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ABO Blood Group and Thromboembolic Diseases

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Abstract

Thromboembolic diseases are usually inherited in the family. The tendency to repeat in an individual is a phenomenon that allows it to be studied. The inheritance and recurrence of thromboembolic diseases, of course, have individual risk factors for this occurrence. In the past, the ABO blood group was only needed for transfusion and organ transplant therapy. Over time, scientists think that blood type is a risk factor for certain diseases, including thromboembolism. Many studies divide between type O and non-O blood groups, both of which are distinguished by the presence of antigens on the cell surface and antibodies in the plasma of individuals. Type O does not have A, B antigens but has antibodies against A, B antigens, and vice versa for the non-O type. Many studies have shown that the non-O blood group has a risk factor for thromboembolic diseases, commonly due to higher levels of von Willebrand factor (VWF) and factor VIII (FVIII). These thromboembolic events can occur in arteries or venous. Thromboembolic manifestations are often associated with cardiovascular diseases for arterial thrombosis; and deep vein thrombosis (DVT) and pulmonary embolism (PE) for venous thromboembolism (VTE).

Keywords: ABO, blood group, arteries, venous, thromboembolic diseases

1. Introduction

The known blood types in the population are A, B, AB, and O. These blood types are inherited from both parents. Antigens in the ABO blood group are complex carbohydrates, found in erythrocytes, lymphocytes, platelets, epithelial and endothelial cells, and organs such as the kidneys. Soluble forms of antigen are also synthesized and secreted by tissue cells [1]. The distribution of ABO blood groups in the population depends on race. For example, in India and Mexico, blood type O is the most common. If data from countries in the world are compared, in India and neighboring countries such as Bangladesh and Pakistan, groups O and B dominate, while populations in Europe and Africa are dominated by groups O and A. This comparison explains that the heterogeneity of blood groups in different places and populations is caused by genetic and environmental factors [2].

Initially, the importance of ABO blood type is needed to obtain a match between donor and recipient in the case of transfusion or organ transplantation. Furthermore, many studies reported the association of blood type with a certain disease, especially in the distinction between blood group O and non-O. The non-O blood type has been reported to be associated with several diseases, including cardiovascular disorders, and the incidence of venous thromboembolism (VTE). The first observation on the association between ABO blood type and VTE was made in

1963 by Dick et al. who found a statistically significant predominance of group A in 461 VTE patients [2–5].

The non-O blood group was at higher risk of thromboembolism due to higher levels of von Willebrand factor (VWF) and factor VIII (FVIII). The rate of proteolytic clearance of VWF by a disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS-13) was relatively lower in plasma of the non-O blood group, resulting in a longer VWF half-life in the non-O plasma group than in the O plasma group. As a result, VWF levels were 25–30% higher in non-O group plasma than in group O plasma. High levels of VWF in non-O plasma always lead to increased FVIII levels due to the physiological role of VWF as carriers of FVIII and protecting it from the proteolytic effects of ADAMTS-13. Higher VWF and FVIII levels in subjects with non-O blood groups were strongly correlated with an increased risk of venous thrombosis, a situation that led to non-O blood type being assessed as a genetic risk factor for venous thromboembolism [6].

Wu et al. result in a meta-analysis study of the association between the ABO blood group and vascular disease, the combined odds ratio of the 21 studies analyzing VTE was 1.79 (95% CI, 1.56–2.05) for the non-O versus O group. In three studies in which blood type genotypes were performed, the combination A1 A1/A1 B/BB gave an odds ratio of 2.44 (95% CI 1.79–3.33), while the odds ratio for A1 O/BO/A2 B was 2.11 (95% CI 1.66–2.68), suggesting that the risk is related to the expression of the O(H) antigen [7].

These results are similar to the study of Spiezia et al. in a retrospective case–control study conducted on Italian patients with DVT and controls, which found that non-O blood group increased the risk of DVT by 2.2-fold than individuals with group O. An up to the 7-fold increased risk of VTE was observed when the condition inherited thrombophilic (factor V Leiden, prothrombin G20210A mutations, antithrombin, protein C and protein S deficiency) were associated with non-O blood group carriers compared with non-thrombophilic group-O carriers [4].

