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Review Article

Blood Group Type, Intercellular Adhesion Molecule-1 (ICAM-1) and Angiotensin-2 Impact on COVID.19 Outcomes

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Abstract

COVID-19 pandemic influences varied people in dissimilar ways. Infected people have had a broad range of symptoms ranged from mild symptoms to severe illness. This review discussed the direct impact of Angiotensin II in the initiation of the pathogenesis of COVID-19 at the primary phase of infection and its indirect influence severity of it, through stimulus of soluble intracellular adhesion molecule type-1, which lead to increased its concentration and that lead to excessive release of cytokines in a condition known as cytokines storm.

Reduction in Angiotensin II at the secondary phase of infection due to cells being invaded with COVID-19 virus leads to reduction of soluble intracellular adhesion molecules which regulate the immune system, then virus pass to different organs in the body.

Individuals with low-level of intracellular adhesion molecules such as aged, diabetic, patients of cardiovascular disease obese, A blood group and rhesus negative developed severe symptoms when infected with COVID.19, due to weak stimulus from Angiotensin II at the first phase and inactivation of soluble intracellular adhesion molecule type-1 at the second phase of infection, which may lead to loss of patient life.

We conclude that the crucial role in pathogenesis of COVID-19 related to Angiotensin -2 concentration, nor soluble intracellular adhesion molecules type -1 neither ABO blood group nor rhesus system.

Keywords: *ABO Blood Group Type; Rhesus System; Intercellular Adhesion Molecule-1 (ICAM-1); Angiotensin-2*

Background

ABO blood group system was formerly discovered in 1901 by Karl Landsteiner. It is the utmost broadly used blood grouping system and encoded by a gene located on the long arm of chromosome nine. This gene control formation of A and B antigens which are carbohydrate molecules created by the consecutive action of the ABO glycosyltransferase [1]. It is essential to understand that blood group antigens are rather simple chemical moieties on the red blood cell surface whose configuration is gradually being elucidated. Some of these antigens (e.g. A, B, H, I, i, P, Lewis) are broadly disseminated throughout the body (e.g. on other cells and sometimes in body fluids). Their role may not be connected directly to the red blood cell; we may have accidentally labelled these chemical moieties as blood groups antigens since they caused problems in blood transfusion. The initial statistical relations of blood groups with illness, that are of the most curiosity, are those with malignancy, peptic ulcers, coagulation, and infection [2]. The molecular base of the ABO blood group system was clarified in 1990. The gene encodes a glycosyltransferase, which transfers N-acetyl D-galactosamine (group A) or D-galactose (group B)

toward the nonreducing ends of glycans on glycolipids plus glycoproteins. The group O phenotype consequences from inactivation of the A1 glycosyltransferase gene, and the nonreducing ends of the consistent glycans in group O subjects present the blood group H antigen [3]. The ratio of ABO blood groups in many forms of cardiovascular disease differs from that in the general population in that there is an excess of non -O individuals. Age and gender are also considered. Age and sex are also consider to be risk factors for atherosclerosis, males being at a higher risk of disease, the gap between genders narrowing considerably with increasing age [4].

Diminishing of gastric secretion was more common in patients of blood group A than in patients of blood group 0. Investigations of the relation between acid secretion, ABO blood groups, and ABH secretor status specify that the rate of blood group 0 is higher among patients with hypersecretion, and these are more frequently non-secretors of ABH substance [5]. The production of effectual immune responses is critically dependent on the capability of white blood cells (neutrophils, lymphocytes, and monocytes) to transfer from the blood into the adjacent tissue at locates of inflammation [6].

Cellular adhesion molecules facilitate connection and transmigration of leukocytes across the endothelial surface and are thought to play a vital task in initial steps of atherogenesis. Therefore, augmented plasma concentrations of intercellular adhesion molecule (ICAM)-1 and P-selectin autonomously foretold myocardial infarction in healthy persons. Numerous studies established that plasma levels of adhesion molecules are amplified in patients with obesity, dyslipidemia, hypertension, and type 2 diabetes, which are well-recognized risk factors for cardiovascular diseases [7].

