018 and June 2019. The procedure of the study was approved by the Ethics Committee. A written informed consent was obtained from all persons who participated in this study. The inclusion criteria are as follows: the subjects included in this study are between the ages of 18–65, the subjects are mainly of South/West Anatolian origin, the subjects are apparently healthy men. The blood phenotype distribution of the 169 health staff who donated blood in this study was a blood group (*n*: 44), B blood group (*n*: 46), and o blood group (*n*: 48) and *n*: 35 subjects in AB blood group.

Venous blood samples were taken from all subjects after an overnight fasting and were examined for ABO blood group and for routine laboratory parameters. Microcolon in ABO blood phenotype determination method was used. For this purpose, gel centrifugation cards with "A, B, AB, DVI–, DVI+, Ctl, N/A1, N/B" configuration (across forward and reverse with DVI-/DVI+) and the manufacturer company (Across Gel, Diapro Medical Products) have been studied according to the instructions. The subjects were grouped according to ABO-blood phenotype. The venous blood samples were allowed to clot and then centrifuged at 3000 rpm for

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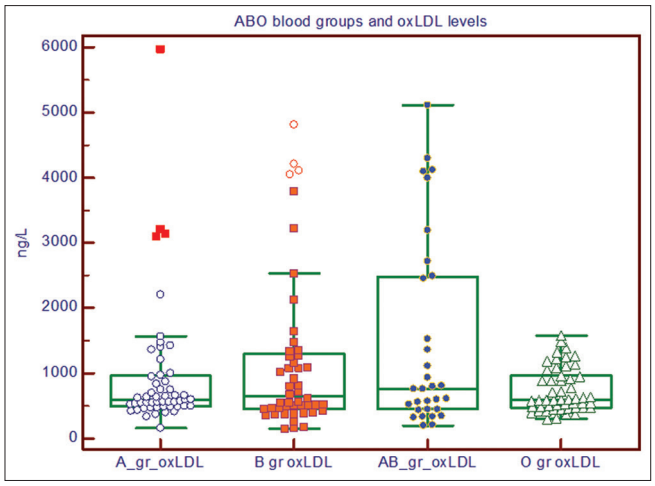

Figure 3: Oxidized low density lipoprotein lipoprotein distribution by blood phenotypes. In the Box-and-whisker plot, the central box represents the values from the lower to upper quartile (25–75 percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding outside and far out values which are displayed as separate points

5 min. Serum was stored frozen at – 20°C, and all analysis was carried out within 1 week of sample collection. Thawed serum was used for laboratory analysis, and parameters were measured using commercially available reagents.

Routine biochemical tests

Autoanalyzer Beckman AU5800® (Beckman Coulter Diagnostics, CA, USA) for the measurement of, creatinine, fasting blood glucose, uric acid, total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TGs) used in the study and commercial diagnostic reagent kits of the same brand were used. TC, LDL-C, and TG were measured by enzymatic methods and HDL-C measured by a direct method. All lipid parameters such as TC, TG, HDL-C, and LDL-C concentrations were double measured in all subjects, and the association between these variables and ABO blood groups was examined.

Measurement of paraoxonase 1, ApolipoproteinA-1 and oxidized low density lipoprotein levels in serum

The serum samples were tested for Human PON1 concentration (Biont®, Catalog no: YLA0984HU) and Human ApoA-I concentration (Biont®, Catalog no: YLA0883HU) and OxLDL Biont®, Catalog no: YLA0257HU) concentration, using a sandwich enzyme-linked immunosorbent assay, according to the manufacturer's instructions. The results were expressed as ng/ml, µg/ml, and ng/L, respectively.

Statistical analysis of data

To determine sample size calculation.net online software was used. Descriptive analysis was performed to determine the number and percentage of demographics. The means and standard deviations (SD) (standard continuous variables were expressed as mean ± SD, and categorical variables were presented as numbers and percentages. The statistical analysis was performed using MedCalc© Statistical Software version 15, 8 (MedCalc Software® bvba, Ostend, Belgium; https://www.medcalc.org; 2018). The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. The significance level (α) was also set at 0.05. In the ANOVA study in MedCalc© software were used to identify the difference among the A, B, AB, and O blood groups in variables pairwise comparisons between the mean and confidence interval (CI). The possible correlation between the measured parameters was determined by Spearman's correlation rank. Graph distributions in some of the parameters were shown using multiple comparison graphics in MedCalc© Statistical software version 15, 8 program.