The data presented by Spiezia et al. cautioned that the high prevalence of non-O blood type in the general population appears to be one of the most important genetic risk factors for venous thrombosis. Like inherited thrombophilic factors (i.e., factor V Leiden and the prothrombin G20210A mutation), non-O blood types are responsible for a moderate increase in the risk of VTE, and, therefore, ABO blood group testing is recommended in individuals with thrombophilia to assess risk thrombotic [7].

2. ABO blood group

The ABO blood group system was discovered by Landsteiner in 1900. A few years later, von Decastello and Sturly discovered the AB type. Landsteiner's rule stipulates that normal individuals have ABO antibodies against an antigen not found on red blood cells. Individuals with blood type A have A antigens, do not have B antigens, therefore these individuals have B antibodies. On the other hand, individuals with blood group B have B antigens, do not have A antigens, therefore they have A antibodies. The four phenotypes were derived from the two main antigens (A and B) of the system. The phenotypes are group A, group B, group AB, and group O. Individuals with blood type AB means they have A, B antigens and do not have antibodies against A, B antigens. On the other hand, individuals with blood type O have antibodies against antigens A, B and do not have antigens A, B [1]. This classification is important for the sake of blood transfusions that must meet certain requirements.

The A and B alleles are located on chromosome 9 at the ABO locus, encoding the A- and B glycosyltransferase enzymes. ABO antigens can be found on blood

cells, lymphocytes, platelets, most epithelial and endothelial cells, and organs such as the kidneys. Soluble forms of antigen can be synthesized and secreted by tissue cells. Soluble antigens can be detected in all body fluids except cerebrospinal fluid. The ABO antigen attached to red blood cells is in the form of glycolipid molecules or glycoproteins, while the main soluble form is the glycoprotein form. Discussion of the ABO antigen requires an understanding of the H antigen. The H gene is located on a different chromosome from the ABO genetic locus and plays a role in controlling the production of H antigen. In addition to the ABO and H genes, the expression of soluble ABO antigens is influenced by the inheritance of the Se gene. The Se gene genetically influences the formation of ABO antigens in saliva, tears, and other body fluids. Consequently, the occurrence and location of ABO antigens are influenced by three genetically independent loci: ABO, H, and Se [1].

The antigen-building block structure for A, B, and H antigens is an oligosaccharide chain attached to a carrier molecule either a protein or lipid. The oligosaccharide chain comprises four sugar molecules linked in simple linear forms or complex branched structures. The two-terminal sugars, d-galactose and N-acetylglucosamine, are coupled in two different configurations. When carbon number 1 of d-galactose is coupled with carbon number 3 of N-acetylglucosamine, the bond is symbolized as $1 \rightarrow 3$. When the number 1 carbon of d-galactose is coupled with the number 4 carbon of N-acetylglucosamine, the bond is described as $\beta 1 \rightarrow 4$. The structure of $\beta 1 \rightarrow 4$ is associated primarily with glycolipids and glycoproteins on the red cell membrane, the structure of $\beta 1 \rightarrow 3$ is located in body fluids and secretions [1].

This transferase catalyzes the addition of certain sugar residues so that the core structure of the H glycan precursor is converted to antigen A (GalNAc $1 \rightarrow 3$ [Fuc $1 \rightarrow 2$] Gal β $1 \rightarrow 4$ GlcNAc $1 \rightarrow$), or antigen B (Gal $1 \rightarrow 3$ [Fuc $1 \rightarrow 2$] Gal β $1 \rightarrow 4$ GlcNAc $1 \rightarrow$). As a result, the A and B structures are differentiated based on a single terminal sugar (N-acetylgalactosamine versus D-galactose respectively). Individual O groups lack A- or B-transferase activity result from the inactivation of the A1 glycosyltransferase gene, and the nonreducing ends of the corresponding glycans, and therefore continue to express the basic structure of the glycan H (Fuc $1 \rightarrow 2$] Gal β $1 \rightarrow 4$ GlcNAc $1 \rightarrow$) at the ends of their oligosaccharide chains [8, 9]. Individuals who synthesize determinant A exclusively have blood type A and have genotypes AA or AO, individuals with blood group B are BB or BO, and individuals expressing one allele A and one B have genotype AB. Individuals with blood type O expressing inactive glycosyltransferase A/B have genotype OO. They express only the H antigen. In terms of nomenclature, blood group O includes the H antigen and sometimes the term ABO(H) is used [10].

