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# Lecithin- cholesterol acyltransferase and relationship with Platelet-activating factor in AB blood phenotype



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## ABSTRACT

**Objectives:** This study aimed to determine the association between Lecithin-cholesterol acyltransferase (LCAT) and Platelet-activating factor (PAF) with atherogenic potential in the ABO blood system.

**Background:** The current study is the first study that focuses on healthy blood donors and investigating a relationship between ABO blood groups and LCAT enzyme and PAF, which plays a notable role in atherogenesis.

**Methods:** ABO blood types characterize the role of the individualistic phenotype. Hence, it is generally assumed that ABO blood phenotypes are involved with many diseases. This cross-sectional study involved 176 healthy subjects with different ABO blood phenotypes. Measurements of routine lipids, LCAT, PAF and atherogenic plasma index (AIP) were performed in these subjects.

**Results:** Our most important finding was that individuals with blood group AB have statistically significant lower LCAT levels in serum. Additionally, there was a moderately negative correlation between LCAT and triglycerides in the AB blood phenotype ( $r=-0.452$ ,  $P=0.02$ ). Nevertheless, there were statistically significant correlations between LCAT levels and PAF levels of subjects with only non-O blood phenotypes (A, B and AB). Serum AIP values were statistically significantly higher in the AB blood group.

**Conclusion:** The present study suggests that blood group AB can be associated with decreased LCAT levels when compared to the non-AB phenotypes. We suggest that LACT and AIP may be helpful biomarkers to illustrate atherogenic risk in AB blood phenotype, although this requires further investigation.

**Keywords:** ABO blood system, AB phenotype, atherosclerosis, atherogenic index of plasma, lecithin-cholesterol acyltransferase, platelet-activating factor, triglycerides, high-density lipoprotein cholesterol.

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## INTRODUCTION

Investigations in populations have shown that the ABO blood system may increase the risk of atherosclerosis. Also, many studies have shown that the ABO blood system can improve people's susceptibility to several disorders, including cancer and infections. Also, in most research conducted in the general population, non-O blood phenotypes were reported as a potential risk factor for the development of atherosclerotic diseases.<sup>1,2</sup> Also, current studies have reported the existence of a significant association between the A and B alleles and cardiovascular diseases.<sup>1,3</sup> A recent epidemiological study said that individuals with the AB blood phenotype had a 23% higher risk of developing coronary heart disease than the "O" blood phenotype.<sup>3</sup>

High-density lipoprotein cholesterol (HDL-C) is a heterogeneous lipoprotein family composed of several subclasses with diverse density, shape and size. HDL-C includes two hundred or more proteins, such as LCAT and platelet-activating factor acetylhydrolase (PAF-AH). HDL-C has strong

antioxidant properties, mediated by molecules achieved by HDL, as well as anti-inflammatory, antithrombotic, cytoprotective, vasodilatory, anti-infectious activities. The extensive spectrum of biologic effects reflects the heterogeneity of HDL-cholesterol; unfortunately, HDL's protective actions might be lost in pathological conditions, and even HDL may gain proatherogenic properties.<sup>4,5</sup>

The PC-sterol O-acyltransferase, EC 2.3.1.43 (LACT) is mainly synthesized in the liver and specially bound to HDL but also low-density lipoprotein cholesterol (LDL-C).<sup>6</sup> LCAT grow phosphatidylcholine and cholesterol into lysophosphatidylcholine and cholesteryl ester (CE) in biological fluids. Esterification of cholesterol in plasma by LCAT is just essential for cholesterol uptake from the hepatocytes either directly through the scavenger receptor class B member 1 (SR-BI) or indirectly through cholesterol ester transfer protein (CETP). Because free cholesterol transport among plasma lipoproteins and various tissues occurs by

complex mechanisms.<sup>6,7</sup> The CEs created by LCAT are most hydrophobic than free- cholesterol and so emigrated into the hydrophobic core of the HDL, with the resulting conversion of small, discoidal pre- $\beta$ -HDL into mature, spherical,  $\alpha$ -HDL. As reported in vitro studies and clinical studies, the role of LCAT in the pathogenesis of atherosclerosis remains controversial.<sup>7-9</sup> Although the relationship of blood groups to lipid metabolism is known, there is not yet much detailed research in the literature.