Results

Age, body mass index, smoking history, hypertension, and all medication were all recorded as the baseline before blood donation. The number and percentage of these items were used to describe and measure the patient demographics in the A, B, AB, and O blood type groups, as shown in Table 1. Four ABO blood phenotypes displayed no significant difference in demographic characters and clinical data. Furthermore, there was no statistically significant difference between the routine laboratory findings of the patients included in this study [Table 1].

The blood phenotype distribution of the individuals involved in our study was tried to be chosen as evenly as possible. For this reason, the Eastern Mediterranean region does not reflect blood group distribution. The blood group distribution of these subjects was 44 people from blood Group A, 46 people from blood Group B, 31 people from blood Group AB, and 48 people from O blood group [Table 1].

When compared with the A, B, and O blood phenotype, the AB blood type group has the lower PON1, ApoA-I and higher OxLDL serum levels [Figures 1-3]. So, statistically significant difference in PON1, ApoA-I and OxLDL levels were found between the AB and non-AB blood phenotypes. The serum levels of PON1 were 9,00 (95% CI: 8.88 –18.81) ng/ml in AB blood phenotype; 9,92 (CI: 13.70–24.61) ng/ml in O phenotype; 12,467 (CI: 14.46–22.10) ng/ml in B blood phenotype and 15,48 (CI: 14.00–18.79) ng/ml in A blood phenotype [Table 1]. Similarly the levels of serum ApoA-I were 1.18 (CI: 0.52–2.73) µ/ml in AB blood phenotype; 1.72 (CI: 0.67–16.79) µ/ml in O phenotype; 1.97 (CI: 0.63–3.87) µ/ml in B blood phenotype and

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2.19 (CI: 0.66–3.57) µ/ml in A blood phenotype. On the contrary, OxLDL levels were statistically significant higher in the AB blood group. The levels of OxLDL were 758.62 (CI: 515.57–2332.97) ng/L in AB blood phenotype; 618.39 (CI: 463.79–1321.49) ng/L in B blood phenotype; 598.85 (CI: (481.03–961.31) ng/L in O blood phenotype and 562,06 (CI: 471.55–724.71) ng/L in A blood phenotype. As a result, the AB blood phenotype was associated with increased serum OxLDL levels and was significantly higher [Table 1].

Indeed all of these three parameters are related to HDL function and can indicate impairment in HDL function of individuals with AB blood phenotype. Interestingly, the HDL-C amount has very similar values in all blood groups (A, B, AB, and O), and no significant difference was found between them. There was no statistically significant difference between the values of TC, TGs, LDL-C, and HDL-C in the distribution of the healthy controls included in the study according to blood groups [Table 1].

Another important findings in this study were that significant correlations of PON1 values with age, ApoA-I and OxLDL values in subjects. As can be seen in Table 1, PON1 values in all blood groups have negative correlations with age. PON1 levels of the AB blood group were statistically strongly decreased with age, r: −0.783, P = 0.0003. Furthermore, ApoA-I levels in subjects had positive correlations with PON1 levels. Especially in O blood group r: 0.857, $P < 0.0001$ and AB blood group r: 0.714 were showed strong positive correlation $P < 0.0001$, Likewise to these findings, PON1 values had statistically significant negative correlations with OxLDL in all subjects. For example, OxLDL levels had a strong negative correlation with PON1 in that O blood phenotype, r: 0, 9106, $P < 0$, 0001 also there was a strong negative correlation in the AB blood phenotype, r: 0, 8691 $P < 0$, 0001[Table 2].

Discussion

This preliminary study was the first one to report the relationship between ABO blood phenotypes and HDL functionality by PON1, ApoA-I, and OxLDL levels. In addition, this preliminary study may provide evidence suggesting the AB blood phenotype is predisposed to some diseases. The major results of this preliminary study are as follows. First, statistically, the differences in AB blood phenotype correlate with the decreased serum levels of HDL-related PON1 and ApoA-I. Specifically, AB blood phenotype subjects had might susceptible with the lower antioxidant potential of PON1 and ApoA-I so that the AB blood phenotype may be a risk factor for some diseases pathogenesis.

