



VON WILLEBRAND FACTOR AND ENDOTHELIAL DAMAGE: A POSSIBLE ASSOCIATION WITH COVID-19

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☼ COVID-19 caused by the SARS-CoV-2 virus is a new type of infection which has caused an enormous social and economic burden across the world. While most people will develop a mild-to-moderate form of the disease or even stay asymptomatic, a certain proportion will get critically ill. COVID-19 mortality risk is higher in elderly patients and in patients with cardiovascular diseases and diabetes. Molecular mechanisms which underlie these risks are not yet understood for COVID-19. Here I discuss a possible association of COVID-19 complications with von Willebrand factor (VWF) level and endothelial damage. VWF is an important prognostic marker of endothelial dysfunction and its level fluctuates depending on age. VWF level is also variable depending on sex and race. Importantly, chloroquine, a drug that showed potential efficacy for COVID-19 treatment, can influence VWF secretion and consequently its level and activity. I propose that VWF level and activity might be predictors of the COVID-19 morbidity and mortality; moreover the VWF might be involved in the pathogenesis of the disease. I suggest that a comprehensive study of VWF level in SARS-CoV-2 positive groups of people with mild and severe course of the disease should be undertaken.

☼ **Keywords:** von Willebrand factor; COVID-19; SARS-CoV-2; endothelial damage.

ФАКТОР ФОН ВИЛЛЕБРАНДА И ПОВРЕЖДЕНИЕ ЭНДОТЕЛИЯ: ВОЗМОЖНАЯ СВЯЗЬ С COVID-19

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☼ Пандемия COVID-19, вызванная новым вирусом SARS-CoV-2, привела к развитию тяжелых социально-экономических последствий по всему миру. Хотя у большинства людей наблюдается легкое или среднетяжелое течение болезни, а некоторые даже переносят заражение без развития симптомов, у определенной доли людей развивается критически тяжелое состояние. Текущая статистика показывает, что смертность от COVID-19 выше среди пожилых пациентов и у пациентов с определенными заболеваниями, такими как сердечно-сосудистые заболевания и диабет. Молекулярные механизмы, которые лежат в основе этих рисков, пока еще не понятны для COVID-19. В данном сообщении я обсуждаю возможную ассоциацию осложнений COVID-19 с фактором фон Виллебранда (ФВ) и повреждением эндотелия сосудов. ФВ является важным прогностическим фактором дисфункции эндотелия сосудов и его уровень в плазме меняется с возрастом. Уровень ФВ также подвержен вариации в зависимости от пола и расовой принадлежности. Важно, что хлорохин — препарат, который в предварительных испытаниях показал эффективность при лечении COVID-19, влияет на секрецию ФВ и может влиять на его количество и активность в плазме. Я предполагаю, что уровень и активность ФВ могут являться важными прогностическими факторами заболеваемости и смертности от COVID-19, а сам ФВ может оказаться вовлеченным в патогенез заболевания. Масштабное и тщательное исследование уровня и активности ФВ у групп людей, инфицированных SARS-CoV-2, у которых наблюдается легкое или тяжелое течение инфекции, должно быть предпринято в ближайшее время.

☼ **Ключевые слова:** фактор фон Виллебранда; COVID-19; SARS-CoV-2; повреждение эндотелия.

SARS-CoV-2, a novel type of coronavirus caused an outbreak of coronavirus disease 2019 (COVID-19) that led to more than 3 millions of total confirmed cases and more than 200,000 deaths worldwide by the end of April 2020. The COVID-19 spread in Wuhan in China, then in the European countries and in the US has shown what certain population groups are at higher risk than the others. The mortality is higher in elderly people and in people with existing co-morbidities such as cardiovascular diseases and diabetes [1, 2]. Gender and race biases were also reported: i. e. men are affected more than women and mortality among African-American is higher than in Caucasians [3, 4]. Pulmonary lesions are diagnostic feature of COVID-19. Acute Respiratory Distress Syndrome (ARDS) was reported in almost 30% cases of patients with severe illness [5].

Several recent studies point at coagulation problems found in patients with severe COVID-19 infection [6–8]. It has been proposed that COVID-19 can lead to hypercoagulability and development of disseminated intravascular coagulation (DIC) [6, 9, 10]. Infection-induced endothelial cells dysfunction can result in a hypercoagulable state characterized by excessive thrombin level, elevated D-Dimer, and problems with fibrinolysis which along with hypoxia was suggested to stimulate thrombosis in COVID-19 patients with severe infection [7, 9]. Early anticoagulant treatment with heparin blocked clotting formation and was associated with better prognosis in COVID-19 patients with sepsis-induced coagulopathy (SIC) [7]. Additionally, anticoagulation drug Dipyridamole can be beneficial as prophylaxis for COVID-19 complications [11].