More conceptions may come from ABO's connotation with malaria infection vulnerability and severity. Recent investigations of Plasmodium falciparum infection demonstrate that the infected erythrocytes mimic the leukocytes' attachment to endothelium by linking to ICAM-1 and P-selectin on endothelium. Erythrocytes also link to the A and B antigens (but not O) on endothelial cells as an extra contributor to cytoadherence. This practical homology suggests the theory that leukocytes might also interact with ABO antigens on endothelium. The A antigen might stimulate stronger (longer) linking of leukocytes to P-selectin and ICAM-1 on the vascular wall, thus caring the protein from enzymatic cleavage which in turn would lead to reduced levels in circulation. Reduced cleavage of adhesion molecules from endothelial cells accompanying with A allele would mean more adhesion molecules on the endothelial cells, amplified adhesion and inflammation [8]. Concentrations of soluble P-Selectin were highest in cord blood specimens collected from all kids and were evidently abridged on day of life 1, irrespective of the consequent progress of bronchopulmonary dysplasia (BPD). In serum specimens attained from cord blood and on days of life 1 and 3, soluble E-Selectin levels were greater in babies that established BPD than in children that did not establish BPD. Also, the highest concentrations of soluble E-Selectin in serum specimens from cord blood and on day of life 1 were linked with the progress of stage 3 or 4 BPD. Soluble intercellular adhesion molecule-1 concentrations were greater on days of life 3 and 7 in the babies that went on to establish BPD than in kids that did not. Polymorphs binding to endothelial cell adhesion molecules is a basic incident in the instigation of an inflammatory response, the connotation of higher primary concentrations of soluble E-Selectin with the establishment of BPD proposes that E-Selectin may show a significant function in the pathogenesis of lung inflammation and the progress of BPD [9].

One of the greatest important illness links described for non-O (subjects of group A, B, or AB) versus O subjects is vulnerability to arterial and venous thromboembolism (VTE). Non-group O patients have a greater risk of VTE than patients of group O and have more levels of von Willebrand factor (vWF) and factor VIII. The jeopardy of VTE is undoubtedly connected to the level of vWF and factor VIII since patients of group A2 have lesser levels of these proteins than A1, B, and AB and have a lower hazard of VTE [3].

Several patients diseased with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) establish a syndrome that accomplishes the Berlin definition for the acute respiratory distress syndrome (ARDS) recognized by extreme mortality The pathogenesis of ARDS is multifaceted and partly reliant on the underlying mechanism; though, neutrophil inflow into the extravascular compartments of the lungs is measured a defining feature of the disease.

P-selectin is an essential membrane protein that arbitrates the adhesion of activated platelets and endothelial cells to polymorph nuclear cells and monocytes. Upon liking to the similar ligand on leukocytes, P-selectin glycoprotein ligand (PSGL)-1, P-selectin arbitrates the early progressing of leukocytes on the inflamed endothelium, which signifies the primarily stage in leukocyte recruitment to locates of inflammation. P-selectin moreover triggers monocytes to create tissue factor, an indispensable cofactor in the commencement of the so-named extrinsic pathway of blood coagulation. A conceivable function for P-selectin-mediated leukocyte recruitment into the lungs throughout ARDS has been explored. Infusion of both a monoclonal antibody to P-selectin or of Sialyl-Lewis-X, a constituent of PSGL-1, affectedly decreased lung injury in a rat exemplary of ARDS. In human beings, soluble P-selectin is amplified in ARDS patients matched with controls and in nonsurvivors likened with survivors. More recently SELPLG, encoding PSGL-1 has been recognized as a special gene susceptibility to ARDS by a genome- wide connotation review [10].

Circulatory illnesses encompass a multifaceted pathological inflammatory course, counting leukocyte migration and adhesion to vascular endothelial cells. This course is arbitrated by adhesion molecules expressed on leukocytes and endothelial cells in response to inflammatory incentives. Several soluble adhesion molecules are recognized as plasma prognosticators for the risk of CVD, significant amongst which are soluble intercellular adhesion molecule 1 (sICAM1) and soluble Pselectin (sPselectin). A metaanalysis stated that the ABO blood group, blood group A in specific, is linked with an upper risk of myocardial infarction, peripheral vascular disease, strokes and venous thromboembolism, signifying that it may have a task in inflammatory adhesion. Particularly, the circulating expression levels of sICAM1 and sPselectin are described to be meaningfully connected with ABO blood group antigens in Caucasian inhabitants [11].

