Prothrombotic status in COVID-19 with diabetes mellitus (Review)

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Received May 6, 2023; Accepted July 26, 2023

DOI: 10.3892/br.2023.1647

Abstract. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused an important social and health impact worldwide and the coronavirus disease-19 (COVID-19) has elicited devastating economy problems. The pathogenesis of SARS-CoV-2 infection is a complex mechanism and is considered to be the result of a challenging interaction, in which host and virus immune responses are the key elements. In this process, several inflammatory pathways are involved, and their initiation can have multiple consequences with a considerable impact on evolution, such as hyperinflammation and cytokine storm, thereby promoting activation of the coagulation system and fibrinolytic activity suppression. It is commonly recognized that COVID-19 severity involves multiple factors, including diabetes which increases the risk of developing different complications. This could be as a result of the low-grade inflammation as well as the innate and adaptive immune response dysfunction that is observed in patients with diabetes mellitus. In patients with diabetes, multiple metabolic disturbances which have a major impact in disturbing the balance between coagulation and fibrinolysis were discovered, thus the risk for thrombotic events is increased. Diabetes has been recognized as an important severity prognosis factor in COVID-19 cases and considering there is a significant association between diabetes and prothrombotic status, it could be responsible for the increased risk of thrombotic events with a worse prognosis.

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Key words: prothrombotic status, coronavirus disease-19 infection, diabetes mellitus

Contents

1. Introduction

The coronavirus disease-19 (COVID-19) pandemic has been the reason of high morbidity and mortality worldwide. Between the start of the pandemic and 23 January 2023, there were 663,640,386 confirmed cases and 6,713,093 deaths (1). During the last decade the first pathogen involved in a global pandemic is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has a significant clinical range, most of the cases are presented with slight or no symptoms but severe cases can lead to severe pneumonia, multiple organ failure and death. Elderly individuals with underlying conditions, such as diabetes mellitus (DM), cardiovascular

diseases and hypertension have a demonstrated higher risk for developing severe complications from COVID-19 (2).

According to pathological and clinical evidence, severe SARS-CoV-2 infection is associated with a prothrombotic status expressed as microvascular or macrovascular thrombosis. Multiple factors are involved, including endothelial dysfunction, systemic inflammation, platelet activation, mechanical ventilation and immobilization (3). Thrombotic events contribute to the mortality and can be mentioned among life threatening complications of the disease. Diabetes is associated with multiple risk factors such as age, family history, race, obesity, hypertension and dyslipidaemia. In patients with DM, a dysregulated immune response and a chronic low level of inflammation with reduced amount of the anti-inflammatory adiponectin and elevated amount of the proinflammatory leptin has been identified. Considering the various spectrum of disorders observed in patients with diabetes, in cases of overlapping SARS-CoV-2 infection, DM has been established as an extremely important risk factor for a severe evolution of the disease. This may be due to the association between diabetes and its high susceptibility to cytokine storm (4). The presence of DM in patients with COVID-19 was associated with the risk of admission to intensive medical care and increased mortality. Different physio-pathological mechanisms were identified and because diabetes is characterized by a syndromic nature, possible responsible factors should be discussed, such as the decreased autoimmune function, the prothrombotic status and the increased susceptibility to hyperinflammatory immune response associated with hyperglycemia (5,6). Patients with COVID-19 are more likely to develop a hypercoagulable status if diabetes is associated. Fibrinogen and D-dimer levels are increased in these cases and glycemic control exert a considerable influence (7).

2. Endothelial dysfunction

Endothelium is considered to have a leading role in several physiological processes and plays a significant role in the homeostasis of healthy individuals. It produces components of the extracellular matrix and multiple chemical mediators, such as endothelin-1, nitric oxide (NO), prostacycline, angiotensin II (ANG-II), plasminogen activator inhibitor-1 (PAI-1), tissue-type plasminogen activator (t-PA), cytokines, adhesion molecules and tumor necrosis factor α (TNFα). An essential mediator synthesized by endothelial cells is NO due to its antiproliferative, anti-inflammatory, vasodilatory, permeability-decreasing and antioxidant properties. Endothelium also has an impact on vascular remodelling through the release of platelet-derived growth factor and ANG-II. It is an important mediator of inflammation and coagulation by controlling leucocytes and platelets adhesion. It controls fibrinolysis and limits activation of the coagulation cascade (8). Endothelial glycocalyx consists of glycoproteins and proteoglycans and prevents the direct contact of blood cells with the endothelial surface. Endothelial dysfunction is defined by increased interactions with white blood cells, smooth muscle growth, vasoconstriction, disrupted coagulation, inflammation, thrombosis and atherosclerosis (9).