Here I would like to point at a possible connection of von Willebrand factor (VWF) and severity of the COVID-19. VWF is an essential factor of the blood coagulation system which is synthesized and secreted by the endothelial cells. VWF multimers secretion from intracellular organelles known as Weibel-Palade bodies is required for platelet adhesion to the damaged vessel walls. Importantly, VWF level in plasma is an indicator of endothelial activation and damage [12]. VWF is also a marker of pulmonary endothelial injury and some studies suggest that level of VWF can be linked to ARDS and Acute Lung Injury (ALI) [13, 14]. It should be noted that autophagy plays an essential role in VWF secretion [15]. Moreover, chloroquine the drug that showed potential efficacy for COVID-19 treatment

inhibits autophagy and therefore can influence the level of secreted VWF multimers [15, 16].

Cell angiotensin-converting enzyme 2, ACE2, is used by Spike protein of the SARS-CoV-2 to penetrate the cell. ACE2 is expressed in many tissues including endothelium and lung parenchyma and plays a major role in the renin-angiotensin regulatory system. It removes terminal amino acid from Angiotensin I and Angiotensin II to produce Angiotensin (1–9) and Angiotensin (1–7) correspondingly: the peptides which promote vasodilation and counteract pro-inflammatory Angiotensin II effects. ACE2 protects endothelial cells from damage upon inflammation [17, 18]. It also plays an important role in preventing lung injuries: in mice it counteracts ALI induced by sepsis or acid [19]. Additionally, the level of ACE2 has inverse correlation with the development of ARDS/ALI caused by the closely-related SARS-CoV virus [18]. Interaction of SARS viruses with ACE2 was proposed to inhibit ACE2 activity and downregulate ACE2 expression on the cell surface [18, 20]. Consequently, this should promote ACE1/ACE2 imbalance and increase in the Angiotensin II level [21]. Such a disbalance in the renin-angiotensin signaling was proposed to mediate lung injury in COVID-19 [22]. Interestingly, VWF might be a missing link in Angiotensin II-mediated endothelial dysfunction [23]. For instance, VWF gene silencing counteracts Angiotensin II-dependent endothelium dysfunction in a porcine model [24]. In addition, the protective role of Angiotensin (1–9) has been linked to the decrease in VWF expression [25]. It is an important question whether a disbalance in the renin-angiotensin system upon COVID-19 infection can lead to a change in VWF production, processing or secretion in the endothelium. Recent reports showing significantly elevated VWF level and activity in a small cohort of intubated COVID-19 patients is in accord with idea that COVID-19 might provoke endothelial activation and dysfunction [26, 27]. It is of great interest if hypercoagulability, ARDS and other symptoms observed in COVID-19 patients could be explained through VWF-dependent mechanism.

Some population studies indirectly suggest that development of severe COVID-19 infection might be linked to the increased VWF level or activity. First, preliminary data show that the risk of developing COVID-19 is somewhat decreased in people with

blood group 0 (this blood group is characterized by the lower level of VWF) [28, 29]. Second, it worth noting that level of VWF depends on age: it tends to be lower in children than in adults and it rises in elderly population [30, 31]. This can explain why risks of COVID-19 are higher for elderly population while children suffering less from the disease. Third, the VWF level demonstrates race and gender differences: for instance it is higher in males vs. females and it is higher in African-American compared to Caucasians [29, 32, 33]. These facts correlate well with factors associated with COVID-19 symptoms severity and mortality, i. e. gender (males are more affected than females), age (older population is of higher risk) and race (African-American are more affected than Caucasians). Moreover, VWF level and activity are essential prognostic biomarkers in cardiovascular, metabolic, and inflammatory diseases [29, 34].

Summarizing these facts, I hypothesize that VWF level/activity might be used as a predictor of COVID-19 symptoms severity. I suggest that comprehensive studies of VWF level/activity correlation with COVID-19 symptoms and mortality rate shall be performed. In addition, it can be assumed that medication improving the endothelium function and antagonizing inflammation in vessels could be beneficial for COVID-19 therapy and as a prophylaxis of severe complications of COVID-19.

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