The glycosylation procedure of ABO antigens may disturb the flaking or clearance of soluble adhesion molecules, as soluble and cellular forms of ICAM1 are known to be glycosylated. Moreover, glycosylation is vital to the connecting action of the Pselectin receptor, Pselectin glycoprotein ligand1. The inferior countenance levels of sICAM1 and sPselectin detected in donors with the A1 allele matched with the A2 allele may reflect the sturdier flaking or clearance aptitude of the A1 allele, as the A1 allele has 3050 fold more a transferase activity than the A2 allele [11].

The dispersal and differences of ABO blood group antigens vary significantly between races; In the European populace, the incidence of the A antigen (25 55%) is much greater than in other parts of the globe, it is established that the ABO blood group and the A allele are expressively linked with the lowermost circulating sICAM1 and sPselectin expression levels in a healthy Chinese populace, independent of differences and distributions of ABO blood groups amongst races. As blood group A is identified to be linked with the lowest sICAM1 and sPselectin expression levels in healthy Asian persons, it is recommended that ABO blood groups be measured when abnormal raised sICAM1 and sPselectin expression levels are apparent as predictors for risk the of CVD [11].

Concentrations of soluble E-selectin (sE-selectin), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble vascular cell adhesion molecule-1 (sVCAM-1) in the fit kids were double those found in adults. Completely three soluble cell adhesion molecules and von Willebrand factor (vWF) were more in the kids with Kawasaki sickness than in the well kids, nonetheless only sE-selectin, a sign for activated endothelial cells, and sICAM-1 were upper than in the fevered kids [12].

There are several documents viewing that thrombosis, serum cholesterol levels and myocardial infarction are more frequent in group A than group O. Consequently, there is a propensity for group A to bleed and group O to thrombose. The exciting fact that group A persons have a upper average level of the coagulation factor, antihemophilic globulin (factor VIII), existing in their plasma than do group O persons [2].

Leukocyte adhesion deficiency (LAD) syndromes are disorders of natural host defenses in contrast to bacteria, fungi, and other microorganisms following from defective tethering, adhesion, and guiding of myeloid leukocytes to positions of microbial invasion. LAD I and variant LAD I syndromes are triggered by mutations that damage expression or role of integrins of the β_2 class (CD11/CD18 integrins,

or "leukocyte" integrins). In difference, persons with LAD II have analogous clinical characters but intact leukocyte integrin expression and function. The molecular base for LAD II is malfunctioning glycosylation of ligands on leukocytes documented by the selectin family of adhesion molecules as well as faulty glycosylation of other glycoconjugates [13]. Amplified jeopardy of venous thromboembolism and stroke has reliably been detected for non-O blood types.

The connotation concerning ABO and stroke is probably arbitrated by the association between glycosyltransferase activity and plasma levels of the procoagulant von Willebrand Factor. Though, a hypothesized process linking ABO to atherosclerotic CVD is that ABO glycosyltransferases also influence circulation of cellular adhesion molecules (CAMs). CAMs are included of several protein families that are presented on the vascular endothelium and recruit leukocytes in response to inflammatory stimuli, and their soluble forms existing in blood are the outcome of shedding or proteolytic cleavage of the ectodomain. Soluble forms of CAMs E-selectin (sE-Selectin), P-selectin (sP-selectin), and ICAM-1 (sICAM-1) are biomarkers of inflammation, and augmented circulation with one or more of these markers has been related with coronary artery disease, myocardial infarction and atherosclerosis [14].

Current studies have showed substantial racial/ethnic changes in endothelial markers between fit individuals. They recognized lesser circulation of sICAM-1 in African Americans compared to persons of European descent, though important racial/ethnic alterations in sICAM-1 concentrations were also detected between Asian, Hispanic, black, and non-Hispanic white persons in the Women's Health Study. Racial/ethnic changes have also been noticed for sP-selectin, sE-selectin and von Willebrand Factor [14].

sICAM-1 concentrations appear to be connected with hypopermeability or hyperpermeability of the blood-brain barrier and thus to impact the communication between the CNS immune system, signified by glia cells, and the peripheral immune system. The equilibrium between the influx and efflux of immune molecules into and out of the CNS may be one of identifies in psychiatric problems [15].

Very important Study done by A Ponthieux., *et al*. showed that; sICAM-1 level was impacted by G/R241 polymorphism and several biological factors such as age, gender, smoking, insulin resistance, Il-6 level, and ALP and AST activities. Concentrations of sICAM-1 reduced throughout childhood and adolescence and diverse very slightly between 38 and 55 years, and men had a slightly greater sICAM-1 concentration than women. Also, connotation between the R241 allele and low sICAM1 concentration noticed [16]. The serum level of sICAM-1 were meaningfully raised in patients with type 1 diabetes mellitus and the correlations detected between sICAM-1 and the incidence of retinopathy [17].

