

RESEARCH ARTICLE

Inflammation and vascular dysfunction: The negative synergistic combination of diabetes and COVID-19

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Abstract

Aims: Several reports indicate that diabetes determines an increased mortality risk in patients with coronavirus disease 19 (COVID-19) and a good glycaemic control appears to be associated with more favourable outcomes. Evidence also supports that COVID-19 pneumonia only accounts for a part of COVID-19 related deaths. This disease is indeed characterised by abnormal inflammatory response and vascular dysfunction, leading to the involvement and failure of different systems, including severe acute respiratory distress syndrome, coagulopathy, myocardial damage and renal failure. Inflammation and vascular dysfunction are also well-known features of hyperglycemia and diabetes, making up the ground for a detrimental synergistic combination that could explain the increased mortality observed in hyperglycaemic patients.

Materials and methods: In this work, we conduct a narrative review on this intriguing connection. Together with this, we also present the clinical characteristics, outcomes, laboratory and histopathological findings related to this topic of a cohort of nearly 1000 subjects with COVID-19 admitted to a third-level Hospital in Milan.

Results: We found an increased mortality in subjects with COVID-19 and diabetes, together with an altered inflammatory profile.

Conclusions: This may support the hypothesis that diabetes and COVID-19 meet at the crossroads of inflammation and vascular dysfunction. (ClinicalTrials.gov NCT04463849 and NCT04382794).

KEYWORDS

COVID-19, diabetes, inflammation, vascular dysfunction

1 | INTRODUCTION

In patients with coronavirus disease 2019 (COVID-19), older age and the presence of comorbidities are associated with poor outcomes.¹⁻⁴ Several reports indicate that diabetes is one of the most represented condition, and it is associated with higher fatality rate, especially if glucose control is inadequate.^{2,3,5-7} While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exerts a direct cytotoxic effect, evidence supports that COVID-19 pneumonia only accounts for a part of COVID-19 related deaths.² The disease is indeed characterised by abnormal inflammatory response and vascular dysfunction, leading to multi-organ involvement and failure.^{8,9} Inflammation and vascular dysfunction are also well-known features of hyperglycemia and diabetes,^{10,11} making up the ground for a detrimental synergistic combination.¹² The purpose of our review is to investigate this connection and to explain mechanisms underlying the increased mortality observed in diabetic patients with COVID-19, with the point-by-point support of findings from our cohort of nearly 1000 patients.

2 | METHODS

Data were collected from patients admitted for SARS-CoV-2 acute infection at ASST FBF-Sacco Milan, Presidio Sacco, from 1 February 2020 to 15 May 2020, in whom COVID-19 was confirmed by RT-PCR detection of SARS-CoV-2 in respiratory samples. All clinical data were extracted from patient electronic medical reports, and all research studies and analysis reported in this manuscript were performed in accordance with the local Ethical Research Committee of Milan (Comitato Etico Milano Area 1, Cobeta, SIDIACO, and registered as NCT04463849 and NCT04382794). Glycaemia was measured in each patient at admission to the emergency room, during in-hospital stay, and at the discharge from hospital. Patients were classified as diabetic patients (type 2 diabetes, T2D) based on a known history of diabetes or if they were on anti-diabetic medications. A magnetic microsphere-based Bio-Plex Pro Human Cytokine 17-plex immunoassay (#M5000031 YV) was used in the analysis of serum cytokine levels on a Bio-Plex 200 system (both from Bio-Rad) according to the manufacturer's instructions as already described.^{13,14}