The involvement of endothelial dysfunction in DM is complex as multiple factors are involved, such as obesity, ageing, hyperlipidemia, hypertension, insulin resistance and hyperglycemia. Possible suggested mechanisms which lead to endothelial micromilieu impairment in patients with diabetes are insulin resistance and hyperglycemia. Chronic hyperglycemia affects protein kinase C, sorbitol and pentose phosphate pathways. This leads to increased oxidative stress and promotes endothelial cells apoptosis. Another mechanism through which hyperglycemia causes endothelial dysfunction is the reduced level of NO. A bidirectional relation and vicious circle in which insulin resistance contributes to endothelial dysfunction and conversely may exist. At normal concentrations, insulin generates anti-inflammatory effects, while hyperinsulinemia increases levels of oxidative stress and can lead to vascular inflammation and simultaneously vascular inflammation causes insulin resistance and compensatory hyperinsulinemia (10).

Dysfunction of the endothelium, inflammatory response, thrombopathy and microvascular obstruction are the suggested physio-pathological components of severe COVID-19 cases. Thrombosis and dysfunction of the endothelium are recognized as pathways contributing to clinical deterioration in COVID-19 patients. SARS-CoV-2 has a particular tropism for angiotensin converting enzyme 2 (ACE2) receptor. This receptor is expressed by endothelial cells but also in multiple organs, such as heart, lung, kidney and intestine (11). Endothelial cells are directly impaired by SARS-CoV-2, suffering cellular injury and finally apoptosis, thus, as a consequence, the endothelium can no longer provide antithrombotic properties. Furthermore, COVID-19 cases were associated with elevated plasma levels of soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1 and endothelial cells.

In the viral genome of SARS-CoV-2 there are over 20 proteins encoded, with the spike protein being one of the most studied. Spike protein contains two subunits, S1 of the receptor-binding domain, which binds ACE2, and S2 which is involved in anchoring the virion to the membrane, which results in the fusion with the host cell, followed by the virus entry into the cell, via endocytosis (12). The ACE2 has an important role in the function of the renin-angiotensin-aldosterone system (RAAS), a signaling pathway which includes rennin, angiotensinogen, ANG-I, ANG-II, as well as the AT1 receptor (12-14). Normally, the activation of ACE2 leads to vasodilation and activation of antioxidant and antiproliferative effects. In the case of SARS-CoV-2 infection, the virus competes with ANG-II for ACE2, resulting in ACE2 downregulation, leading in an imbalance of the ACE/ACE2 ratio and in an increased peripheral vascular resistance (12). Furthermore, it is known that chronic inflammatory states, such as diabetes, are associated with impaired RAAS function. Therefore, these patients have a higher risk of developing infections, as well as a higher risk for the development of complications. In addition, other factors, such as hypomagnesiemia, that triggers oxidative stress and leads to an increase in proinflammatory cytokines, have also been associated with endothelium dysfunction in patients with COVID-19 (15). Endothelium has the key role in controlling the mechanisms, with a considerable impact on the progress of COVID-19 in patients, for instance, by regulating haemostasis and fibrinolysis. Additionally, a previous study has also demonstrated that through delayed fibrinolysis, low magnesium levels in these patients are associated with a higher

risk of thrombotic events. Furthermore, decreased intracellular magnesium is associated with platelet-dependent thrombosis (15). The trigger for immuno-thrombosis in patients with COVID-19 is established to be the endothelial dysfunction which is the cause of the COVID-19-related coagulopathy. The factor of risk in microvascular impairment is the endothelial dysfunction which can enhance ischaemia and inflammation. In addition, the vascular wall permeability is increased, and as a result of the inflammatory status, tissue factor (TF) is expressed and activated on endothelial cells. Therefore, the coagulation cascade, which involves the activation of a series of clotting factors, is initiated. All of these elements support the assumption that endothelial dysfunction is the main feature of COVID-19-associated coagulopathy (16).