The next aim of this study was to demonstrate the likely relationship of ABO blood group distribution with the potent lipid mediator PAF. Because PAF is the mediator to the material released by activated leukocytes that induced platelet aggregation in blood.<sup>10,11</sup> Therefore, PAF is an effective lipid mediator of chronic low-grade inflammation and thrombocytes aggregation that participates in the initiation and prolongation of vascular endothelial dysfunction.<sup>10,12</sup> In many pathological states can generate PAF by enzymatically as well as PAF-like lipids produced by the free radical-mediated of glycerophosphocholines. Also, PAF is generated non-enzymatically along with oxidized phospholipids (oxPL) during pathologically LDL oxidation. However, under physiologic conditions, a small and continuous amount of PAF is made from cell membrane phospholipids by de novo synthesis, which is responsible for the functional regulation of plasma membranes.<sup>10,13</sup> Indeed, PAF <has a short Half-Life of 15 minutes and its degradation is catalyzed by PAF-AH, which is involved in the HDL structure.<sup>10,11</sup> Furthermore, hydrolysis of PAF by LCAT is similar to hydrolysis of other water-soluble esters, since it is not dependent on the apolipoprotein activator. Thus, chronic effects of PAF appears to be more “anti-inflammatory”, as opposed to the general “pro-inflammatory” effects attributed to the acute effects.<sup>10,11,14</sup> Unfortunately, we could not find the study in the literature that reported the relationship between ABO blood system, LCAT and PAF. After all, this study is perhaps the first to investigate the relationship between ABO blood groups and LCAT and PAF.

It is somewhat known that dyslipidemia plays an essential role in the pathogenesis of atherosclerosis.<sup>1</sup> However, despite their apparent clinical importance, the calculation atherogenicity risk of ABO blood group system remains an unknown because the significance of novel atherogenic indices in the ABO blood system of apparently healthy subjects is not broadly discussed in the literature yet. Some scientists are speculated that calculated AIP denoted a balance between the current amount of blood lipids which might pre-determine the direction of cholesterol carriage in the intra-vascular

reserve, e.g. the efflux of freshly produced CEs by LCAT towards bad cholesterol LDLs or beneficial HDLs.<sup>15,16</sup> Therefore, the strong correlation of AIP with the amount of pre- and anti- atherogenesis lipoprotein might explain its highly expected amount. The increased number of small dense LDL and low HDL particles in the blood may be associated with increased risk of CAD.

In contrast, the increased number of large size HDL may be associated with a decreased risk of atherogenesis. If the calculation of AIP needs to be described more clearly, AIP is defined as the base ten logarithms of the ratio of the concentration of triglycerides (TGs) to HDL-C.<sup>17</sup> Thus the principal goal of this study is to display whether there is a relationship between ABO blood system and serum LCAT, PAF and AIP levels.

## MATERIAL AND METHODS

### Sampling and ABO blood tests

The data were derived from apparently healthy (according to blood bank form) 176 male medical staff. Blood samples were taken from healthy male staff at the hospital to laboratory tubes with vacuum separator gel after 12-hour fasting at night from applicants for blood donation. Serum samples taken after blood centrifuge were stored at -80°C. This research began after the approval of the local ethics board received in the 2018 year and was completed in the 2019 year. Those selected for inclusion into the study were adults who were at least 18 years old and voluntarily consented. Their ages ranged from 18–58 years. Those with features suggestive of dyslipidemia, diabetes, heart or kidney failures or with acute/chronic illness were excluded. Also, non-fasting subjects and those who declined consent were excluded from the study.

Whole blood samples were taken from all subjects after 12 hours of fasting and were examined for the ABO blood system and routine laboratory parameters. Microcolon in ABO blood group determination method was used. For this purpose, gel centrifugation cards with “A, B, AB, DVI-, DVI+, Ctl, N/A1, N/B” configuration (Across Forward & Reverse with DVI/DVI+) and the manufacturer company (Across Gel, Diapro Medical Products, TR) were studied according to the instructions. Subjects were classified as: A blood phenotype (n: 48), B blood phenotype (n: 48), AB blood phenotype (n: 32), O blood phenotype (n: 48) and non-O blood phenotype (n: 128).

Blood samples were allowed to clot in a non-additive tube and then centrifuged at 3000 rpm for five minutes. The Serum was stored frozen at -20°C, and all analyses were done within a week of

the sample being collected. The serum was used for LCAT, and PAF analysis and the routine biochemical parameters were determined using commercially available reagents.