3. Thromboembolic diseases

Venous and arterial thrombotic disorders have different pathophysiological entities, as a result of anatomical differences and different clinical presentations. In particular, arterial thrombosis results from the phenomenon of platelet activation, whereas venous thrombosis is largely a matter of activation of the clotting system [1].

There are fundamental pathophysiological differences between arterial and venous thrombus. Arterial thrombi which are happened in small arteries and arterioles are occlusive. Thrombus that occurs in the ventricles of the heart and the great arteries and the aorta, the common carotid artery is nonocclusive. Arterial thrombus is formed in response to increased local shear and exposure to thrombogenic material in damaged vessels, occurs in high-pressure and high-flow systems. Arterial thrombus, referred to as white thrombus, due to consists mainly of

platelets and a small amount of fibrin or red blood cells. Leukocytes are also actively recruited to platelet-rich arterial thrombi [11].

The differences from a clinical point of view are as follows: (1) hereditary hypercoagulation (occurs in the “thrombophilia” state), characterized by chronic hyperactivation of the coagulation system, this condition mainly associated with venous rather than arterial thrombosis; and (2) anticoagulant agents (e.g., heparin, warfarin) are usually used to prevent venous thrombosis, whereas antiplatelet agents (e.g., aspirin) are used to prevent arterial thrombosis. In both types of thrombus consists of platelets, fibrin, erythrocytes, and leukocytes with different compositions. Moreover, all thrombi are undergoing propagation, organization, embolization, lysis, and thrombolysis, and this dynamic remodeling results in a changing composition [11].

3.1 Arterial thromboembolism

Rudolph Virchow describes three conditions that induce thrombosis, called the Virchow triad. This triad includes endothelial injury, blood flow stasis or turbulence, and blood hypercoagulability. Abnormalities of one or more of these conditions more often manifest the occurrence of DVT. DVT after trauma is more common in conditions of stasis and endothelial injury while spontaneous DVT is more common in cases of hypercoagulability. Risk factors can be classified as acquired or genetic. Genetic risk factors can be divided into strong, moderate, and weak factors. Strong risk factors include deficiency of antithrombin, protein C and protein S. Moderate risk factors include factor V Leiden, prothrombin 20210A, non-O blood type, and fibrinogen 10034C > T. Weak genetic risk factors include fibrinogen variants, factor XIII, and factor XI [11, 12].

Normal wall shear rates range from 300 to 800/s in the large arteries and increase to about 500 to 1600/s in the arterial of microcirculation. However, in pathological stenotic vessels, the wall shear rate can be up to 10,000/s or even higher. The increased shear stress in the microenvironment of the atherosclerotic plaque area of the stenotic vessel is exacerbated by turbulent blood flow. This high hemodynamic force can activate platelets as they pass through the region. This abnormal flow can cause local endothelial dysfunction. High shear stress, especially with a marked shear gradient around the site of the stenosis, is sufficient to induce VWF from endothelial cells and binding of VWF to platelets via glycoprotein Ib-V-IX. This interaction does not occur in normal circulation, result mediating platelet adhesion to the intima surface and triggering platelet thrombus formation [11].

Heterogeneity is seen in the composition of atherothrombotic plaques, even within the same individual. In addition to plaque composition, differences in the basic structural features of the arteries contribute to differences in thrombogenic substrates. For example, the carotid and iliac arteries contain relatively more elastic fibers and proportionately fewer smooth muscle cells than the coronary arteries. Therefore, coronary artery thrombosis usually results in slightly stenotic, lipid-rich plaque, whereas carotid artery usually results in severe stenotic and high-risk plaque [11].