3. Haemostasis and inflammatory immune response

An efficient reaction in case of tissue damage or infection depends on the ability of the living organisms to use the innate defence mechanisms such as the immune system and the haemostatic system. To re-establish physiological tissue function, immune and haemostatic systems have a strong and active interplay. In either non-infectious or infectious inflammatory states, haemostatic system activation is the critical component of the host defence mechanism. An overstated and insufficiently controlled activity may contribute to disease severity (17).

The haemostatic system and the inflammatory cascade act in collaboration producing an inflammatory-haemostatic cycle with a positive feedback system, in which each one of the processes triggers the other one. Several factors affect the haemostatic system and especially cytokines, which take a lead in influencing the process during the inflammatory reaction through endothelial impairment, activation of the coagulation cascade and increased platelet reactivity. The interplay between homeostasis and inflammation clarifies the prothrombotic tendency. In case of inflammation, haemostatic activity is changed by proinflammatory mediators which cause imbalance between the coagulation system and the fibrinolytic activity, thus, the prothrombotic state is initiated (18).

Inflammatory immune response, irrespective of the etiology, contributes to an imbalance among proinflammatory and procoagulant properties and anticoagulant and anti-inflammatory features of the vascular endothelium which acquires a procoagulant phenotype. The connection between haemostasis and inflammation is a bidirectional process, thus, activated haemostatic system also significantly modulates inflammatory activity. Activated or injured endothelium secrete mainly antifibrinolytic or procoagulant components into the surrounding area, such as thromboxane A2, von Willebrand factor (vWF) and PAI-1, whilst the expression of constituents with profibrinolytic and anticoagulant properties is considerably reduced. When a vascular injury arises, endothelial cells excrete TF, which subsequently binds to factor VII and forms the TF-VII complex which initiates the activation of the coagulation cascade. The resulting product is thrombin, that converts fibrinogen into fibrin. Cellular activation in inflammation is a process mediated by fibrinogen and fibrin, these mediators stimulate the expression of proinflammatory cytokines on monocytes and the expression of chemokines on endothelial cells and fibroblasts. Adhesion molecules intercede the procoagulant actions of the vascular endothelium by managing the interplay among platelets, neutrophils and proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-1 (IL-6) and TNFα (19). There is an important association between coagulation and inflammation which is characterized by the adhesion of coagulation factors to the protease-activated receptors (PARs) which thus increase the inflammatory response. PAR receptors are located on endothelial cells, white blood cells, platelets, fibroblasts and smooth muscle cells. There are four members, PAR-1 to PAR-4 and have different functions, PAR-1, PAR-3 and PAR-4 are thrombin receptors while PAR-2 receptor can be activated from the TF-factor VIIa (FVIIa) complex. Inflammatory response can be upregulated by connecting activated coagulation factors to the PAR receptors. The result is the production of multiple proinflammatory mediators such as cytokines, growth factors, chemokines and cell adhesion molecules (20).