3 | COVID-19 PREVALENCE AND OUTCOMES IN TYPE 2 DIABETES AND THE RELEVANCE OF GLYCEMIC CONTROL

Diabetes is reported to increase the susceptibility to infections and their complications^{15,16}; poor glycaemic control is a predictor of worse outcomes.¹⁷⁻²⁰ Impaired neutrophil chemotaxis and adherence to vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonisation, and cell-mediated immunity were described in patients with hyperglycemia and T2D, and could partially explain this increased susceptibility.²¹⁻²⁴ Viral infections may impair glucose balance,²⁵ and viral clearance resulted in an improved metabolic control.²⁶ An increase of cases among diabetic subjects were confirmed during Severe Acute Respiratory Syndrome (SARS) outbreak in 2003^{27,28} and Middle-East Respiratory Syndrome (MERS) outbreak in 2012²⁹; however, it is still not completely clear if this is the case for COVID-19. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) to enter the cell,^{30,31} and is capable of using human ACE2 as efficiently, if not more, as SARS coronavirus (SARS-CoV)³²; therefore, an enhanced ACE2 expression likely facilitates viral homing at target tissues in primary invasion sites.³³ Following entry into the pneumocyte, the virus replicates and ACE2 gets downregulated³⁴; this, together with the activation of ADAM-17 that detaches the catalytic active domain of ACE from the cell surface, leads to ACE2 depletion.³³ ACE2, the 'good' ACE, is a homologue of ACE that cleaves angiotensin II (AngII) to form Ang-(1-7) with a high catalytic efficiency, suggesting an important role in preventing AngII accumulation, while enhancing Ang-(1-7) formation,³⁵ and thus contributing to keep in balance the pro-oxidative effects of AngII in the vascular system, and also in pancreatic islets. ACE2 expression is sometimes reduced in subjects with diabetes³⁴ and the subsequent pro-inflammatory condition represents an important contribution to the development of vascular and renal diabetes complications.³⁶ In a recent study, a phenome-wide Mendelian randomisation suggested that diabetes and related traits may increase ACE2 expression, which could influence susceptibility to infection,³⁷ but these data need to be further confirmed. Some authors also speculated that potentially an aberrant glycosylation of ACE2 in the lung, nasal airways, tongue, and oropharynx in uncontrolled hyperglycemia may serve as increased SARS-CoV-2 viral binding sites and lead to a higher propensity to infection.^{38,39} However, glycosylation does not seem to be crucial for the SARS-CoV-2

receptor binding domain (RBD)/ACE2 interaction.⁴⁰ A lower ACE2 expression before infection indicates a more likely evolving imbalance between the pressor and counteracting depressor arm of the angiotensin family during COVID-19 infection predisposing to greater disease severity.³³ Two other major components of the renin-angiotensin-aldosterone system (RAAS) probably play an important role in disease development: the kinin-kallikrein and the chymase pathways; they both exert pro-inflammatory and procoagulant effects (via AT1R and BKB-1R, respectively), and BKB-1R is upregulated in subjects with diabetes.⁴¹ Diabetes severely increases the need for medical interventions and the mortality risk in subjects with COVID-19.^{1,42} In an early report⁷ of 193 patients with severe COVID-19, nearly 25% had diabetes, and 36% of non-survivors had diabetes versus 11% of survivors. Diabetic patients had almost double mortality compared to non-diabetic patients, together with higher rates of ICU hospitalisation and need of mechanical ventilation, when experiencing COVID-19.⁷ Also, in other reports with higher numbers of patients, subjects with diabetes showed worse outcomes compared to sex- and age-matched controls without diabetes, with hypertension and older age as independent contributors to in-hospital death.^{6,43} This was confirmed in our cohort (Figure 1), where diabetic subjects had an almost double mortality risk independent of age and sex (OR 1.876, 95% CI 1.250–2.850, $p = 0.0027$). Interestingly, we observed that higher mean glycaemic levels measured during hospitalisation in patients with T2D and COVID-19 may predict poorer outcomes as compared to subjects with a better glycaemic control (Figure 2). In a previous report, authors found that patients with hyperglycemia during hospitalisation, although with normal HbA1c, had higher mortality than subjects with a history of diabetes.⁴⁴ Stress-hyperglycemia is indeed known to be associated with worse outcomes, irrespective of pre-existing diabetes.^{45,46} With regard to this, other studies suggest that uncontrolled cardiovascular risk factors

