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Blood groups: in Health and Diseases

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Abstract

ABO blood type antigens are polymorphic, inherited structures presented on the surface of red blood cells. Although ABO blood group antigens are the most important antigens in transfusion medicine but their main role is not clearly clarified yet. The correlation between ABO blood group and susceptibility to certain infectious and non-infectious diseases is a controversial issue because lack of blood type antigens has not been related to significant diseases or health risks. There are many studies that aim to prove that blood antigens are biologically active and carbohydrate structures involving to the "cell physiology and human pathology". This review summarizes the available data concerning the correlation between blood group antigens and different aspects of health. We therefore investigated whether certain blood type antigens could affect susceptibility to diseases or make a phenotype resistant.

Keywords: Blood groups; ABO; Cancers; Cardiovascular disease; Infectious disease; Health

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Introduction

The ABH histo-blood group antigens are a set of polymorphic and inherited glycoconjugate structures that are expressed on the cell surface of human erythrocyte (1). The carbohydrate antigens have several functions, including transporters and channels, receptors for ligands, viruses, bacteria and parasites, adhesion molecules, enzymes, and structural proteins (2).

The presence and lack of blood antigens in some blood groups induce blood membrane changes, morphologically and functionally. The structure-dependent functions of blood types can link the blood groups to health and diseases (3). Here we reviewed the ABO blood types and their possible role in different aspects of human's health.

History

ABO blood types were discovered by Karl Landsteiner in 1901 when he worked on human serum derived from six scientists working in his lab, including himself with serological methods, cross-testing of sera and analysis of the agglutination (4). The first study on blood groups was performed by Ludwik Hirszfeld and his wife, Hanka in a large number of soldiers during World War I at the Macedonian front. They found that soldier's blood types were differently distributed; soldiers from North Central Europe were more common in A type, but B type was prevalent in Eastern Europe (5). The first scientific article that discussed the relationship between blood types and diseases was published in 1917 and revealed the association of ABO blood types and tuberculosis. Later, many studies supported the hypothesis that ABO blood types could be related to the infectious diseases (6).

ABO blood types

The ABO blood type is the main type of blood group.

The human blood type grouping is involved in three carbohydrate antigens (ABH). AB blood type depending on glycosyltransferase activity that converts H antigen into A and B antigens. The transferase activities of A and B alleles are different because of a single-base replacement in A and B genes and four amino-acid residues. The O gene consists of a single-base deletion that produces an inactive protein which fails to convert H antigen (7). Therefore, individuals expressing N-acetyl D-galactosamine transferase and D- galactose are group A and B, respectively (8). Rh (Rhesus) blood group is the most important group after ABO blood type in transfusion medicine. It is also a major player of hemolytic disease of the newborns (HDN) (9) often called Rh disease. The Rh blood group antigens (D and Cc/Ee) are encoded by two highly related genes, RHD and RHCE located on 1p36-p34 (10) that represent RhD-positive phenotype to individuals.

Hypothesis

Blood type antigen system may be apparently involved in the pathophysiology of a wide range of human diseases by interaction between glycan structures on red blood cell surfaces and different agents.

Evidences for association of ABO blood types with different diseases

Cardiovascular disease

Von Willebrand factor (vWF) involves in homeostasis and thrombosis by taking part in platelets aggregation and adhesion at vascular damage sites (11). It is also a carrier for factor VIII (FVIII) and protects this factor from proteolysis degradation. The plasma level of vWF was clinically used for estimation of cardiovascular risk and for determination of arterial thrombosis (12). The ABO blood groups and their locus are important genetic factors that affect the plasma level of vWF (13). Increased risk of cardiovascular disorders in non-O individuals can be attributed to the plasma level of vWF. Interaction between ABO blood group antigens and vWF participates in vWF-related diseases such as cardiovascular disorders (14). It was known that non-O blood groups (A, B, and AB) have 25% higher level of vWF than O blood type. This is due to high capacity of O blood type in cleaving by protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). ABH blood group antigens are expressed and identified on N-glycan chains of circulating vWF which plays a major role in vWF clearance (15, 16).

The presence of the N-glycan oligosaccharide chain on the vWF is important for interaction between vWF and ADAMTS13. In other words, the N-glycan chain may induce a conformational change and modulates this interaction by flanking to the cleavage site. Consequently, N-linked glycan chains limit interaction capability and prevent vWF from ADAMTS13 proteolysis (17).