A remarkable example of viral disease is SARS-CoV-2 infection, in which systemic inflammatory reaction and the coagulation cascade are two important mechanisms with mutual potentiating activity. Multiple immune cells are the target of SARS-CoV-2 such as macrophages, monocytes, endothelial cells, dendritic cells, T-cells and natural killer cells. Following the cells activation, the viral particles stimulate multiple inflammatory pathways, producing large quantity of chemokines (CCL-2, CCL-3, CCL-5, CCL-7, CCL-8, CXCL-9, CXCL-10) and cytokines (IL-6, TNFα, IL-1β, IL-2, IL-7, IL-8, IL-10,), which leads to hyperinflammation and cytokine storm and leading to vascular permeability increase and risk of multi-organ failure. Several changes occur in cases of COVID-19, such as the increase of the level of inflammatory mediators, chemokines, cytokines and neutrophil-to-lymphocyte ratio, with a significant association to severity. Whereas the initial release of cytokines helps with virus removal, the uncontrolled cytokine secretion is detrimental as they begin to target host cells. The cytokine storm changes the balance between pro and anticoagulant mechanisms, elevating the levels of vWF and TF and promoting activation of coagulation cascade (21) (Fig. 1). Among the released cytokines, IL-6 has a significant role assigned. Cytokines influence different functions and the medical literature revealed that IL-6 has a greater influence on coagulation activation than TNFα, therefore being the most important mediator (22,23). IL-6 has a prominent role in the induction of TF expression, it also promotes the synthesis of coagulation factors such as factor VIII (FVIII) and fibrinogen, and its action on endothelial cells lead to increased vascular permeability by stimulating vascular endothelial growth factor secretion. Soluble IL-6 receptor (sIL-6R) is connected to various cells, such as leukocytes, macrophages, monocytes and B cells, and during infection with SARS-CoV-2 these cells go through a process leading to increased separation of soluble receptor from cells. According to medical studies, elevated concentrations of sIL-6R were observed in plasma of patients with COVID-19. Multiple cells including endothelial cells can be activated by complexes of IL-6 and sIL-6R found in the circulatory system of COVID-19 cases. The cytokine storm can stimulate megakaryocytes proliferation, thus leading to thrombocytosis (23-25). Additionally, in the setting of inflammation, platelets can be directly activated by inflammatory

