Relation of ABO blood groups to coronary lesion complexity in patients with stable coronary artery disease

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ABSTRACT

Objective: We aimed to investigate the relationship between ABO blood groups and complexity of coronary lesions assessed by SYNTAX score (SS) in stable coronary artery disease (CAD) patients.

Methods: Our cross-sectional and observational study population consisted of 559 stable CAD patients. From all patients, ABO blood group was determined and the SS was calculated as low SYNTAX score (0-22), intermediate SYNTAX (23-32) score and high SYNTAX score (>32). Statistical analysis was performed using Student’s t-test or Mann-Whitney U test, ANOVA, or Kruskal-Wallis test and chi-square test. Multiple logistic regression analysis was used to identify the independent predictors of high SS.

Results: The analysis between the SS tertiles revealed that the frequency of non-O blood group was significantly higher in the upper SS tertiles (56.2% vs. 75.9 vs. 80.2%, p<0.05). However, the frequencies of Rh types were similar in all tertiles. Multiple logistic regression analysis was applied for determining the predictors of high SS. Accordingly, non-O blood group (OR: 2.68, 95% CI 1.65-4.35, p<0.001), LV-EF (OR: 0.93, 95% CI 0.91-0.95, p<0.001), LDL(OR: 0.98, 95% CI 0.97-0.99, p<0.001), and e-GFR (OR: 0.99, 95% CI 0.98-0.98, p<0.001) were found to be the independent predictors of high SS.

Conclusion: We showed that there were significant associations between ABO blood groups and complexity of angiographic CAD.

Key words: ABO blood group, SYNTAX score, coronary artery disease, multiple logistic regression analysis

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Many studies have been performed to understand the factors and mechanisms underlying atherosclerotic heart disease. Ischemic heart disease is a multifactorial complex pathology, wherein inflammatory process plays an important role in the onset and progression of the disease (1, 2), and influenced by many risk factors (arterial hypertension, diabetes mellitus, hypercholesterolemia, and family history for ischemic heart disease) and genetic properties (3-5).

ABO blood groups are composed of complex carbohydrate molecules with different antigenic structures (6). The A and B alleles of the ABO locus encode A and B glycosyltransferase activities, which convert precursor H antigen into either A or B determinants, the A and B antigens having an extra saccharide unit to the O unit (N-acetylgalactosamine and galactose, respectively). Group O individuals lack such transferase enzymes (loss of function) and express basic, unchanged H-antigen (7, 8).

Previous studies have revealed that there are differences in the development of coronary artery disease between ABO blood groups and it is a well-known fact that atherosclerotic heart disease is more commonly encountered in people of blood type other than O (9).

The SYNTAX score (SS) is an angiographic lesion-based scoring system originally invented to evaluate the complexity of CAD (10). It is able to aid revascularization decisions and predicts mortality and morbidity in patients with CAD (11-14). The relationship between ABO blood group and the severity of CAD assessed by SS in patients with CAD has not been clearly determined.
Therefore, in this study, we aimed to assess relationship between the severity of coronary atherosclerosis assessed by SS and ABO blood group in patients with stable coronary artery disease.

Methods

Study design
This is an observational cross-sectional study

Study population
Our study population was selected among 1098 eligible consecutive patients who underwent coronary angiography for suspected or known coronary atherosclerosis between June 2010 and September 2012. Exclusion criteria were SS=0 (n=342), clinically significant valvular heart disease (n=65), significant congestive heart failure (n=55), hematomal disease (n=34), cancer (n=4), severe renal or liver disease (n=16), ongoing infection or chronic inflammatory disease (n=21), and autoimmune disease (n=2). Finally, 559 eligible patients were included in the study. All participants gave an informed consent and the study protocol was approved by local Ethics committee.

Data collection or baseline clinical variables
Evaluations were visually performed by 2 experienced angiographers. Patients’ laboratory and clinical characteristics, such as age, sex, diabetes mellitus (DM), hypertension (HT), smoking, height, and weight, were accessed through the medical records. By dividing weight in kilograms by height in squared meters (kg/m²), the body mass index (BMI) was calculated.