P-selectin and intercellular adhesion molecule-1 (ICAM-1) are adhesion molecules that participate in inflammatory process and cardiovascular diseases. There are different single nucleotide polymorphisms (SNPs) in P-selectin and ICAM-1 genes that are associated with ABO gene variants (18). ABO affects the soluble level of P-selectin and ICAM-1 during the interaction between glycosylated antigens and P-selectin and ICAM-1 (18). Soluble ICAM-1 (sICAM-1) presents in plasma is an inflammatory marker and correlated with different disorders like heart disease and myocardial infarction. It was found in a genome-wide association study that an SNP (rs507666, $P = 5.1\times10^{-29}$) at the ABO locus (9q34.2) is significantly associated with concentration of sICAM-1. This may reflect the regulatory role of ABO group antigens in heart disease (19).

Infectious diseases

The probable association between infectious agents and ABO blood antigens is dependent on its carbohydrate moieties on RBC surface. This structure may act as a receptor for some viruses, bacteria, and parasites and mediate their entrance (20, 21). Some parasites cannot bind to RBCs that lack other blood group antigens, thus, these are important structures for adherence (22). This was approved in Norwalk virus (NV) infection which is more common in blood type O but individuals with blood type B are resistance to NV infection. This ability may occur due to the expression of ABH carbohydrate antigens. The existence of terminal α-galactose can modify the NV ligand and make it hidden for NV binding and block the binding site. Lack of ABH antigens expression in O lead to susceptibility of individuals to infection after exposure to NV (23). In the same way, histo-blood group antigens (HBGAs) B were protected against Noroviruses (NoVs) gastroenteritis by interfering with virus binding to H antigens (24).

The association between hepatitis infection and blood group antigens is not exactly determined. There are different studies with variety of results so more knowledge improvements are needed. It was reported that A blood type was associated with HBV (hepatitis B virus) infection and pancreatic cancer in a synergistic manner (25).

Aljooni *et al* observed a significant association between ABO blood type and hepatitis infection. They indicated that HBV and HCV (hepatitis C virus) infections were high in O blood type but low in AB

(26). Similar results were reported by Behal *et al* who found variation in susceptibility to HCV infection among ABO blood groups. High seroprevalence of HCV were seen in people with O, but the lowest level was detected in AB blood type (27). They did not find any significant association between infection with HBV and ABO blood types (28). Some infections, including HBV, HCV, HIV, and syphilis were analyzed for their relationship with blood groups in a study conducted among Iranian individuals. The results showed low frequency of blood group B in HBV infected patients and significant association between A blood group and HIV infection. They also found no correlation between Hepatitis C and syphilis infections and ABO blood groups system (29). Woo *et al* revealed that non-O blood types were at increased risk for hepatitis C virus and pancreatic cancer but similar association was not observed for HBV infection (30). These results were also found in a study conducted by Shavakhi *et al*. They suggested non-O blood groups as genetic risk factors for HCV infection and liver fibrosis progression (31).

The same results were also found in another study performed by Poujol-Robert *et al* (32).The high percentage of hepatitis B- surface antigens diagnosed in the blood group A proves HBV is more prevalent among A than other types (33). In one study, a high level of HBsAg was observed in blood group A negative and HCV and HIV infections were more prevalent among O negative donors (34). The same analysis was performed on 6000 donors and came to a conclusion that blood group A negative was more susceptible to HIV and HBV but blood group B negative was influenced by HCV (35) Recently, different results were found in a study that reported high prevalence of HCV in individuals with blood group B (36).

In one analysis, subjects with O "positive" blood group were found to be common in blood donors who are affected by HIV, HBV, and HCV (37). The same results were previously reported by Sayal *et al* (38). Recently Onsten *et al* proved the high frequency of blood type B among HIV patients through its mechanism: B blood type has limited antigen recognition ability of galactosylα1-3 galactose (Galα1-3Gal) and antigen binding capacity of anti-A antibodies. Other mechanisms are involved in glycosylation patterns of HIV envelop. Blood type glycosyltransferase add ABO glycan structure to glycoprotein 120 (gp120) and invade from recognition of immune system and neutralizing antibodies by masking within host glycans (39). However, Dirisu *et al* determined high prevalence of blood group O "positive" among HIV, HBV and HCV (40). In another study, high rate of HIV-2 infection was reported for blood group AB (41).

The results from the investigation of the correlation between ABO blood groups and influenza virus indicated that blood group AB subjects are more susceptible to influenza A and B with high rates of attacks (42, 43).

The presence of A and B antigens and acting as a receptor is not only limited to virus but also found in parasites such as *Plasmodium falciparum*. *P. falciparum* can lead to severe form of disease through parasite virulence factor like rosetting that blocks microvascular blood flow. A and B trisaccharide structure antigens act as a receptor for rosettes formation on erythrocytes. Lack of terminal glycosyltransferases activity causes blood type O to be a structurally disaccharide and possesses lower rosetting ability. It forms small and reduced rosettes effect that is easily disturbed. Therefore, individuals with blood group O may be protected against severe malaria (44).