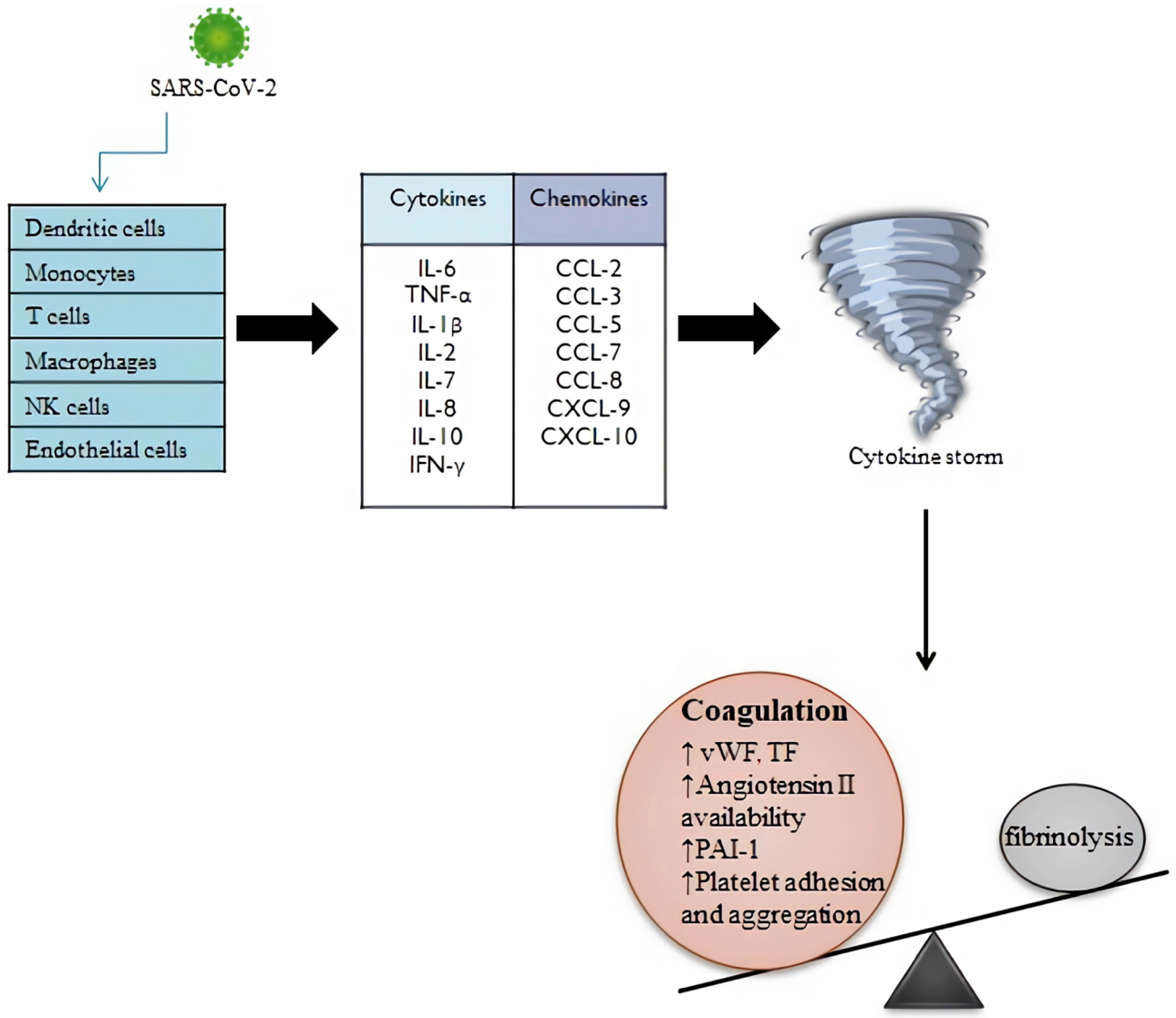

Figure 1. Impact of SARS-CoV-2 infection on immune cells and the consequences on the coagulation process. Multiple immune cells are the target of SARS-CoV-2, such as macrophages, monocytes, endothelial cells, dendritic cells, T-cells and NK cells. Following the cells activation, the viral particles stimulate multiple inflammatory pathways, producing large quantity of chemokines and cytokines, which leads to cytokine storm. The cytokine storm changes the balance between coagulation and fibrinolysis, elevating the levels of vWF, TF, angiotensin II, PAI-1 and the platelet adhesion and aggregation (27,51). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NK, natural killer; vWF, von Willebrand factor; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1.

mediators. Activated platelets secrete proinflammatory and procoagulant substances into the local environment, such as cytokines, chemokines, adhesion molecules, growth factors and coagulation factors. Therefore, a link between infection and thrombosis can be deduced (26).

DM has been established to be a proinflammatory condition which comes as a consequence of excessive cytokine production. Increased concentrations of fibrinogen, lactate dehydrogenase, C-reactive protein, TNFα, IL-1 and IL-6 detected in patients with DM are the reason of chronic inflammation in patients with diabetes. Inflammatory cytokines increase vascular permeability, adhesion of white blood cells to the endothelium and promote thrombus formation (27,28). In patients with DM, expression of protease-activated receptor 4 is increased by chronic hyperglycemia. In return, the release of activated platelet-derived microparticles (PMPs) is enhanced by the Ca^{2+}-calpain pathway. Released PMPs trigger IL-6 secretion, with a proinflammatory and pro-thrombotic activity in diabetes. Hyperglycemia decreases the membrane fluidity of platelets through glycation of the membrane proteins, directly promoting platelet activation and aggregation. Additionally, hyperglycemia diminishes endothelial function by causing oxidative stress and inflammation, therefore decreasing NO and prostaglandin I2 synthesis and release, and as a consequence promoting platelet aggregation (29). Insulin resistance can be caused by several factors including the proinflammatory cytokine TNFα. Therefore, this sheds some light about the close relation between endothelial dysfunction, insulin resistance and thrombosis. In DM, insulin resistance and hyperglycemia exert synergistic effects on TF pathway, which leads to increased procoagulatory activity. Patients with DM have an inflammatory state, defined by the elevated levels of inflammatory biomarkers, and this

process directly upregulates TF expression, contributing to the prothrombotic status (30).

4. Hyperglycemia: A prothrombotic factor?

DM is characterized by a high risk of atherothrombotic events. The prothrombotic state associated with diabetes is sustained by laboratory results of impaired fibrinolysis and raised coagulation factors. Hyperglycemia plays a significant role in the development of these hemostatic disorders. Various processes are suggested to explain the coagulability changes that can develop in case of metabolic imbalance with hyperglycemia. For instance, depletion of the extracellular matrix that covers the apical side of endothelial cells which shelters coagulation factors. Furthermore, the activity of coagulation factors can be modified by the glycation process, additionally, oxidative stress has a significant impact. In addition, hyperglycemia is frequently associated with hyperinsulinemia, which leads to prothrombotic consequences (31).