may worsen the progression of COVID-19 more than previous history of major cardiovascular events with well-controlled metabolic risk factors.⁴⁷ In the CORONADO Study, in subjects with diabetes hospitalised for COVID-19, BMI, but not long-term glucose control, was positively and independently associated with tracheal intubation and/or death within 7 days.⁴⁸ The follow-up study indicated no association between BMI, HbA1c, and other comorbidities with negative outcomes, but showed that a history of microvascular complications, routine anticoagulant therapy, dyspnoea, and biological markers of COVID-19 severity are associated with a reduced chance of hospital discharge by day 28.⁴⁹ In agreement with this, Maddaloni et al. reported that cardiovascular disease (CVD) prevalence does not differ between people with diabetes with and without COVID-19 requiring hospitalisation, and described an increased prevalence of chronic obstructive pulmonary disease (COPD) and chronic kidney disease in COVID-19 patients with T2D.⁵⁰ In addition, the CovidiablI study provided a deeper view about cardiometabolic risk factors, and showed that subjects with cardiometabolic multimorbidity have higher risk of negative outcomes if compared to subjects without such conditions.⁵¹ Since all risk factors together contribute to the cytokine storm and therefore to disease severity, the metabolic unbalance at the moment of viral infection is probably crucial; subjects with diabetes present an increased risk of negative outcomes also because diabetes often clusters with other metabolic conditions. Of note, we recently demonstrated that the dipeptidyl peptidase-4 (DPP4) inhibitor sitagliptin, as an add-on therapy to standard of care, may improve clinical outcomes in patients with T2D and COVID-19⁵²; the effect may be linked to metabolic and inflammatory mechanisms.⁵³ However, other reports did not confirm these results.^{54–56}

4 | ALTERED INFLAMMATION IN COVID-19 AND DIABETES

Together with direct viral infection, an abnormal and aggressive inflammatory host response is strongly implicated in COVID-19 severity.⁸ Host cells infected by SARS-CoV-2 undergo pyroptosis, a highly inflammatory form of programmed cell death, and release damage-associated molecular patterns. As a consequence, epithelial cells, endothelial cells, and alveolar macrophages produce pro-inflammatory cytokines and chemokines (including IL-6, IL-1 β , IP-10, MIP1 α , MIP1 β , MCP1) that attract monocytes, macrophages, and T cells^{2,8} towards a Th1-polarized response.⁸ This pro-inflammatory feedback loop may be associated with vascular leakage, as seen in patients with SARS-CoV,⁵⁷ and is the trigger to a cytokine storm that can in some cases result in multi-organ failure. Consistent with these findings, some studies have reported the association of COVID-19 severity and elevated plasma levels of inflammatory markers, such as IL-6, IL-8, IL-1 β , IL-2, IL-2 R, IL-7, IL-17, IL-10, G-CSF, IP-10, MCP1, MIP1 α , and TNF α .^{2,58–60} Increased white blood cells and neutrophil count, lactate dehydrogenase, C-reactive protein, and D-Dimer are associated with poor prognosis too.⁵⁸ T-cells are instead decreased and exhausted in subjects with

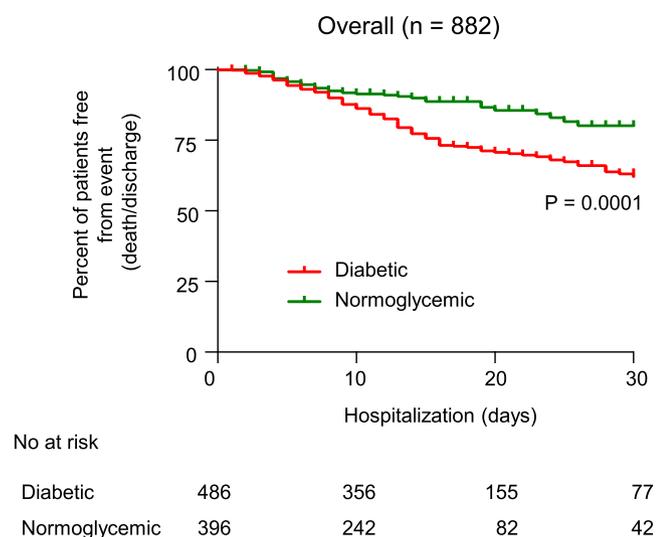


FIGURE 1 Time to endpoint analysis (death/discharge) in patients with type 2 diabetes ($n = 486$) or not ($n = 396$) and admitted to the hospital for COVID-19. Log-Rank (Mantel-Cox) analysis