### Routine biochemical tests

Autoanalyzer Beckman AU5800<sup>®</sup> and reactive (Beckman Coulter Diagnostics, CA, USA) was used for the measurement of creatinine, fasting blood glucose (FBG), uric acid (UA), TC, LDL-C, HDL-C and TG. Non-HDL-C was calculated using the formula as follows: non-HDL-C = (TC) – (HDL-C). TC, LDL-C, and TG were measured by enzymatic methods, and HDL-C was measured by a direct approach. All lipid parameters such as TC, TGs, HDL-C and LDL-C concentrations were double measured in all subjects, and the association between these variables and ABO blood groups was examined. The computational formula used was  $\log_{10}(\text{TG}/\text{HDL-C})$  for AIP.<sup>18</sup>

### Immunoassay analysis of LCAT and PAF levels

The stored serum of subjects was analyzed for Human PAF concentration (Biont<sup>®</sup>, Catalog no: YLA1737HU) and Human LCAT concentration (Biont<sup>®</sup>, Catalog no: YLA1929HU) applying a sandwich enzyme-linked immunosorbent assay (ELISA), according to the test instructions. The obtained values were described as mg/L and U/L, respectively.

### The statistical analysis method of the obtained data

Calculation.net used to determine the number of samples in the study. Descriptive analysis was performed to determine the demographic records and percentage of participants. Then the mean and standard deviations (SD) for continuous standard variables were calculated, and it was expressed as mean $\pm$ SD. Also, categorical variables were written as numbers and percentages. The program was used in this study is medcalc © Statistical Software version 15, 8 (MedCalc Software<sup>®</sup> bvba, Ostend, Belgium; <https://www.medcalc.org>; 2018). First, the Kolmogorov-Smirnov test was used to show the distribution of continuous variables. The significance level ( $\alpha$ ) of all tests was also 0.05. The ANOVA analysis in the software used was applied to identify the difference between the A, B, AB and O blood group groups in pairwise comparisons between the mean and confidence interval (CI) in the measured variables. The possible correlation between the measured parameters was determined by Spearman's correlation rank. Graph distributions in some of the settings were shown using multiple

comparison graphics in MedCalc<sup>®</sup> Statistical Software version 15, 8 programs.

## RESULTS

There was no statistically significant difference between clinical characteristic and measured routine laboratory parameters findings of the volunteer healthy male individuals included in this study (Table 1). The most important finding of this study is that the AB blood phenotype has a lower amount of LCAT enzymes than the A, B, O and non-AB blood phenotypes.

Perhaps, this study presents the first findings in the current literature showing changes in serum LCAT level depending on blood groups. LCAT levels of AB blood phenotype (15.32 U/L) were found to be 60% lower than non-AB blood phenotype (25.28 U/L) (Table 2,  $p < 0.001$ ). The most important finding was that serum LCAT enzyme amounts were statistically significantly higher in individuals with blood phenotypes B, A and O than in individuals with AB blood phenotypes (Table 2). Serum LCAT level was 18 U/L in individuals in the "O" blood phenotype. In the B blood phenotype, serum LCAT level was highest, and the second-highest, serum LCAT level was in the A blood phenotype (Table 2). The distribution chart of serum LCAT amount of ABO blood system is shown in figure 1. However, LCAT levels had no statistically significant differences between A, B and O blood phenotypes.

Furthermore, another important finding of this study was the significant positive, strong correlation between serum PAF enzyme amounts and serum LCAT enzyme amounts of individuals with only non-O blood phenotype (Figure 2). Also, statistically significant Spearman's coefficient of rank correlations ( $\rho$ ) were demonstrated between LCAT and PAF in ABO blood system; A,  $r: 0.859$   $p < 0.0001$ , B;  $r: 0.789$ ,  $p < 0.0001$ , AB;  $r: 0.819$   $p < 0.0001$ , O;  $r: 0.171$   $p = 0.2414$ . Also, there was a moderate negative correlation between LCAT and TGs in the AB blood phenotype,  $r: -0.452$ ,  $P = 0.02$ .

However, contrary to expectations, our findings did not show a statistically significant difference between the ABO blood system and serum PAF enzyme amounts. Another important finding in this study was that AIP was statistically higher in the AB blood phenotype (Table 2). Interestingly, AIP has very similar ratios in all three other blood phenotypes (A, B, and O), and the calculated AIP values in these three blood phenotypes showed no statistically significant difference. On the other hand, the lipid parameters we measured in the laboratory did not differ significantly in any ABO blood