Individuals with group O were observed to constitute a large number of cholera patients with significant differences to other patients (45, 46). In one study, cholera infected patients were two times more likely to be the blood group O (47). The possible mechanism is that the A and B blood group carbohydrates interfere with binding of cholera toxin to its intestinal receptor (ganglioside GM_1) (48).

Toxoplasma gondii (*T gondii*) is a protozoan parasite that infects human and causes toxoplasmosis. *Toxoplasma gondii* (*T gondii*) the causative agent for human toxoplasmosis is a protozoan parasite. Toxoplasma latent infection induces behavioral changes in rodent and human hosts. The latent toxoplasmosis-personality profiles consist of reduced psychomotor performance and increased reaction time of traffic accidents, possibly related to the level of dopamine and testosterone (49). It was found that RhD phenotype can modulate the latent infection effects probably via membrane pump of red blood cells (50). It was also shown that Rh-positive individuals are protected against the *T. gondii*-induced personality trait changes (51).

Diabetes

There are conflicting results reported by different researchers on the hypothesis that there is an association between ABO blood types and diabetes. In one research, a strong relationship of diabetes mellitus with blood groups, especially A, AB and Rh-positive was found (52, 53). The increased frequency of diabetes mellitus among B blood type may prove this association. It was also indicated that blood type AB has low distribution (54). Similarly, high frequency of blood type B was detected among patients with diabetes mellitus but distribution of blood type O was low (55). Similar results were

achieved from a large cohort study evaluating the involvement of ABO blood types and Rhesus factor (and the combination of both) in development of type 2 diabetes mellitus. It was also found that blood type O had a lower risk of type 2 diabetes mellitus (56). In another investigation, blood type B was more prevalent in diabetic patients while blood group O was less affected (57). Significant association between blood type B and diabetes was reported in a research conducted in Iran (58), which is consistent with other investigations (59, 60). In contrast, Waseem et al suggested a negative relationship between blood groups A and B and diabetes since they were less common in diabetic patients. They also found high frequency of blood group AB in diabetic group. They attributed these incompatible results to different ethnic and geographical factors and small sample size (61). Considering all studies, some researches believed that ABO blood types were not really related to diabetes mellitus (62).

Cancer

The expression of blood group antigens alters during the process of cell differentiation and malignancy. Lack of A and B antigens resulted in promotion of cell motility, proliferation, invasion, and metastatic tumor formation (63, 64). Cancer is abnormal proliferation of different kinds of cells in the body and is categorized into three groups (carcinomas, sarcomas, and leukemia or lymphomas) based on the primary types of cell where cancer cells originate. The most prevalent form of human cancers is carcinomas that are the malignancies of epithelial cells (65). Most of the epithelial and endothelial cells can express ABO blood antigens which are normally present on the red blood cells (66). ABO blood antigens are carbohydrate structures relating to the cell-surface glycolipids and/or glycoproteins. Tumor development and progression are correlated with glycosylation modification. The expressions of blood group antigens are different in human normal tissue and carcinomas; while the type of differentiation of the epithelium determines ABO antigens, they are decreased in carcinoma such as oral carcinoma. Possible mechanisms by which blood antigens relate to cancers includes hypermethylation of ABO gene promoter (67, 68), loss of heterozygosity (LOH) at ABO locus at chromosome 9q34 (69), variant ABO alleles and SNPs (i.e. SNPs correlated with TNF-α) (70-72), and presence of H blood-group antigens on CD44 adhesion molecule (73). It was statistically proved that ABO gene variability can affect glycosyltransferase expression and activity and result cancer development. These mechanisms decrease the activity of glycosyltransferase and increase tumor progression, metastasis, and migration. For example, methylation in A promoter lead to changes in A transcription and expression level; on the other hand, A (also B and H) expression is correlated with tumor proliferation and metastasis (74), therefore is defined as a possible mechanism in ABO antigens-related cancers by controling the A expression and A transferase activity (75). Thus, human ABO (H) blood antigens possess carbohydrates, which contribute in different cell events such as cell proliferation and tumorigenesis; maybe they can be correctly named as "tumor-associated markers" (76). Class 1 carcinogen has been attributed to *Helicobacter pylori* (Hp) because of its role in gastric carcinogenesis. Severe gastritis, glandular atrophy, and intestinal metaplasia are the results of chronic *H. pylori* infection. VacA, CagA, and blood group antigens are gastric adenocarcinoma-associating factors (77). The perquisite step for Hp infection is its colonization on mucosal surface and invasion to the epithelium which needs to interact with glycan structures. Attachment of Hp to the stomach epithelial lining is mediated by fucosylated blood-group antigens (78). The ABO glycoconjugate antigens facilitate Hp intracellular adhesion by acting as a receptor for binding to the outer membrane protein, BabA, *H. pylori*. This attachment leads to release of virulence factor such as CagA into the cytoplasm of host cells. This initiates IL-8 secretion and its inflammatory response, increasing cell proliferation and migration (79). The association between A blood type and gastric cancer was confirmed in different studies (80, 81).