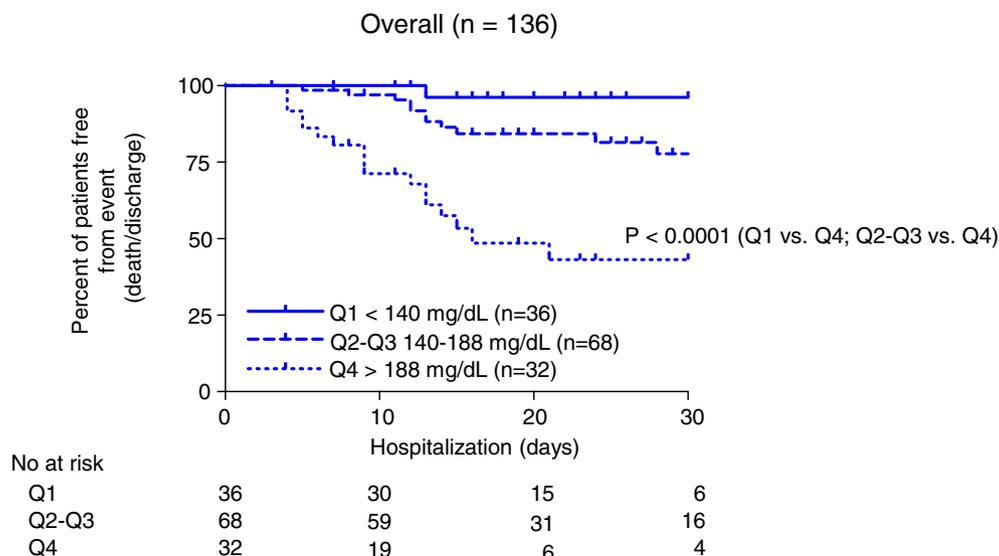


FIGURE 2 Time to clinical endpoint (death/hospital discharge) in all patients grouped according to quartiles of in-hospital mean blood glucose level (Q1 mean glycaemia < 140 mg/dl; Q2–Q3 mean glycaemia comprised between 140 and 188 mg/dl; Q4 mean glycaemia > 188 mg/dl). Log-Rank (Mantel-Cox) analysis

COVID-19, and reduced lymphocyte count is associated with worse outcomes.^{58,61} An underlying pro-inflammatory status is a typical feature of insulin resistance and T2D, and increased circulating levels of IL-6 and TNF α can be detected in diabetic patients.^{10,62} Some reports suggest that COVID-19 patients with diabetes show increased levels of some circulating cytokines compared to non-diabetic patients.^{7,43,63} Subjects with diabetes also show reduced lymphocyte count,⁴³ and a reduction of CD4⁺ and CD8⁺ T-cell was associated with lower survival rates.⁶ Our data showed an altered secretome in patients with T2D and COVID-19 as compared to those with COVID-19 but without T2D (Figure 3 and Figure S1). Particularly of interest are the increased levels of IL-1ra, IL-6, IL-8, MCP-1, IFN- γ , and IP-10 (Figure 3), which may explain the propensity to develop excessive inflammation after SARS-CoV-2 infection.

5 | VASCULAR DYSFUNCTION IN COVID-19 AND DIABETES

There is an inseparable link between inflammation and vascular dysfunction, and it seems particularly strong in patients with COVID-19.^{64,65} The endothelium is altered by SARS-CoV-2 infection: direct viral damage, the presence of inflammatory and vasoactive molecules, reduced ACE2 activity, and neutrophils activation determine the loss of its barrier function and lead to vascular leakage.⁶⁶ As a consequence, tissue oedema in pulmonary endothelium is the basis for acute respiratory distress syndrome propagation.^{66–68} Monocyte-derived tissue factor and PAI-1 are increased,^{69,70} and both the extrinsic and intrinsic coagulation pathways are involved.⁷¹ Patients with COVID-19 show a procoagulant pattern, with platelet activation and increased clot strength,⁷² and an increase in vascular complications, such as microvascular thrombosis, disseminated intravascular