Concerning G/R241 ICAM-1 polymorphism, there is a heterogeneity in the genotype spreading in fit inhabitants across the globe with ethnic changes in R241 allele frequency. In specific, through Europe, R241 allele frequency was greater in the north compared with the south: 18% in Poland; 14.3% in Estonia; 11.4% in Germany; 9.4% in the UK; in Northwestern Spain, 8.1% in Italy, 5.7, 4.0 and 3.1%. Values of R241 allele frequency (9.7 - 11.9%) got in the north-east of France [16].

In the last month of 2019, an epidemic of pneumonia with unidentified source initiated in China's Hubei Region, increasing worldwide health anxieties due to the easiness of transmission. To rapidly investigate and control the extremely infectious disease, supposed persons were isolated and diagnostic/ therapeutic processes were established via patients' epidemiological and clinical informations. After several studies, a unique severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized as the causative agent of the disease, and the disease was named "coronavirus-19" (COVID-19) by Chinese Scientist [18]. Up to now, the SARS-CoV-2 infection is still scattering, and this virus poses a grave hazard to public health. Because of a lack of specific antiviral therapies and stress of clinical treatment, thousands of severe cases have died every day globally [19].

Infectious characteristics of COVID-19 S protein Like to what was eventually found for SARS-CoV, the linking of SARS-CoV-2 S protein to its cell surface receptor, angiotensin converting enzyme 2 (ACE2), establishes viral entrance into type II pneumocytes in the human lung. The COVID-19 S protein comprises two chief domains: the S1 domain at the N-terminus of the protein arbitrates connecting to ACE2 and

the C-terminal S2 domain stimulates merging of the virus cell membrane with membrane of the host cell. The receptor-binding domain is a subdomain of S1 that contains 424-494 aa. This theme derives into direct contact with the extracellular connecting position on ACE2 known as the peptidase domain. There are two cleavage positions in the S protein, arginines R667 and R797. The R667 location is at the division amid S1 and S2 and cleavage at the R797 position consequences in the final S2 polypeptide. Several cellular proteases can cleave the S sequence at these two positions, counting cathepsin L, trypsin, elastase, serine transmembrane proteases (TMPRSSs), and factor Xa, amongst others. Cleavage at together S protein positions is vital to stimulate entrances of SARS-CoV and COVID.19 into the host cell; the initial is important for S1 linking to ACE2 and the second is crucial for membrane fusion [20].

COVID-19 infection usually causes minor symptoms (80%), while mortality upsurges (50%) in patients who need admission to Intensive Care Units with invasive mechanical ventilation. ABO antigenic determinants are also expressed in cells of definite endothelial and epithelial tissues for example the respiratory system. The existence of A and B antigens is linked with superior vulnerability to infections, cardiovascular diseases and cancer, whereas group O is frequently related with greater resistance to diseases [21].

Type-1 (sICAM) soluble adhesion molecule reveals a circulating form of it that is constitutively displayed or inducible on the cell surface of different cell lines. It functions as a counter-receptor for the lymphocyte function-associated antigen (LFA-1) [22]. LFA-1 shows a significant role in the building of the immunological synapse. Aimed at antigen-specific recognition, the immunological synapse can be commonly defined as the physical structure of the interacting surfaces of T cells and APCs [23]. IFN-γ has been revealed to be one of the most powerful stimuli of ICAM-1 expression at the molecular level [24]. A great concentrations of pro inflammatory cytokines such as IL-1, TNF- IL-12 are significant factors in dropping the entire number of white blood cells and the amount of lymphocytes, positive significant correlation between sICAM-1 and total white blood cell count [25]. ICAM-1 shows a vital role in the recruitment of activated lymphocytes to positions of inflammation within the CNS [26].

Great sICAM-1 blood concentrations have also been detected in depression comorbid to a somatic disease condition [15]. Patients infected with SARS had meaningfully lesser lymphocyte and platelet counts and meaningfully upper sVCAM-1 and sFasL levels likened to healthy controls. sVCAM-1 levels correlated negatively with total white blood cells and thrombocytes counts [27]. Some cell surface proteins deficient to a transmembrane polypeptide domain and are attached to the cell surface via an unusual glycolipid moiety comprising phosphatidylinositol [28].