Hyperglycemia and hyperinsulinemia increase the expression of PAI-1, thus its concentration and activity are increased. In consequence, the fibrinolytic capacity is decreased due to diminished t-PA activity. Furthermore, an assumption has been made about the substantial impact of hyperglycemia and hyperinsulinemia on gene transcription (32). PAI-1 transcription process is elevated through nuclear factor kappa-B (NF-kB), as a result of increased NF-kB activity in hepatic cells and PAI-1 gene transcription. Hyperglycemia along with hyperinsulinemia are the underlying reasons of all these changes. Advanced glycation end products (AGEs), which are overproduced in hyperglycemia, have an impact on TF expression, thereby increasing TF levels and procoagulant activity (33). The receptor for AGEs (RAGE) is a multi-ligand receptor which is able to interact with many non-AGE ligands, with an impact on different chronic inflammatory diseases (34-36). The RAGE axis activation was proposed among the mechanisms demonstrating the worse prognosis of the association between diabetes and COVID-19, as in animal models with acute respiratory distress syndrome (ARDS) it was observed that RAGES inhibition led to reduced lung damage as well as restored alveolar fluid clearance (34,37,38). The vulnerability of vascular endothelium is directly affected by hyperglycemia, through the impairment of the glycocalyx integrity. This leads to a release of coagulation factors sheltered within the endothelial glycocalyx and amplify platelet-endothelial cell adhesion. In fibrinolysis and coagulation, different types of proteins are implicated, and as hyperglycemia may induce protein glycation, these effects must be taken into consideration upon establishing further care. Fibrin clots from patients with diabetes have high density compared with controls, and this leads to longer clot lysis time. The non-enzymatic glycation of fibrin is a likely explanation (39).

Several studies revealed two types of effects on thrombotic markers in the context of hyperinsulinemia and hyperglycemia, an independent and an additive action when they are concurrently existing. Although insulin has an inhibiting effect on platelet activation, a previous study demonstrated that platelets of patients with DM are resistant to this function, becoming more prone to be activated (40).

Thereby, hypercoagulability can be induced by hyperglycemia through different complex mechanisms and the impact is more important along with hyperinsulinemia (41).

5. Hypercoagulable state

In order to halt bleeding and form a dense clot, platelets act along with blood coagulation factors, a number of molecules with protein structure, which have a key role in the coagulation process. In patients with DM, qualitative and quantitative changes of coagulation and anticoagulation factors were observed. In DM, insulin resistance and hyperglycemia exert synergistic effects on the TF pathway, causing factor VIIa (FVIIa) consumption and increased procoagulatory activity (42). The intrinsic pathway of blood coagulation implies successive activation of factor XII (FXII), factor XI (FXI) and factor IX (FIX). Previous findings have showed impairment of intrinsic blood coagulation correlated with hyperinsulinemia and hyperglycemia in DM. A reduced activated partial thromboplastin time along with an increased synthesis of FXII, FXI and FIX were identified in cases with diminished insulin sensitivity, influenced by an inflammatory response as a consequence of insulin resistance (43). The final phase in extrinsic and intrinsic blood coagulation pathways ends with the transition of fibrinogen to fibrin, and in patients with DM, higher circulating fibrinogen levels were noticed, revealing a more compacted clot structure with increased resistance to fibrinolysis. Furthermore, there are several factors that can explain hyperfibrinogenemia in DM (44).

Fibrinogen synthesis occurs in the liver and different factors can determine a significant influence on fibrinogen production, including the most common comorbidities observed in patients with DM, such as dyslipidemia, obesity and non-alcoholic fatty acid diseases. The underlying mechanisms of diabetes, insulin resistance and hyperglycemia enhance hepatic fibrinogen synthesis. Considering that patients with DM have a low-grade inflammation, this leads to an additional increase of fibrinogen synthesized in hepatocytes. Previously, it has been proved that the quality of fibrinogen is modified in DM (45). An increased glucose level amplifies glycation of fibrinogen and disrupts the fibrinolytic process. The configuration of fibrinogen and fibrin can be modified by persistent inflammatory reactions and oxidative stress, contributing to clot durability. An important element in the coagulation process is thrombin, which converts fibrinogen into fibrin. In patients with DM, increased thrombin levels have been noticed, which cause an elevation in fibrin production and clot density, thus having an important impact in the prothrombotic status. Moreover, hyperinsulinemia and hyperglycemia stimulate prothrombin production in the liver (46).