coagulation, and venous thromboembolic events,^{73,74} together with a directly and indirectly increased cardiovascular risk.^{75–78} However, the lung pathology observed in these patients appears somehow distinct from the one usually observed in macrophage activation syndrome or disseminated intravascular coagulation; the suggested ‘diffuse pulmonary intravascular coagulopathy’ definition indicates an extensive lung immunothrombosis, as this condition mainly affects lungs, with reduced systemic bleeding risk.⁷⁹ Plasma levels of α -defensins, antimicrobial peptides released from activated neutrophils with antifibrinolytic and prothrombotic effect, were reported to be elevated during COVID-19⁸⁰; α -defensin is also increased in patients with diabetes,⁸¹ putting these subjects at greater risk of vascular dysfunction. Another feature in common between hyperglycemia and COVID-19 is represented by alterations of the glycocalyx. Endothelial glycocalyx is impaired in diabetic condition, and changes in the structure and function of the glycocalyx promote an inflammatory response.^{82–84} An undersulphated glycocalyx may not only increase susceptibility to SARS-CoV-2 infection, but would also result in a procoagulant and antifibrinolytic state associated with poorer outcomes.^{85,86} The competitive action of heparin with heparan sulphate, which is used by SARS-CoV-2 to adhere to vascular wall and to bind to ACE2, may explain some of the positive effects of heparin therapy in COVID-19. Insulin resistance and hyperglycemia affect vascular wall by a series of events.⁸⁷ Decreased nitric oxide bioavailability,⁸⁸ PI3-K/Akt pathway disorders,⁸⁹ increased cytokine levels,^{10,89} and platelet hyperactivity¹¹ altogether impair endothelial function. Hyperglycemia increases the production of reactive oxygen species, impairs the function of endothelial progenitor cells, and activates the protein kinase C, hexosamine, and polyol pathways,^{90–93} and a better glucometabolic control, as that obtained with successful islet transplantation, may improve vascular dysfunction.^{94–96} Interestingly, the vessel ultrastructure, as observed at electron microscopy, suggested