**Table 1** The clinical characteristics of the study population

Baseline characteristics	A phenotype	B phenotype	AB phenotype	O phenotype	non-O phenotypes
Age (years)	34.9 ± 11	33.9 ± 8.4	37.03 ± 8.	34.05 ± 10	36.2 ± 9.6
BMI (kg/m <sup>2</sup> )	26.3 ± 3	25.8 ± 2.9	26.8 ± 2.61	25.4 ± 2.77	26.3 ± 2.92
Smoking (%)	30	36	40*	19	35
HT (%)	6.2	6.8	7.2	6.9	6.73
FBG (mg/dl)	103 ± 11	99 ± 9	102 ± 12	100 ± 13	101.3 ± 9
UA (mg/dl)	5.72 ± 1.3*	5.6 ± 1.4	5.6 ± 1.46	5.46 ± 1.24	5.64 ± 1.5
Traditional lipid Parameters	A phenotype	B phenotype	AB phenotype	O phenotype	non-O phenotypes
TC (mmol/L)	4.75 ± 1.2	4.70 ± 1.1	5.1 ± 1.2	4.81 ± 0.98	4.85 ± 1.2
TG (mmol/L)	2.05 ± 1.3	2.07 ± 1.4	2.71 ± 1.5	2.27 ± 1.1	2.2 ± 1.1
LDL (mmol/L)	2.67 ± 0.8	2.74 ± 0.9	2.7 ± 0.75	2.69 ± 0.06	2.7 ± 0.7
HDL (mmol/L)	1.03 ± 0.29	1.04 ± 0.29	1.05 ± 0.28	1.14 ± 0.31	1.04 ± 0.24
Non-Traditional Lipid Parameter					
AIP	0.29 ± 0.26	0.29 ± 0.27	0.40 ± 0.33*	0.29 ± 0.25	

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,

\*Pearson Chi-Square test for frequencies, Mean±SD / One-way ANOVA test were used to identify the difference among the A, B, AB, and O blood type groups in some. The difference of AB blood group from A, B and O blood group, p=0.01.

**Table 2** The distribution of LCAT and PAF among the study population

Variables	Overall (n=176)				
	A (n=48)	B (n=48)	AB (n=32)	O (n=48)	Non- AB(n=144)
LCAT(U/L)IQR	27,6(13,64-58,9)***	28,9(17-53,6)*	15,32(9,6-24,2)	18,52(9,6-55,4)****	25,2(13,6-54,9)**
PAF (mg/L)IQR	4,01(3,54-5,26)	3,64(3,07-5,8)	2,67(2,54-5,4)	3,88(2,77-8,84)	

One-way ANOVA test was used to identify the difference among the A, B, AB, and O blood type groups in some. \* The difference of AB blood group from B blood group, p=0.012, \*\* The difference of AB blood group from non-AB blood group p=0, 0026. \*\*\* The difference of AB blood group from A blood group p<0, 0032, \*\*\*\*The difference of AB blood group from O blood group p=0.029.

IQR=Interquartile range Pearson Chi-Square test for frequencies, Median (IQR).

groups. As expected, there was no statistically significant difference between the routine lipid values of the healthy individuals included in this study compared to the ABO blood system.