A significant physio-pathological particularity of COVID-19 is the occurrence of a prothrombotic status. Increased levels of vWF, fibrinogen and D-dimer, a by-product of fibrin degradation, regulate the specific coagulopathy of COVID-19. Considerably higher D-dimer levels were consistently noticed in severely affected patients (47). D-dimer levels can reveal the need for mechanical ventilation and therefore constitute one of the most important laboratory parameters. If during hospitalization, extremely high levels or a progressive elevation are detected, the risk of complications and even death

Table I. Articles investigating the impact of metabolic imbalance on COVID-19 cases and pro-thrombotic changes.

First author	Study period	Region	Main findings	(Refs.)
Haowei Li	From February 4th to April 14th, 2020	Wu Han, China	This study includes 2,467 patients with COVID-19, 1,269 males and the average age is 59 years. Elevated D-dimer levels and higher fasting blood glucose is observed in 1,100 patients, thus demonstrating an increased risk for thrombosis. COVID-19 prognosis is considerably influenced by increased D-dimer and hyperglycemia, which exhibit a synergistic effect.	(54)
Stefania L. Calvisi	From April to May 2020	Milan, Italy	This study analyses 169 hospitalized patients with COVID-19 in which 51 patients have diabetes. Diabetes/stress hyperglycemia is associated with inflammation and tissue damage markers. An increased risk of thromboembolic events is linked to glucose variability.	(5)
Yogendra Mishra	From July 12th to August 31th, 2020	North India	In this study, patients with COVID-19 and diabetes exhibit D-dimer levels of 1509±2420 ng/ml and cases without diabetes 515±624 ng/ml. Patients with diabetes have greater D-dimer levels and these results are statistically significant.	(55)
Anees A. Sindi	From April to December, 2020	Jeddah, Saudi Arabia	This study reveals the impact of diabetes on mortality rates in patients with COVID-19. Including 198 patients, 86 are diabetic and 139 are males with a mean age of 54.14 years. Mortality rate is higher in diabetic patients and the most frequent comorbidity is hypertension.	(56)
Fien A. von Meijenfeldt	From April 9th to June 8th, 2020	Stockholm, Sweden	Patients with COVID-19 and respiratory support have elevated levels of D-dimer, fibrinogen, FVIII and vWF. Decreased levels of prothrombin, antithrombin, reduced number of platelets and higher levels of vWF factor are associated with short-term mortality.	(57)
Chaymae Miri	From November 01st to December 01st, 2020	Oujda, Morocco	In this analysis, 201 patients with COVID-19 are included, average age is 64 years and 56% are male. D-dimer levels are statistically higher in diabetic patients. D-dimer levels >2,885 ng/ml is a significant predictor of mortality in diabetic patients.	(58)
Hermina Novida	From May 1st to August 31th, 2020	Surabaya, Indonesia	This research includes 201 subjects, 108 are categorized as severe and 93 as non-severe COVID-19 cases. The average age is 55.69 years, diabetes onset is <10 years and most of the patients have hypertension, blood sugar levels of ≥200 mg/dl and HbA1c ≥8%. The presence of hypertension, HbA1c ≥8%, age ≥60 years and male sex are associated with severe COVID-19 in cases with diabetes.	(59)

COVID-19, coronavirus disease-19; vWF, von Willebrand factor; HbA1c, glycated haemoglobin.