Stable angina was defined as discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress, and relieved by rest or nitroglycerin. HT was defined as systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg, or use of antihypertensive medications. The diagnosis of DM was based on previous history of diabetes treated with or without medical therapy. Hypercholesterolemia was described as total cholesterol ≥200 mg/dL. BMI was calculated by dividing the weight (kg) of an individual by the square of his/her height (m). A BMI value ≥30 kg/m² was defined as obese. Current smokers were defined as having a history of smoking for a certain period within the past year. Estimated glomerular filtration rate (e-GFR) was calculated by using the Cockgroft Gault formula = (140-age)*[(Weight in kg)*0.85 if female)] / (72* Creatinine). Chronic kidney disease was defined as e-GFR<60 (mL/min/1.73m²).

Transthoracic echocardiography was performed on patients before they were discharged using a system V (Vingmed; GE, Horten, Norway) with a 2.5-MHz phased-array transducer. Recordings were taken on patients positioned in the left lateral decubitus position. The left ventricular ejection fraction (LV-EF), was measured using modified Simpson rule.

Coronary angiography
All patients recruited in the study underwent coronary angiography [(Siemens AXIOM-Artis (Siemens AG 2001Muenchen-Germany)] for the presence of chest pain or had objective signs of ischemia (treadmill exercise or myocardial single photon emission computed tomography).

Coronary angiographies were performed in our clinic using the standard Judkins method using iohexol (Omnopaque, Nycomed Ireland ltd., Cork, Ireland). During each injection, 6-10 mL contrast agent is manually delivered and nitroglycerin is not routinely applied. Coronary angiograms were assessed independently by two invasive cardiologists who were blinded to the clinical findings.

SYNTAX score
SYNTAX score is an angiographic tool used in grading the complexity of CAD. Each coronary lesion with a diameter stenosis ≥50%, in vessels ≥1.5 mm must be scored. The parameters recorded in the scoring process are summarized in Table 1. The on-line latest updated version was used in the calculation of the SYNTAX scores (www.syntaxscore.com) (15). After receiving the basic training from the SYNTAX score website, the interventional cardiologists calculated the SYNTAX score. SYNTAX score, both numeric values of the score and tertiles (≤22, >22 - ≤32, >32) of the score were used.

Laboratory data
In our hospital the blood samples are collected from the antecubital vein by a traumatic puncture prior to the coronary angiography and are sent to the laboratory for analysis within 1 hour after collection. Routinely venous blood is collected in a tube containing K3 EDTA for measurement of hematologic indices in all patients undergoing the coronary angiography. ABO blood group determination was done using a commercially available hemagglutination technique (Erytype S ABO Microplates, Biotest, Germany). Low (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides (TG), were measured using the Abbott Architect C16000 auto analyzer (Abbott Laboratory).

Statistical analysis
All statistical studies were carried out with the SPSS program (version 15.0, SPSS, Chicago, Illinois, USA). Continuous variables are expressed as mean±SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, Student’s t-test or analysis of variance (ANOVA) were used; to compare nonparametric continuous variables, Mann-Whitney U or Kruskal-Wallis test were used. Tukey test and Mann-Whitney U test were used in post-hoc analysis. Chi-square test was used to compare the categorical variables. Multiple logistic regression analysis was used to identify the independent predictors of High SS. All variables showing significance values <0.10 in univariate analysis were included in the
model. Two-tailed p values <0.05 were considered as statistically significance.

Results

Baseline characteristics

In this study, 559 patients with angiographic coronary artery disease were enrolled. The mean age was 61.6±11.8 and 75.1% of the study population was male. The mean SS of the patients was 26.2±13.7 (median, 23; IQR, 15-37). The study population was split into three groups relative to SS, as described in the previous section: low, intermediate, and high SS tertiles. Baseline clinical and laboratory characteristics of the SS tertiles are shown in Table 1.

 Clinically predictors of high SS

As 32% of the whole study population were of O blood group, 68% were of non-O blood group (Type A, 46.2%; Type B, 17.9%; and Type AB, 3.9%). Furthermore, 92.3% of the study population was Rh positive and 7.7% were Rh negative. The analysis between the SS tertiles revealed that the frequency of non-O blood group was significantly higher in the upper SS tertiles (56.2% vs. 75.9 vs. 80.2%, p<0.05) (Fig. 1). However, the frequencies of Rh types were similar in all tertiles. The levels of BMI, LV-EF, eGFR, LDL, and TG were found to be significantly lower in the upper tertiles, as well.