3.2 Venous thromboembolism (VTE)

Venous thrombi are formed mainly from fibrin and red blood cells. Thrombogenic stimulation is caused by (1) stasis of veins, (2) activation of clotting factors, and (3) vascular damage. Anti-thrombogenic properties through mechanisms (1) inactivation of activated coagulation factors by natural inhibitors such as antithrombin and activated protein C, (2) elimination of activated coagulation factors and soluble fibrin

polymer complexes by mononuclear phagocytic cells and liver, and (3) lysis of fibrin by enzymes fibrinolytic from plasma and endothelial cells [11].

In the adult group, the predisposition factors to VTE are increasing age, cancer, prolonged immobilization, stroke or paralysis, varicose veins, prolonged air travel, acute inflammatory bowel disease, rheumatic disease, and nephrotic syndrome, oral contraceptive pills, especially those containing third-generation progestins. In the pediatric group, the risk factors for thromboembolism are central venous lines, cancer, and chemotherapy [13].

Venous thrombi are almost always occlusive and can form casts of the vessels in which they arise. Unlike arterial thrombus, severe vascular damage is generally not found at the site of venous thrombosis. Therefore, in low-flow and low-pressure venous systems, decreased blood flow (stasis) and systemic activation of the coagulation cascade play a major pathophysiological role. Venous thrombi consist mostly of red blood cells trapped in fibrin and contain relatively few platelets; hence, they have been described pathologically as red thrombi [11].

The study of Sun et al. in 1412 patients with VTE (consisting of 600 DVT patients, 441 PE patients, and 371 patients having a diagnosis of DVT and PE) and 199,248 controls the results of VTE patients were significantly higher in the non-O blood group compared to all non-VTE discharge patients with OR 1.362 (95% confidence interval, 1.205-1.540). When the non-O group was classified into A, B, and AB and a pairwise comparison test was performed on VTE and non-VTE patients, the results were not statistically different [14].

4. The relation of ABO blood group and thromboembolic diseases

ABO blood group has been recognized as a risk factor for thromboembolic diseases since the 1960s. Many studies have shown that the non-O group had a higher incidence of ischemic heart disease. ABO blood type is important in relation to VWF and FVII levels because in turn confer a clear risk of increased VTE especially in non-O blood groups which provide a higher increase. This association is less clear for CAD and MI but a similar pattern emerges with most studies finding group O to be at lower risk [15].

The Framingham Heart Study, and others, resulted in blood group A having an increased risk of CAD [16–18] and MI [19]. More specifically, blood type A is associated with early detection of CAD [19, 20] and predominates in patients with MI [21]. Another study reported that groups B [22, 23] or AB [24] had a higher incidence of CAD. In contrast, Mitchell [25] reported that cities with a higher prevalence of group O had higher rates of cardiovascular mortality and a study in India showed that blood type O increased the risk of CAD [26]. Further studies did not identify any association between blood type and CAD [27, 28]. Based on these inconsistent results, He et al. [29] conducted a meta-analysis found the highest risk of CAD was observed in blood group AB, followed by groups B, A, and O. This is similar to ABO-associated vWF/FVII levels which the highest in group AB, followed by groups B, A and O [18].

The theory proposed to explain the relationship between ABO blood group and CAD is as follows. Fibrinogen together with vWF activates platelet aggregation and adhesion which in turn plays a role in the development of atherosclerosis. On the other hand, blood group A has been reported to have higher cholesterol levels and lower lipoprotein density, this may explain the association with an increased risk of CAD. In addition, ABO loci have been reported to be associated with inflammatory-forming CAD, including intercellular adhesion molecule-1, soluble P selectin, soluble E selectin, and tumor necrosis factor- α . Meanwhile, the interaction between

genetic factors (genes known to increase susceptibility to CAD and the ABO locus) and environmental factors still contribute to the risk of CAD and MI [15].