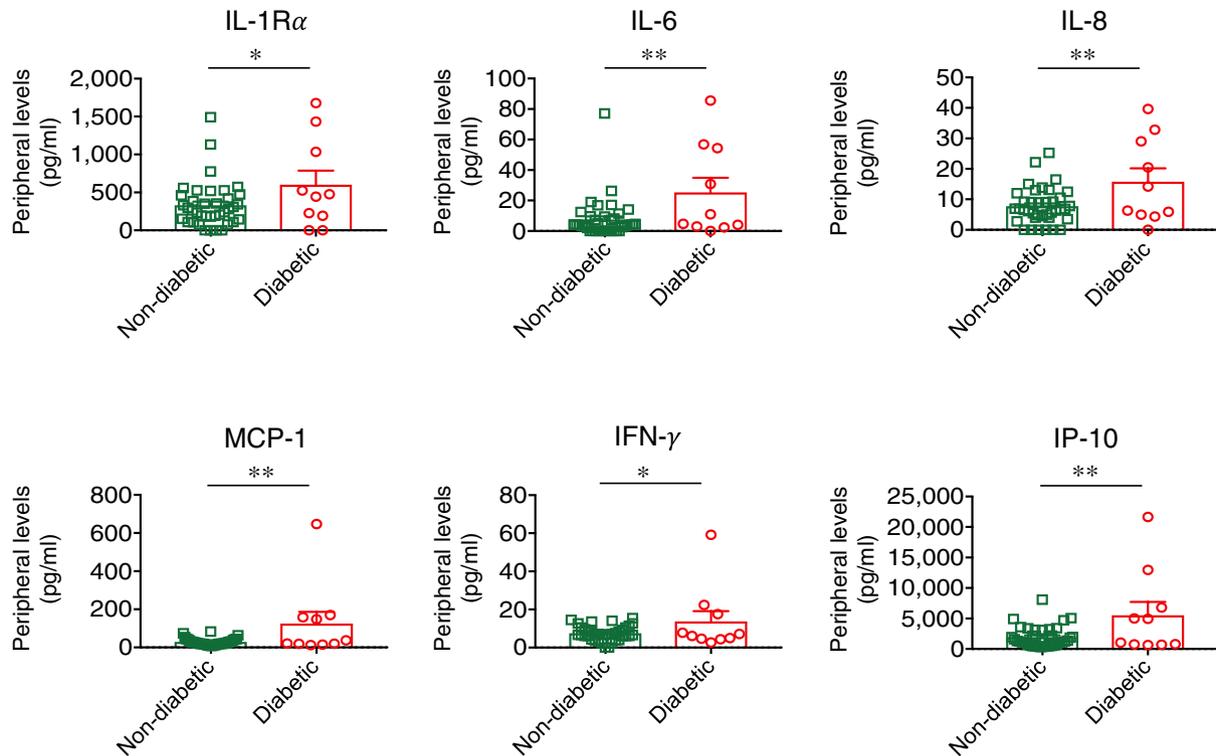


FIGURE 3 Differential plasma levels of peripheral cytokines in patients with type 2 diabetes ($n = 10$) or not ($n = 38$) and admitted to the hospital for COVID-19. Analysis performed by a Bio-Plex Pro Human Cytokine 17-plex immunoassay on a Bio-Plex 200 system (both from Bio-Rad). Two-tailed t -student test. * $p < 0.05$, ** $p < 0.01$

that COVID-19 induces wide abnormalities, somehow mimicking those observed in patients affected with T2D (Figure 4).^{97,98} Endothelial cells show extensive vacuolisation, an endothelial cell pyknotic nucleus, and Weibel-Palade granules loss. Skin capillary endothelial cells in patients with COVID-19 also show, contained in the vacuoles, some small vesicles that could be interpreted as viral particles (Figure 4).

6 | THE MOLECULAR LINK BETWEEN HYPERGLYCEMIA, INFLAMMATION, AND VASCULAR DYSFUNCTION

Hyperglycemia acutely increases circulating cytokine concentrations by an oxidative mechanism,¹⁰ and circulating levels of IL-6 and TNF- α are elevated in diabetic patients,^{62,99,100} with increased M1 macrophage polarization.⁸⁹ Insulin resistance and hyperglycemia also determine endothelial dysfunction and increased platelet activity.^{11,87,88,101} This makes up the ground for a detrimental synergistic combination with what is observed in COVID-19. After SARS-CoV-2 entry into the cells, innate immunity activation leads to the nuclear translocation of NF- κ B and interferon regulator factors, resulting in the secretion of type I interferons and pro-inflammatory cytokines/chemokines such as TNF α , IL-1, IL-6, CXC-chemokine ligands, and CC-chemokine ligands^{69,70}; higher monocyte-derived TF and PAI-1 expressions were also observed.^{70,72} This is exactly what we

observed in subjects with T2D and COVID-19 in our cohort: the increase in IL-6, IL-8, MCP-1, IL-1ra, IFN- γ , and IP-10 is the expression of an excessive Th1-polarized immune response. As a result, hyperglycemia may be responsible for an amplified pro-inflammatory and procoagulant milieu during SARS-CoV-2 infection, and therefore explain why diabetic people, especially if having poorly controlled blood glucose levels, have greater risk to develop a severe form of COVID-19 (Figure 5).^{5,6} Interestingly, Codo et al. also showed that SARS-CoV-2 replication and cytokine production in monocytes are promoted by elevated glucose levels through a mitochondrial ROS/HIF-1 α dependent pathway, which results in T cell dysfunction and epithelial cell death.¹⁰²

7 | TARGETING INFLAMMATION AND VASCULAR DYSFUNCTION IN COVID-19

Vaccination is the most effective strategy we nowadays have to prevent the severe forms of the disease,¹⁰³ and should for this reason be the priority. When facing the clinical course of COVID-19, improving inflammation and vascular dysfunction may represent an important strategy to reduce disease severity.^{65,104,105} Thanks to its anti-IL-6 action, tocilizumab, a monoclonal antibody, has been among the first agents considered for COVID-19 therapy: one first retrospective study suggested a reduced risk of invasive mechanical ventilation or death¹⁰⁶; treatment with this drug was also described