Multiple logistic regression analysis was applied for determining the predictors of high SS. Accordingly, non-O blood group

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Table 1. Baseline clinical and laboratory characteristics according to SYNTAX score tertiles

<table>
<thead>
<tr>
<th>Variables</th>
<th>SS&lt;22 (n=265)</th>
<th>SS (23-32) (n=112)</th>
<th>SS&gt;32 (n=182)</th>
<th>*P</th>
<th>*F or chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>60.9±12.5</td>
<td>60.5±11.8</td>
<td>63.3±11.3</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td><strong>Sex, male, %</strong></td>
<td>73.2</td>
<td>78.6</td>
<td>75.8</td>
<td>0.481</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus, %</strong></td>
<td>19.2</td>
<td>27.7</td>
<td>25.8</td>
<td>0.085</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension, %</strong></td>
<td>45.7</td>
<td>49.1</td>
<td>52.2</td>
<td>0.172</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking, %</strong></td>
<td>40.4</td>
<td>42.9</td>
<td>33</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>28.2±6.3</td>
<td>29.1±5.5</td>
<td>27.5±3.6</td>
<td>0.014 &amp; 3.08</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic kidney disease, %</strong></td>
<td>15.8</td>
<td>13.4</td>
<td>19.8</td>
<td>0.315</td>
<td></td>
</tr>
<tr>
<td><strong>LV-EF, %</strong></td>
<td>54.0±9.4</td>
<td>47.8±9.3</td>
<td>45.2±9.8</td>
<td>&lt;0.001 $&lt;0.026 ^&amp; 48.7</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated GFR, mL/min/1.73 m²</strong></td>
<td>97±40</td>
<td>99±45</td>
<td>80±27</td>
<td>&lt;0.001 $&lt;0.026 ^&amp; 14.0</td>
<td></td>
</tr>
<tr>
<td><strong>LDL-cholesterol, mg/dL</strong></td>
<td>97±38</td>
<td>92±37</td>
<td>74±30</td>
<td>&lt;0.001 $&lt;0.026 ^&amp; 20.4</td>
<td></td>
</tr>
<tr>
<td><strong>HDL-cholesterol, mg/dL</strong></td>
<td>40.5±11.5</td>
<td>42±19</td>
<td>38±9</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td><strong>Triglyceride, mg/dL</strong></td>
<td>140±116</td>
<td>131±96</td>
<td>111±54</td>
<td>0.003 ^&amp; 4.60</td>
<td></td>
</tr>
<tr>
<td><strong>O group, %</strong></td>
<td>43.8</td>
<td>24.1</td>
<td>19.8</td>
<td>&lt;0.001 32.5*</td>
<td></td>
</tr>
<tr>
<td><strong>Non-O group, %</strong></td>
<td>56.2</td>
<td>75.9</td>
<td>80.2</td>
<td>&lt;0.001 32.5*</td>
<td></td>
</tr>
<tr>
<td><strong>A group</strong></td>
<td>41.5</td>
<td>51.8</td>
<td>49.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B group</strong></td>
<td>11.3</td>
<td>19.6</td>
<td>26.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AB group</strong></td>
<td>3.4</td>
<td>4.5</td>
<td>4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rh (+) group, %</strong></td>
<td>93.2</td>
<td>90.2</td>
<td>92.3</td>
<td>0.668</td>
<td></td>
</tr>
<tr>
<td><strong>Rh (-) group, %</strong></td>
<td>6.8</td>
<td>9.8</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medications, %

| Aspirin                          | 16.6          | 17                 | 18.7         | 0.577  |
| ACE-i/ARB                        | 22.6          | 26.8               | 29.1         | 0.118  |
| Beta blocker                     | 6             | 9.8                | 7.7          | 0.452  |
| CCB                              | 8.7           | 8.9                | 10.4         | 0.539  |
| Statin                           | 14.7          | 17                 | 20.3         | 0.122  |

Data are presented as mean±SD and percentage

*ANOVA, Kruskal-Wallis or chi-square tests

†indicate SS<22 vs SS (22-32), ‡indicate SS<22 vs SS>32, §indicate SS (22-32) vs SS>32 in post-hoc Tukey test analysis.