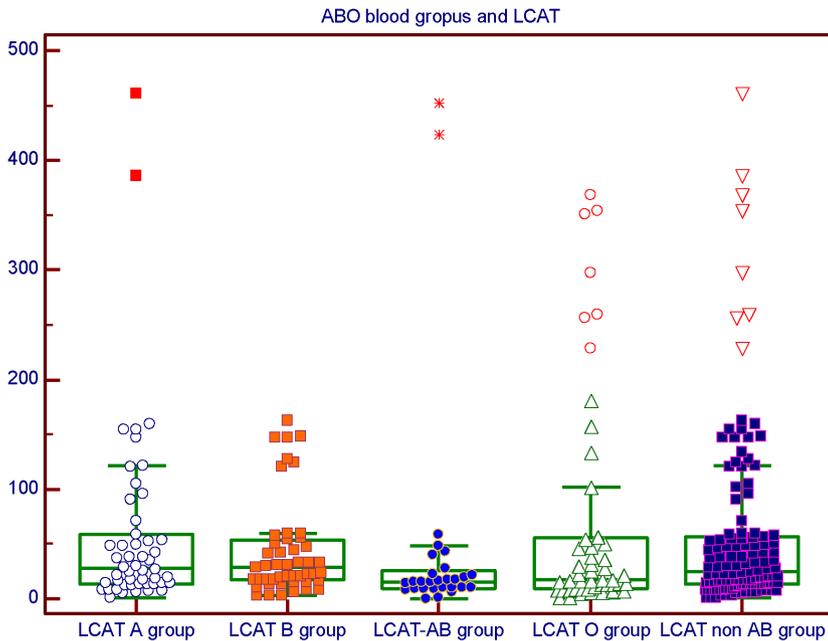
## DISCUSSION

The most striking finding of this study is undoubtedly that healthy people with AB blood phenotype have low LCAT levels and increased AIP index levels. There is currently no article in the medical literature showing that serum LCAT levels change according to the ABO blood system. Thus, the regulation of serum LCAT expression is not well understood in a 1972 study by Hernell et al., serum LCAT activity was measured only in A and O blood groups. In this study, which consisted of a working group of 39 people, the researchers found no difference in LCAT enzyme activity between A and O blood phenotypes.<sup>19</sup>

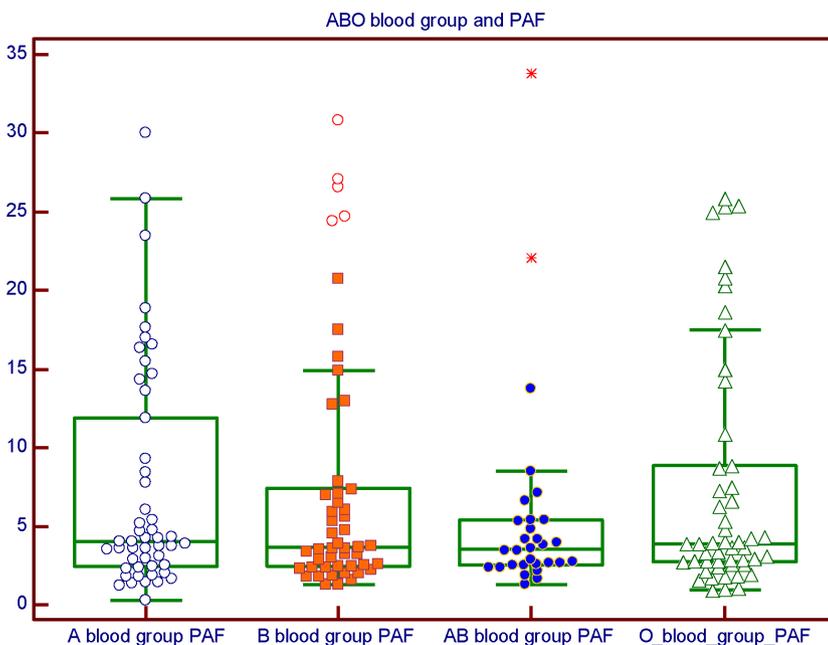
The distribution of ABO blood system differs greatly by area and ethnicity. When we consider

that the AB blood phenotype distribution is between 3% - 8% in the European continent, we can say that the AB blood phenotype has undergone less scrutiny. We know well that the "O" blood phenotype is the most common blood phenotype in most Mediterranean countries. For example, the percentage of people with O blood phenotype is 46% in Italy, 45% in Spain, 44% in Greece and 42% in France. The most interesting fact is that the AB blood phenotype in these Mediterranean countries has the lowest rate of distribution (3-5%).<sup>20,21</sup>

The reason for low mortality due to cardiovascular disease may be due to the Mediterranean diet 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. They're the most common blood group in our country where we did the study is A blood phenotype (42%). Moreover, it has the highest AB blood phenotype (8%) in the



**Figure 1** Distribution of serum LCAT in the ABO blood system. In the Box-and-whisker plot, the central box represents the values from the lower to upper quartile (25 to 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** Distribution of serum PAF in the ABO blood system. In the Box-and-whisker plot, the central box represents the values from the lower to upper quartile (25 to 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

European continent.<sup>20,21</sup> There is no doubt that it is necessary to examine the molecular changes in lipid metabolism linked to AB blood phenotype as

well as the Mediterranean diet for atherosclerosis in more detail.

In a recent cohort study, researchers reported that having an “AB” blood phenotype in Nurses’ Health Study, increased the risk of CAD. Also, He. et al. concluded that blood groups B and A were associated, to a lesser extent, with higher risk. Because some other studies have also clinically shown an increased risk of CAD among people with AB blood phenotype.<sup>3</sup> Also, one study reported that according to the Cox multivariate-adjusted hazard ratio for coronary, cerebrovascular or peripheral diseases was 1.19 (95% confidence interval: 1.01-1.40) for AB blood phenotype compared to those with “O” blood phenotype in Canada.<sup>22</sup> These new findings are noteworthy for AB blood phenotype nowadays. The association of A blood phenotype or non-O blood phenotype with CAD, has been known since its demonstration in the last four decades in the many studies.<sup>23,24</sup>