are significantly increased. The high level of D-dimers can be suggestive for coagulation cascade activation and amplified thrombin generation (48). Decreased antithrombin levels were associated with inadequate outcomes in cases of SARS-CoV-2 infection, particularly among overweight individuals or individuals with obesity. A further aspect which is important in cases with SARS-CoV-2 infection is the antithrombin activity, which can be influenced, depending on the severity of the infection. As a result of the inflammatory status, the cytokine secretion is increased and is presumed to be the cause of the imbalance of the anticoagulant levels. An important association has been established between IL-6 and D-dimers levels, thus, the more the level of proinflammatory cytokine increases, the more the level of D-dimers elevates. As a result, this proves the connection between COVID-19-associated inflammation and procoagulant status. These outcomes shed light on the prothrombotic nature of SARS-CoV-2 infection, regarding both immuno-thrombosis and hemostasis (49). COVID-19-induced endothelial impairment affects the subendothelial TF and collagen, and as a result of the coagulation pathway activation and the aggregation of platelets, it starts thrombus development. In the coagulation process, several mechanisms act together, for instance, cytokine secretion with the help of neutrophil extracellular traps may promote aggregation of the platelets (fibrinogen and fibrin can activate neutrophils). Innate immunity may be triggered simultaneously by thrombin and factor Xa. Fibrinogen is considerably increased in patients with COVID-19, which reflects the inflammatory acute phase response (50). A meta-analysis of 34 studies revealed that increased D-dimer levels, low platelet count and prolonged prothrombin time occur more frequently in patients with severe COVID-19 (51). International Society on Thrombosis and Haemostasis released a guide for the management of coagulopathy in COVID-19 which recommends testing and monitoring of prothrombin time, D-dimer and fibrinogen levels, as well as the platelet count. Thrombin-antithrombin complex (TAT) and prothrombin fragment have also been measured in patients with COVID-19. In a comparison between the intensive care unit (ICU) patients with COVID-19 with non-ICU patients, the plasma levels of TAT where considerably higher in patients with severe condition and ICU necessity. To identify thrombotic manifestations, TAT was more determinative than D-dimer levels. In addition, vWF and FVIII are considerably elevated in patients with COVID-19 (52).

Considering all the aforementioned results, patients with COVID-19 should be investigated with extreme caution since this is a severe disease with various inflammatory and haemostatic abnormalities that are compatible with a prothrombotic status. Therefore, it can be assumed that if severe SARS-CoV-2 infection is combined with diabetes, the development of coagulopathy and multiple complications are more likely to occur, considering the important impact of DM on evolution and prognosis. In a recent review presenting the relationship between DM and COVID-19, it was emphasized that ever since the emerging of the virus, it was observed that patients with DM had a worse outcome when contracting SARS-CoV-2, presenting statistically higher rates of ARDS, organ damage, necessity of hospitalization in ICUs and higher mortality rates, regardless of the geographical area where the studies were performed (53). Some of the most relevant studies regarding the association between DM and COVID-19 that demonstrated the prothrombotic state observed in these patients are summarized in Table I (5,54-59).

A post-mortem study performed in patients affected by COVID-19 who also presented associated comorbidities, such as hypertension, chronic kidney disease, and metabolic diseases including diabetes, obesity and obstructive sleep apnoea, have shown specific organ damage at pulmonary and renal level, as well as small vessel injury (60). The aforementioned study has demonstrated that coagulation dysfunction is common in severe cases of SARS-CoV-2 infection, with thrombogenic microangiopathy being a frequent occurrence when autopsies were performed (60). In patients with DM, microvascular complications are a risk factor for severe COVD-19, as in these patients, endothelial dysfunction as well as microcirculatory impairments are present at organ level, including pulmonary microvascular lesions, which are responsible for a decrease in pulmonary diffusing capacity, which can be translated into a poor adaptability of the lungs in case of a SARS-CoV-2 infection (61). Therefore, the specificity of the lung injury and susceptibility to COVID-19 that affects life expectancy of patients with DM is also associated with the prothrombotic status.

6. Conclusions

Diabetes is the most common comorbidity in patients with SARS-CoV-2 infection. Considering that patients with DM have a low-grade chronic inflammation, the risk of developing an increased level of inflammatory cytokines is significantly higher in the presence of SARS-CoV-2 infection. As reflected by different pathophysiological mechanisms, patients with COVID-19 and diabetes are more likely to develop a hypercoagulable state, and are associated with severe disease and poor prognosis. An important feature of the relationship between DM and COVID-19 is the prothrombotic status, which is linked with a poor prognosis and higher mortality rate in these patients. Consequently, a growing understanding of the mechanisms involved in this association will contribute to an earlier diagnosis of thrombotic events as well as an early initiation of antithrombotic therapy, resulting in an improved outcome for patients with DM that develop COVID-19.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

RM, VP, AM, DT, MR, DC, AE, RP, TC and IV contributed equally to acquisition, analysis and classification of data, manuscript writing and for critical revision of the

manuscript for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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