The incidence of VTE is more often due to factor VIII (FVIII) and von Willebrand Factor (VWF) levels are higher in the non-O blood group than in the O blood group. Moeller et al. comparing VWF and FVII levels in individuals with ABO phenotype found the following order $O < A < B < AB$ for vWF levels and $O < A < AB < B$ for FVII levels [30]. Nevertheless, Simangunsong et al. found no significant differences were present in factor VIII activity between A, B, and O blood types [31].

A blood type that is identical to high vWF, is an important genetic factor that explains around 30% of the variation in factor VIII levels. There is a relationship between factor VIII and vWF. However, attempts to find other genetic loci associated with high vWF and factor VIII levels have not been successful to date. Most likely, the high factor VIII levels are due to increased synthesis or decreased clearance of the vWF-factor VIII complex [32]. Furthermore, non-O blood groups are associated with increased arterial and venous thrombotic events possibly mediated by increased levels of von Willebrand factor and factor VIII in non-O blood groups [33].

Meanwhile, several studies have confirmed that the level of vWF is lower in people who have blood type O, therefore FVIII: C is reduced due to the stabilizing function of vWF as an FVIII: C carrier. Factor VIII affinity for vWF may also differ from individual to individual, which is genetically determined [30].

Blood group A is associated with an increased odds of major adverse cardiovascular events (MACE), whereas blood group O was associated with a reduction in the odds of MACE in patients with COVID19. These findings suggest an association between blood group type and cardiovascular complications in COVID-19. The biological mechanism behind the role of ABO blood groups in COVID-19 remains elusive. Natural anti-glycan ABO antibodies have been shown to inhibit SARS-CoV1 interaction of spike protein and angiotensin-converting enzyme 2 (ACE2) [33].

In the cellular experimental model approach, it can be proven that the binding of the SARS-CoV S protein with ACE2 on target cells can be blocked by anti-A antibodies in the blood group, because the S protein is synthesized by A-antigen-expressing cells, after transfection by cDNA glycosyltransferases. in accordance. When produced in cells expressing blood type A or B enzymes, SARS virions are decorated by appropriate glycan antigens, consequently, the presence of anti-A and anti-B antibodies in blood type O individuals can block the attachment and entry of the virus thereby preventing infection. Therefore, individuals with blood type O will have a lower risk of infection than non-O individuals. This phenomenon occurred during the 2003 Hong Kong SARS hospital outbreak, and a similar trend was recently observed for COVID-19 in China, the infectious SARS virions are decorated by glycan antigens corresponding to blood group A or B, and the presence of anti-A antibodies and anti-B in individuals with blood type O can prevent infection by blocking the attachment and entry of the virus [34, 35].

Vasan study used data on 1.1 million healthy blood donors from the binational database SCANDAT2 (Scandinavian Donations and Transfusions), which contains national data on blood donation and transfusion from Sweden and Denmark, to investigate the association between ABO blood type and arterial thrombotic events. or veins. And the results confirm that there is a consistent relationship between non-O blood type and VTE and cardiovascular events, with a greater risk in the venous. The proposed basic mechanisms driving this association include higher concentrations of factor VIII and von Willebrand factor in individuals with non-O blood types. This study provides strong evidence of a consistent relationship between the non-O blood group and VTE, and the incidence of cardiovascular thrombosis, with a greater risk of recurrence in non-O blood groups. Also, non-O blood groups confer an increased risk of thromboembolism, ABO blood groups may

have a role in thrombosis risk assessment and could potentially be added to existing clinical prediction systems [5].

Sickle cell disease or what is known as sickle cell trait (SCT) in individuals will provide a risk of DVT even though it is weak. This potential risk will increase if the patient has a non-O blood group. This combined effect will increase the activation of clotting factors and increase the risk of DVT. Thus, caution should be exercised in co-inheritance of non-O blood group and SCT, in which case it should be paid attention to assess the risk profile of DVT in patients in Africa and other areas where SCT is common [6].