ACE-i - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; CCB - calcium channel blocker; GFR - glomerular filtration rate; HDL - high density lipoprotein; LDL - low density lipoprotein; LV-EF - left ventricular ejection fraction; SS - SYNTAX score

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(OR: 2.68, 95% CI 1.65-4.35, p<0.001), LV-EF (OR: 0.93, 95% CI 0.91-0.95, p<0.001), LDL (OR: 0.98, 95% CI 0.97-0.99, p<0.001), and e-GFR (OR: 0.99, 95% CI 0.98-0.99, p<0.001) were found to be the independent predictors of high SS (Table 2).

**Table 2. Independent predictors of high SYNTAX score tertile: logistic regression analysis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate OR, 95% CI</th>
<th>Univariate ( P )</th>
<th>Multivariate OR, 95% CI</th>
<th>Multivariate ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>O/Non-O blood group</td>
<td>2.92(1.92-4.43)</td>
<td>&lt;0.001</td>
<td>2.68 (1.65-4.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.97(0.94-1.00)</td>
<td>0.079</td>
<td>1.00 (0.96-1.04)</td>
<td>0.780</td>
</tr>
<tr>
<td>LV-EF</td>
<td>0.92(0.90-0.94)</td>
<td>&lt;0.001</td>
<td>0.93 (0.91-0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td>0.99(0.98-0.99)</td>
<td>&lt;0.001</td>
<td>0.99 (0.98-0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>0.98(0.97-0.99)</td>
<td>&lt;0.001</td>
<td>0.98 (0.97-0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trygliceride</td>
<td>0.99(0.98-0.99)</td>
<td>0.015</td>
<td>0.99 (0.99-1.00)</td>
<td>0.305</td>
</tr>
</tbody>
</table>

GFR - glomerular filtration rate; LDL - low-density lipoprotein; LV-EF - left ventricular ejection fraction

**Discussion**

In the present study, we demonstrated that the frequency of non-O blood group was observed to increase with increasing angiographic CAD complexity; furthermore, being a member of Non-O blood group was an independent predictor of complex CAD shown by high SS. To our knowledge, the present study is the first report evaluating the relationship of ABO blood groups with the severity and complexity of coronary artery disease by measuring SYNTAX score among patients with stable coronary artery disease.

Although the pathophysiologic relationship between the blood groups and coronary artery disease has not been revealed clearly, several mechanisms have been proposed. ABO blood groups have been shown to be inherited via chromosome 9 (locus 9p34). Since the gene involved in the cholesterol balance [the ATP-binding cassette 2 (ABCA2)] is also located in the same location, investigators have claimed that there might be a possible genetic interaction between blood groups and coronary artery disease (16). In consistence with this proposition, patients of non-O blood group have been found to show a significant relationship with family history of coronary artery disease and hypercholesterolemia along with having a higher mortality rate associated with ischemic heart disease (17). Among other possible mechanisms, biomarkers have also been noted as likely factors in coronary artery disease, particularly von Willebrand Factor (vWF) and factor VIII (FVIII) (18). Most circulating vWF is synthesized as pro-vWF from endothelium and a part from platelets, after undergoing several maturation steps as it moves along the secretory pathways becomes active vWF (15). vWF is a glycoprotein molecule playing an important role in the interaction between platelets and vascular wall as well as acting as a significant factor in FVIII function. vWF is a markedly specific molecule to endothelial cells and has an important role in platelet adhesion particularly under increased shear stress. While its deficiency was found to be associated with bleeding, its redundancy was found to be associated with thrombosis (19-22). vWF is known to be a risk factor for coronary heart disease (23, 24). Animal studies have shown that vWF is involved in the development of atherosclerosis. The platelet adhesion around the atherosclerotic plaques has been observed to enhance plaque formation, while vWF increase in response to endothelial activation without endothelial damage is thought to be an underlying mechanism contributing to the development of early atherosclerotic lesions (20). Furthermore, although the reason behind varying vWF levels between ABO groups has not been clearly understood, the endothelial interaction of ABO groups due to their different antigenic properties may have an influence on vWF biosynthesis and secretion rate (7). Gill et al. (25) performed a study on 1117 healthy individuals wherein the lowest plasma vWF levels [mean von Willebrand Factor antigen (vWF:Ag), 75 IU/dL] were observed in the O group and the plasma vWF levels were found to be higher (mean vWF:Ag, 123 IU/dL) in the non-O group. In another study, FVIII level was found to be higher in the blood groups A and B than in the O group (26).