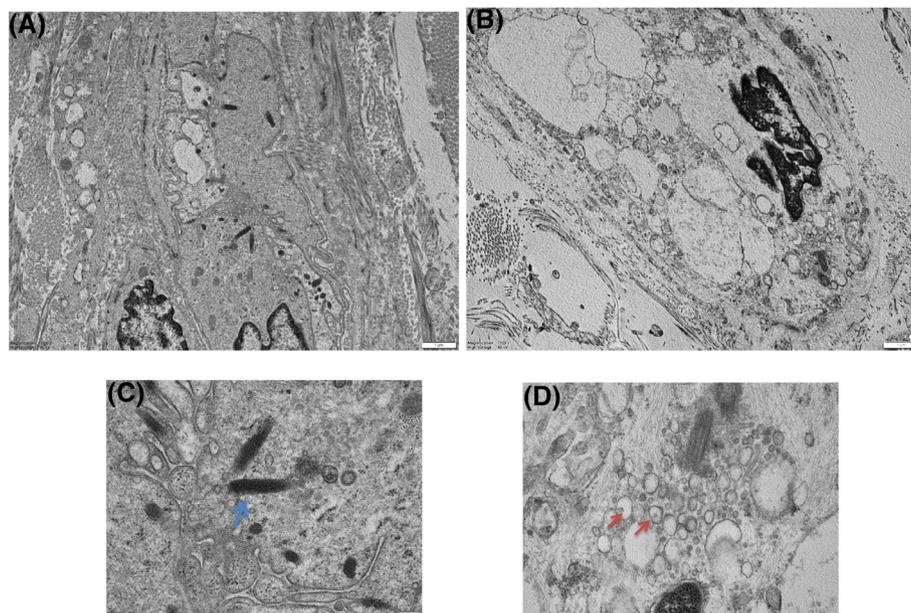


FIGURE 4 Electron microscopy of skin capillary sections in healthy control (Panels A and C) and in subject with COVID-19 (Panels B and D). Panel C: blue arrows indicate Weibel-Palade granules in endothelial cells. Panel D: red arrows indicate small vesicles within vacuoles

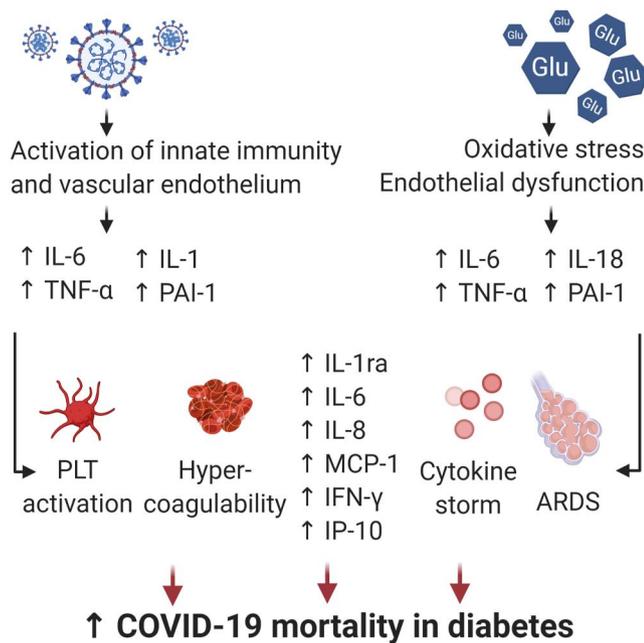


FIGURE 5 Excessive inflammation and vascular dysfunction are a key feature of both hyperglycemia and COVID-19, making up the ground for a detrimental synergistic combination. The increase of IL-1ra, IL-6, IL-8, MCP-1, IFN- γ , and IP-10 observed in subjects with type 2 diabetes and COVID-19 may contribute to explain the greater disease severity observed in diabetic patients

to improve endothelial dysfunction¹⁰⁷ and its efficacy in COVID-19 was reduced by hyperglycaemic state.¹⁰⁸ Unfortunately, a following randomized controlled trial did not confirm the efficacy.¹⁰⁹ In a small randomized controlled trial, a short course of methylprednisolone in hospitalised patients did not reduce mortality¹¹⁰; however, the larger RECOVERY trial indicates, in subjects requiring respiratory support,