Table 1. different types of cancers associated with ABO blood groups

Blood type	Susceptible cancer
A	Breast (86), Pancreatic (87-90), Non-small-cell lung cancer (NSCLC) (91, 92), Skin (93, 94), Gastric (95), Nasopharyngeal (96), Bladder (97), Hepatocellular (98), Lung (99), Ductal breast/ Breast (100, 101), Ovarian (102), Gall bladder (103), Cervix (104), Oral (105, 106), Esophageal (106), Salivary gland (106), Basal cell carcinoma (107, 108)
B	Cardiac (109), Pancreatic (110), Ovarian (111), Breast (112), Liver, Genitourinary (113), Laryngeal (106), Oral and non-squamous cell oral (114), Central nervous system tumors (115), Gastrointestinal tract and Gall bladder (115) ,
AB	Nasopharyngeal carcinoma (116), Lung and Gastrointestinal (117)
O	Malignant melanoma (118)

In this section, we will discuss different types of cancer that are prevalent among special blood type (Tab 1). Iodice *et al* studied the association between ABO blood types and pancreatic cancer. They found low frequency of patients with O blood type in exocrine pancreatic cancer compared to other types of cancers (82). Different types of skin cancer including, melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) were examined in respecting to their relationships with blood types. Non-O blood types were significantly correlated with non-melanoma skin cancers. The results of a large cohort study declared that non-O blood types (A, AB, and B) are in decreased risk for skin cancers, including squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) (14% and 4%, respectively) (83). The association between ABO blood types and colon cancer showed an increased risk of colon carcinoma in AB blood type (84). Non-O blood types and Rh- negative are in high risk of lung cancer (85).

Personality traits

There are many studies that proved the association between blood groups and personality traits. Obsessional personality traits were analyzed among 600 individuals, and the results showed high incidence of A type and low incidence of O in obsessive compulsive patients (119). A similar analysis was recently performed in Iran that failed to find any significant relationship between blood types and personality traits (120). In another study, significant incidence of A phenotype was found in patients suffering from hysteria (121). The relationship between blood group and mental health was demonstrated in a study which revealed ABO blood types were associated with schizophrenia and different types of depressions. In addition blood type O is believed to be tightly linked with depression and evolutional depression (122). Therefore, ABO blood group may affect the human's traits and habits. Hobgood investigated the possible link between blood groups and personality traits (123). The author hypothesized that personality traits were correlated with catecholamine genes. On the other hand, catecholamine genes such as COMT catechol-O-methyltransferase (COMT), monoamine oxidase A (MAOA), and dopamine beta hydroxylase (DBH), were associated with ABO blood groups (124). Because DBH locus was found to be in linkage disequilibrium with ABO genes on chromosome 9q34 (124), so other catecholamine genes may act similarly. Hobgood classified ABO blood types and attributed the traits to them, which were consistent with the pattern of catecholamine genes activity. He found that A blood type was correlated with non-submissiveness, non-perfectionism, and non-aggressiveness. B phenotype was correlated with submissiveness, perfectionism, and non-aggressiveness on the basis of the level of catecholamine. With the same reasons, blood type O was correlated with non-submissiveness, non-perfectionism, and aggressiveness (123).

Conclusion

There are many studies that focused on the association between ABO blood types and diseases. Although many studies proved this relationship by describing probable mechanisms, others did not confirm it. Making exact decision fall into trouble due to contradictory results. Nevertheless, we collected here evidences to make clear this hypothesis. ABO may influence the risk of different diseases by different known and unknown mechanisms. It is now clear that ABO blood types are not the exact cause of diseases but they affect susceptibility and resistance to disease and health factors. Collectively, non-O blood types are in more susceptibility to diseases than O. It can be beneficial to increase knowledge in this aspect because individuals with high risk blood types could be screened and trained for modifying their lifestyles, health behavior and environment, and other attempts that may increase public health.

Authors' contributions

AO contributed to researching data and writing the draft, RA making study design, discussing the content, and editing the manuscript. AA, JG, and HM contributed to discussing of the content, HZ searching data. VR editing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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