Non-group O patients have susceptibility and greater risk of VTE than patients of group O and have greater levels of von Willebrand factor (vWF) and factor VIII. The risk of VTE is probably related to the level of vWF and factor VIII. A, B, and H blood group antigens are expressed on N-glycans of VWF and influence the half-life of the protein (10 hours for group O and 25 hours for non-O subjects), explaining the greater levels in non-O patients [8].

In the report of Rejtő et al. who investigated the effect of ABO, VWF level, age on the variability of F VIII levels in 8 patients non-severe Hemophilia A results that ABO and VWF levels did not influence the variability of FVIII levels, whereas age had only a small influence [36].

The coagulation process is under the control of several inhibitors which limit clot formation. A balance between procoagulants and anticoagulants is necessary for maintaining hemostasis. A thrombus is formed as a result of a disturbance in this balance. Thrombus is formed when the procoagulant activity of one of the coagulation factors is increased or the activity of one of the natural inhibitors is decreased, a condition called thrombophilia can occur in inherited deficiency of natural inhibitors, as well as with inherited gain-of-function mutations of some coagulation factors. The deficiency of natural inhibitors such as antithrombin, protein C and inherited protein S is a strong risk factor for venous thrombosis; they have little or no effect on arterial thrombosis. Antithrombin directly inhibits several activated coagulation factors, notably thrombin, and activated factor X, and the inhibitory effect is amplified by its binding to glycosaminoglycans on the endothelial surface carrying heparin-like activity. The effect of increasing the tendency for clot formation is especially in the venous system where the coagulation pathway (different from that of platelets) plays a major role. The anticoagulant protein C on the surface of the endothelium is very important in the down-regulation of thrombin formation. Activated protein C inactivates factor Va and factor VIIIa proteolytically, the two most important activated cofactors of the coagulation cascade, causing a slowdown in the rates of thrombin and fibrin formation. The inhibitory effect of activated protein C is accelerated by its main cofactor, protein S. Inherited deficiency of one of these inhibitors leads to increased thrombin formation, increasing susceptibility to VTE [37].

Ahmed et al. hypothesized that if Sickle Cell Trait was a risk factor for DVT, individuals with non-O blood group and SCT (Hb AS) would have a higher risk of DVT than those with non-O blood group and normal hemoglobin (Hb AA) phenotype. The results of this study indicate that SCT itself is a weak risk factor for DVT, but would have the potential to increase the risk of DVT in patients with non-O blood groups. Therefore, co-inheritance of SCT and non-O blood groups is an important risk factor for DVT [6].

The study of Vasan et al. results almost in all age groups, the incidence of VTEs and cardiovascular events is higher in non-O than O blood groups. The incidence rate ratio (IRR) was highest for the venous events, with all venous thrombotic events combined for individuals with non-O blood group compared with blood group O having an IRR of 1.80 (95% CI, 1.71–1.88). The risk patterns were similar

for pulmonary embolism and deep vein thrombosis. Among arterial events, IRRs were generally lower with IRRs of 1.10 (95% CI, 1.05–1.14) for myocardial infarction and 1.07 (95% CI, 1.02–1.12) for stroke in individuals in non-O blood groups compared with those in blood group O [5].

5. Summary

ABO blood type is associated with the risk of thromboembolic diseases. Non-O blood type has a greater risk than O blood type. Thromboembolic events occur in both arteries and venous, which are venous more often, one of the causes is FVIII and VWF clearance in non-O blood groups are longer, results found high levels of both in the non-O blood group. While the manifestation of arterial thromboembolism commonly happened in cardiovascular diseases including coronary arterial disease and myocardial infarct.

Conflict of interest

No conflict of interest in this article.

Abbreviations

ADAMTS-13	a disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13
CAD	coronary artery disease
CI	confidence interval
COVID-19	Coronavirus disease-19
DVT	deep vein thrombosis
FVIII	factor VIII
Hb	hemoglobin
IRR	incidence rate ratio
MACE	major adverse cardiovascular events
MI	myocardial infarction
PAR	population-attributable risk percent
PE	pulmonary embolism
PY	patient-year
SCT	sickle cell trait
VTE	venous thromboembolism C1
VWF	von Willebrand Factor

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