Second, in this preliminary study, decreased serum PON1 levels are correlated with age, ApoA-I, and OxLDL. Third, higher distribution of the AB blood phenotype is could be identified as the risk factor which is with geographic and ethnic. In fact, that ABO blood phenotypes, as the indicator of genetics, were identified to have a critical role in mediating numerous medical conditions, including tumors, immune diseases, endocrine diseases, infectious diseases, and mental disorders.[11] Because some other studies have also clinically shown an increased risk of

Table 1: The clinical characteristics and laboratory parameters in ABO blood system

Baseline characteristics	A phenotype (*n*=44)	B phenotype (*n*=46)	AB phenotype (*n*=31)	0 phenotype (*n*=48)
Age (years)	34.90±11	33.90±8.4	37.03±8.0	34.05±10
BMI (kg/m^2)	26.3±3.0	25.8±2.9	26.8±2.6	25.4±2.8
Smoking (%)	30	36	40*	19
HT (%)	6.2	6.8	7.2	6.9
FBG (mg/dl)	103±11	99±9	102±12	100±13
UA (mg/dl)	5.72±1.3*	5.6±1.4	5.6±1.5	5.46±1.2
Traditional lipid parameters	**A phenotype**	**B phenotype**	**AB phenotype**	**0 phenotype**
TC (mmol/L)	4.75±1.20	4.70±q1.10	5.1±1.20	4.81±0.98
TG (mmol/L)	2.05±1.3	2.07±1.4	2.71±1.5	2.27±1.1
LDL (mmol/L)	2.67±0.80	2.74±0.90	2.7±0.75	2.69±0.06
HDL (mmol/L)	1.03±0.29	1.04±0.29	1.05±0.28	1.14±0.31
HDL related parameters				
PON1, ng/ml (mean, IC)	15.48 (14.00-18.79)	12.467 (14.46-22.10)	9.00 (8.88-18.81)[a]	9.92 (13.70-24.61)
ApoA-I, µ/ml (mean, IC)	2.19 (0.66-3.57)	1.97 (0.63-3.87)	1.18 (0.52-2.73)[b]	1.72 (0.67-16.79)
OxLDL, ng/L (mean, IC)	62.06 (471.55-724.71)	618.39 (463.79-1321.49)	758.62 (515.57-2332.97)[c]	598.85 (481.03-961.31)

One-way ANOVA test were used to identify the difference among the A, B, AB, and O blood type groups in some. *Pearson Chi-square test for frequencies, P=0.012, [a]The difference of AB blood group from A, P=0.0022, B blood phenotype P=0.02 and O blood phenotype P=0.048. [b]The difference of AB blood group from blood phenotypes A P=0.0002, B P=0.0042 and O P=0.0.047, [c]The difference of AB blood group from non-AB blood phenotype P=0.03. BMI=Body mass index, HT=Hypertension, DM=Diabetes mellitus, SD=Standard deviation, TC=Total cholesterol, HDL-C=High-density lipoprotein-cholesterol, LDL-C=Low-density lipoprotein-cholesterol, TG=Triglycerides, CI=Confidence interval for the mean±SD/analysis of variance for independent samples, ApoA-I=ApolipoproteinA-1, OxLDL=Oxidized low density lipoprotein, PON1=Paraoxonase 1

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Table 2: The significant correlations of paraoxonase with age apolipoproteinA-1 and oxidized low density lipoprotein in ABO blood system

PON1 ng/ml	A blood phenotype (*r*, *P*)	B blood phenotype (*r*, *P*)	AB blood phenotype (*r*, *P*)	O blood phenotype (*r*, *P*)
Age, years	−0.3392, 0.0149	−0.2677, 0.0561	−0.783, 0.0003	−0.2812, 0.0457
ApoA-I, μg/ml	0.677, <0.0015	0.562, <0.0023	0.714, <0.0001	0.857, <0.0001
OxLDL, mg/dl	−0.7389, <0.0001	−0.4594, 0.007	−0.8691, <0.0001	−0.9106, <0.0001

r: Sperman rank correlation. ApoA-I=ApolipoproteinA-1, OxLDL=Oxidized low density lipoprotein, PON1=Paraoxonase 1

coronary artery disease (CAD) among people with AB blood phenotype.[12] In a recent cohort study, researchers reported that having an AB blood phenotype in Nurses' Health Study, increased the risk of cardiovascular diseases.[5]

Moreover, ABO blood phenotypes might play an essential role in cardiovascular diseases.[13] In our study, ApoA-I and PON1 values, which play an important role in anti-atherosclerotic HDL structure, were statistically lower in subjects in the AB blood group. The functional deficiency of HDL is intimately associated with changes in HDL composition.[10] Indeed, recent research in the literature is consistent with our findings. For instance, a notable meta-analysis of six prospective studies indicated that non-O (A, B, AB) blood phenotypes were associated with an 11% increased risk of CAD compared with O blood phenotype.[5] Furthermore, individuals with the AB blood phenotype have the highest risk for CAD. Moreover, one study reported that the hazard rate adjusted according to Cox multivariate or cardiovascular, cerebral, peripheral vascular diseases was 1.19 (range 95% confidence: 1.01–1.40) for the AB blood phenotype compared with that of the non-AB blood phenotype.[14] Recently, the correlation between preoperative anxiety and AB blood phenotype was demonstrated in a clinical cross-sectional study. Furthermore, in one study, blood type AB was associated with increased stroke risk.[15]