improved outcomes with dexamethasone.¹¹¹ IL-1 blockade with anakinra showed promising results in severe forms of COVID-19,¹¹² and JAK inhibition with baricitinib was able to prevent disease progression by modulating the patients' immune landscape.¹¹³ Intriguingly, the cyclosporine-analog alisporivir has been shown to inhibit SARS-CoV2 in vitro,¹¹⁴ thus indicating a potential role of calcineurin inhibitors^{115,116}; blocking IL-17 could also provide a novel therapeutic strategy.¹¹⁷ Coagulopathy with prominent elevation of D-dimer is associated with high mortality. Considering also its anti-inflammatory action, anticoagulation with heparin is considered a paramount in COVID-19 therapy.^{118,119} Critically ill patients showed an increased incidence of venous thromboembolic events despite prophylaxis with low-molecular-weight heparin^{65,120} but, on the other hand, bleeding was recently described as a significant cause of morbidity.¹²¹ Prophylaxis with heparin is therefore recommended but the appropriate type, dose, and timing of administration is still debated.^{122,123} RAAS inhibitors do not increase the risk of severe COVID-19 outcomes and may be helpful to restore ACE1/ACE2 balance.¹²⁴⁻¹²⁷ Since in diabetic subjects a good glycaemic control is associated with better outcomes, normalising glycaemia is mandatory in all patients with COVID-19. Insulin is known to have some potential anti-inflammatory effects^{128,129} and is the drug of choice for hyperglycemia management in hospitalised patients.^{130,131} One interesting aspect regarding DPP4 inhibition: it was speculated that gliptins may reduce viral entry into the cells,^{53,132} and a recent study showed that treatment with sitagliptin is associated with reduced COVID-19 mortality,⁵² thus suggesting a potential therapeutic role in subjects with and without diabetes. On the other hand, other works suggested no effect of DPP4 inhibitors on COVID-19 clinical course.^{54,55} The reason may lie in the observational nature of available studies, the heterogeneity of data, and the resulting potential

biases. Thus far, evidence suggests that DPP4 inhibitors are safe but does not provide sufficient evidence to strongly recommend their use against COVID-19.⁵⁶

8 | CONCLUSIONS

Our data confirmed an increased COVID-19 mortality in subjects with diabetes, and a better glycaemic control during hospitalisation was associated with improved outcomes. COVID-19 severity is strongly related to an abnormal inflammatory response and a hypercoagulable state, and oxidative stress, cytokine release, and endothelial dysfunction are also a hallmark of hyperglycemia, making up the ground for a detrimental synergistic combination. This was confirmed by the observation of increased levels of IL-1ra, IL-6, IL-8, MCP-1, IFN- γ , and IP-10 in subjects with T2D and COVID-19 in our cohort, suggesting a propensity to develop excessive inflammation and endothelial dysfunction that may contribute to explain the greater disease severity observed in diabetic patients. COVID-19 was also recently shown to be associated with insulin resistance on an inflammatory basis.¹³³ For all these reasons, treating inflammation, preventing coagulopathy, and, importantly, normalising glycaemia should be a priority in these patients.

AUTHOR CONTRIBUTIONS

Andrea Mario Bolla reviewed literature, contributed to data collection and analysis, and wrote the manuscript. Cristian Loretelli, Giovanna Finzi, and Francesca D'Addio contributed to data collection and analysis. Ida Pastore, Reza Abdi, Moufida Ben Nasr, Joseph V. Bonventre, Manuela Nebuloni, Stefano Rusconi, Pierachille Santus, Gianvincenzo Zuccotti, and Massimo Galli critically reviewed the manuscript. Laura Montefusco and Maria Elena Lunati contributed to data collection and manuscript revision. Paolo Fiorina conceived the study, contributed to data collection and analysis, and wrote and edited the manuscript. Paolo Fiorina is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose related to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval was obtained by the local Ethical Research Committee of Milan (Comitato Etico Milano Area 1, Cobeta, SIDIACO, and registered as NCT04463849 and NCT04382794).

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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