Recent studies have established that the ABO gene can disrupt soluble intercellular adhesion molecule 1 (sICAM-1) levels of circulating expression. Consequently, it can be suggested that ABO blood groups may need attention when soluble adhesion molecules are recognized as prognosticators for cardiovascular disease. Blood group A persons were found to have meaningfully lesser sICAM-1 expression concentrations (252.2 ng/ml), likened with those in group O [29].

Clinical studies have extra presented that augmented plasma concentrations of ICAM-1 and VCAM-1 predict progress of multiple organ dysfunction syndrome and that ICAM-1, is not measured to be a significant facilitator of neutrophil (PMN) adhesion to the endothelium, since PMNs express slight very late antigen-4 (VLA-4), the ligand for VCAM-1 [30].

The soluble intracellular adhesion molecule type-1, is the main factor that lead to the appearance of most clinical features and complications of Covid.19, due to the presence of many evidences that support this assumption such as; lately the expression of ICAM-1 on vascular endothelial cells in the brain was recognized to be correlated with the progress of depression [31]. Elevated intercellular molecule-1 (ICM-1) and vascular cell adhesion molecule1 (VCAM-1) concentrations can be associated with cardiovascular disease and are associated with obstructive sleep apnea (OSA) and obesity [32]. The communication of both the LFA-1/ICAM-1 and the TCR/MHC consequences in an intensification of the inflammatory course with the release of inflammatory cytokines and recruitment of extra T cells to the position of inflammation [33], which lead to a condition known as cytokines storm in Covid.19 patients.

The lymphocyte function-associated antigen-1 (LFA-1) linking of a distinguished class of small-molecule antagonists as that of soluble intercellular adhesion molecule-1 (sICAM-1) [34], topical SAR 1118, a unique antagonist of lymphocyte function-associated antigen-1 leads to instillation site irritation and dysgeusia [35], and that resemble sore throat and loss of taste observed in significant number of SARS COV-2 infected persons.

A soluble form of ICAM-1 that includes all five Ig-like domains was recognized in the normal rat testis and enriched in germ cells. Consequent investigation to overexpress this sICAM-1 in Sertoli cells *in vitro* was found to provoke an adverse consequence on the Sertoli cell barrier [36]. The existence of these activating proteases as well as ACE2 in the sperm plasma membrane would be probable to permit the COVID-19 virus to attach to the cell surface and finally fuse, either in the testes or throughout the prolonged sojourn of these cells in the epididymis [37]. COVID.19 utilizes the angiotensin-converting enzyme 2 receptor to go in the target cells, subsequent in activation of the renin-angiotensin system [38]. Angiotensin-2 enhances human vascular endothelial cells expression of intercellular adhesion molecule-1 (ICAM-1) and increases soluble ICAM-1 release *in vivo* [39]. Persons with A blood group have meaningfully lower ACE activity compared to O histo-blood group individuals [40]. The RH blood group type, and sex were recognized to be meaningfully related with apo-A levels [41].

Relative genomic analysis of SARS-CoV-2 recommended that it is enhanced for binding to human ACE2 and in this approach it exploits the membrane-bound receptor in host cells to start and disseminate infection. Significantly ACE2 is expressed on varied human cells counting epithelial cells in the lung and small and large intestines, tubular cells of the kidney, vascular endothelial and smooth muscle cells and cardiomyocytes. Lessening in ACE2 is well identified to be connected with hypertension, diabetes, coronary artery disease, myocardial infarct repair and heart failure [42]. The pathogenesis of COVID-19 is highly complex, with multiple factors included. As well as the direct viral influences and inflammatory and immune factors, the downregulation of ACE2 and inequity amid the renin-angiotensin system and ACE2/angiotensin- (1-7)/MAS axis may also participate to the many organ injuries in COVID-19 [43].

Conclusion

In this review we end that COVID.19 reduce Angiotensin-2 levels, which lead to stimulation of soluble intracellular adhesion molecule type-1 with inadequate effectiveness and increase its levels in patients' serum. Severity of COVID-19 pandemic varies between patients according to their age, gender, race, ABO blood group type, rhesus system and presence of comorbidities such as diabetes, cardiovascular disease, and obesity.

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