Most, academic studies indicate that the HDL proteome can change in a variety of disease states, and these modifications are often related to the proteomic analyses of HDL-function.[10] However, we have not yet found a study showing changes in HDL structure depending on blood phenotypes in literature. Indeed alterations occurring in serum PON1, ApoA-I, and OxLDL composition and metabolism according to ABO blood phenotype were may be intimately associated with impaired biological activities. The anti-oxidative properties of the HDL-related enzyme PON1 have been well reported. The anti-oxidant enzyme PON1, which suppresses the formation of oxidized lipids and lipoproteins, is active in preventing the formation of OxLDL.[10] The anti-oxidant enzyme PON1, which is suppresses the formation of oxidized lipids and lipoproteins, such as LDL. Protective effects of PON1 on many diseases (e.g.,: CAD, cancer, diabetes) are quite likely due to their ability to counteract the effects of OxLDL.

In addition, ApoA-I is synthesized in the intestines and liver and is thought to be largely responsible for the anti-atherogenic effects of HDL.[9,10] Evidence is accumulating that ApoA-I is the major antiatherogenic and anti-oxidant factor in HDL. Plasma ApoA-I concentrations are strongly associated with the metabolism of many diseases. When LDL lipid peroxide concentrations were determined, ApoA-I and PON1 were both found to inhibit LDL oxidation in the absence of HDL, increasing the ability of HDL to inhibit LDL oxidation.[10]

Finally, the decrease in PON1 and ApoA-I in subjects with AB blood phenotype in this study have been caused a significant increase in OxLDL levels in subjects with AB blood phenotype. However, the decrease in PON1 and ApoA-I in subjects with AB blood group in this study have, as expected, caused a significant increase in OxLDL levels in subjects with this blood group.[10]

Indeed, if we are to strongly confirm our findings in this study, healthy male subjects in the AB blood group need to be monitored for a long time. In this way, only in the future will it be possible to determine whether subjects with AB blood type are predisposed to atherosclerosis or some other diseases such as cancer, diabetes, and mental disorders. These new findings are noteworthy for AB blood phenotype in nowadays. As the association of A blood phenotype or non-O blood phenotype with cardiovascular disease has been well known since its demonstration in the last four decades in the many studies. Previous studies also found that blood phenotype O was a protective factor for coronary atherosclerosis.[6-8] However, none of these studies measured serum levels of PON1, ApoA-I, and OxLDL, as well as levels in the ABO blood system. Currently, a large number of studies consistent with our main findings have been reported in the literature, but there is no study showing a decrease in PON1 and ApoA-I for impaired HDL functionality in subjects with AB blood phenotype.

The distribution of the ABO blood system differs greatly by area and ethnicity in continental Europe.

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In the European continent, the AB blood phenotype distribution is between 3% and 9%.[16] Thus, the always AB blood phenotype is less remarkable for scientists. Whereas the O blood phenotype is the most common blood phenotype in some Mediterranean countries. For example, 39% in Italy, 35% in Spain, 37.4% in Greece and 36% in France have individuals with O blood phenotype. What is really interesting is that it also has the lowest distribution rate of the AB blood phenotype in these Mediterranean countries (3%, 9%).[16] Perhaps, the lesser incidence of cardiovascular diseases in these countries is due to the low distribution of the AB blood phenotype.[17] For hypothetically the reason for low mortality due to cardiovascular disease may be due to the Mediterranean lifestyle as well as the low distribution of this AB blood phenotype. This idea gives us a new perspective, because in many countries where cardiovascular diseases are common, the AB blood phenotype distribution may be higher. There is no doubt that it is necessary to examine in more detail the molecular changes in lipid metabolism linked to the AB blood phenotype as well as the Mediterranean region for diseases.

Conclusion

The study was the preliminary study to show a decrease in serum PON1 and ApoA-I values and an increase in serum OxLDL according to the ABO blood system. The relationship between blood groups and diseases should be investigated more. The distribution of ABO blood group and ethnic relations may be related to the frequency of diseases may also be an issue to be considered.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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