Adhesion molecules are crucial to platelet leukocyte interaction and leukocyte migration into the vessel wall and thus important players in the atherosclerosis process (27). Previous studies increased CHD risk has been associated with high soluble intercellular adhesion molecule-1 (sICAM-1), soluble P-selectin (sP-selectin), and soluble E-selectin (sE-selectin) levels (28, 29). Genome-wide association studies of sICAM-1,
sP-selectin and sE-selectin levels have shown that they are associated with single nucleotide polymorphisms at the ABO locus. Unexpectedly, the A allele’s association with decreased levels of sICAM-1 and sP-selectin but increased risk of CVD (30, 31). In addition, meta-analysis showed that conferring elevated CHD risk were associated with decreased levels of soluble adhesion molecules. This situation seems paradoxical; it could be explained as in the presence of endothelial dysfunction soluble adhesion molecules compete with leucocytes to adhere endothelium. Therefore, their amount decrease, due to binding to the endothelium, although expected to increase in circulation (32). Decreased cleavage of adhesion molecules from endothelial cells associated with A allele would mean more adhesion molecules on the endothelial cells, increased adhesion and inflammation (31) and most of which suggested A allele association with increased risk of CVD (30).

Several previous studies have shown that patients of non-O blood group have significantly higher rates for myocardial infarction (33), peripheral vascular disease, and venous thromboembolism and mortality (17) as compared with the patients of blood group O (7). In the Northwick Park Heart Study, blood group AB has been noted to have a higher risk compared to the other blood groups. In addition, Framingham study revealed a higher incidence of ischemic heart disease in phenotype A (34). Similarly, Lee et al. (35) suggest that blood group A is an independent risk factor for coronary artery disease and myocardial infarction in Taiwanese men younger than 45 years and women younger than 55 years. He et al. (36) found that blood group B was an independent risk factor for myocardial infarction. A recent meta-analysis including a follow-up period of more than 20 years showed that blood type O individuals had a moderately lower risk of developing coronary artery disease compared with the other groups (36). Apart from these studies, Amirzadegan et al. (37) found no difference between ABO blood groups with regard to coronary artery disease. Biancari et al. (9) studied the relationship between ABO blood groups and severity of coronary artery disease among patients with a history of coronary bypass grafting; while they found no difference with regard to distribution of coronary artery disease in ABO groups, blood group B demonstrated a significantly higher rate for history of myocardial infarction, stroke, lower limb ischemia, need for emergency revascularization, as well as higher coronary angiography score.

ABO blood groups are composed of complex carbohydrate molecules. The A and B carbohydrate antigens have been shown to be present not only in the blood cells but also in other tissues such as platelets and vascular endothelium, however, the role of this presence on atherosclerotic lesion development is not yet clearly understood (38). However, Reilly et al. (39) found that glycotransferase activity in the non-O group was associated to coronary thrombus rather than atherosclerosis. Although previous studies appear to reveal contradictory results, the data in them are supportive of our study. In the present study, non-O group demonstrated coronary lesions with higher complexity and severity among stable coronary artery cases. Non-O group patients have the need for closer follow-up and/or preventive treatment against the risk of further cardiovascular accident. Previous studies have shown non-O group to be under higher risk for myocardial infarction and thrombosis, both of which lead to elevated mortality rates, and we believe that, as shown in our study, these elevated risks may be associated to higher coronary lesion complexity. Furthermore, the presence of raised vWF and FVIII levels in the non-O group along with higher coronary lesion complexity and severity in addition to the varying antigenic structures of the blood groups, warrants closer attention and monitoring for the risks of coronary heart disease and coronary vascular event in this group.

**Study limitations**

There are several limitations to our study. We did not measure vWF or Factor VIII levels. Another limitation is that we did not test correlations between ABO genotypes and clinical events. Association of ABO blood group distribution with cardiovascular disease including MI needs to be clarified with multicenter, prospective, and large-scale studies.

**Conclusion**

The relation between ABO and atherosclerotic cardiovascular disease might be more complex than it seems and various distinct pathways related to cardiovascular risk factors may be involved. We showed that there were significant associations between ABO blood groups and complexity of angiographic CAD.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.


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