However, none of these studies measured serum LCAT levels and their distribution in the ABO blood system. Currently, a large number of similar studies consistent with our atherogenic risk findings have been reported in the literature. Still, there is no study showing an increase in AIP (log TGs/HDL-C) for CAD in people with AB blood type.<sup>25,26</sup> Although studies showing that there is a risk of atherosclerosis in the “AB” blood group are included in the literature, there is no complete consensus on this issue yet. Furthermore, the positive correlation between serum LCAT level and serum TG level among the findings of this study was only in the AB blood phenotype. Our findings are valuable in terms pathogenesis of atherogenesis, as the decrease in the number of LCAT enzymes is often associated with hypertriglyceridemia in animal models and humans.<sup>25-27</sup> Hypertriglyceridemia, especially low HDL-C levels, is an important sign of insulin resistance and metabolic syndrome. Therefore it is a marker of atherosclerotic diseases that may occur.<sup>25</sup> According to the data from this study, serum LCAT enzyme quantity in healthy people may be associated with TG level, especially in individuals with AB phenotype. Still, the underlying mechanisms have not yet been investigated. So much so that because high AIP levels in AB blood group-bound subjects were mainly due to a higher concentration of TGS, it may be of interest to study the metabolic background in future research. The AIP measurement may reflect the balance between TGS and HDL-cholesterol, atherogenic and protective lipoproteins. Because it is also associated with the size of AIP, pro, and antiatherogenic lipoprotein particles. In many studies, AIP has been clearly shown to predict cardiovascular risk. Perhaps in the future, AIP will be an easily available atherosclerosis

risk marker or pharmacological treatment measure between different blood groups.<sup>17,25</sup>

Higher LCAT activity, therefore, would be expected to be associated with protection from atherosclerosis and cardiovascular risk; however, data from human and animal studies have provided conflicting results.<sup>26,28</sup> However, in previous studies, the effect of non-O blood phenotype, especially the A blood phenotype, on routine plasma lipid levels has been reported many times. Because in some studies, serum TC and LDL-C increases have been reported in patients with “A” blood phenotype.<sup>29</sup> However, we did not find a relationship between routine lipid parameters and the ABO blood system in healthy male subjects. The physiological significance of the correlation between LCAT and PAF in people with non-O phenotype included in our findings can only be speculative at this time. Probably it can be assumed that PAF-AH activity is limited to LCAT enzyme and that LCAT may have an additional role in the degradation of PAF, especially in HDL-C. According to all these results, there may be evidence for the different function of the LCAT enzyme in PAF metabolism in different blood groups.<sup>6-8,29</sup>

The most important restrictive feature of our study is that the number of subjects is low. Also, the concentrations of LCAT and PAF, as well as the measurement of activity, could have been valuable. In this case, it should be taken into account that our study group has consisted of only male individuals and smaller populations. Although the link between the ABO blood system and routine lipid parameters has been described, the basis of these relationships and their possible potential for personalized medicine are not clear. In the future, more comprehensive and detailed research should be carried out on lipid metabolism, especially in individuals with the AB blood phenotype. Because of the results of this research base the being of significant associations between ABO blood phenotype and circulating levels of LCAT, PAF and novel atherogenic risk index AIP in healthy male staff.

In the AB blood phenotype, what role does LCAT play in modulating HDL functional composition or therefore determining the atheroprotective potential of HDL? It is important to understand better the role of LCAT enzyme function in determining HDL-C functionality due to ABO blood phenotyping, and therefore its atheroprotective potential. Results from this and future clinical trials will clarify many of the long-standing mysteries about LCAT.<sup>6-8</sup>

Further experimental and clinical studies are needed to assess the AB-blood phenotype related influence on the LCAT PAF and AIP parameters,

as well as for elucidating the underlying molecular mechanisms.

## LEARNING POINTS

There is no doubt that it is necessary to examine in more detail the molecular changes in HDL metabolism linked to AB blood phenotype. It is also exciting that the AB blood phenotype in many Mediterranean countries has the lowest rate of distribution. The increase in serum AIP level can be supported by more extensive research, with the possible contribution of the decreased LCAT enzyme, which has an essential role in HDL maturation, in the AB blood phenotype.

## CONCLUSION

Healthy male subjects with AB blood group may have a decrease in HDL function and an increase in atherogenic risk. This conclusion is supported by a decline in LCAT enzyme and an increase in serum AIP levels in the subjects participating in our study.

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