Issues of Cardiovascular Risk Management in People With Diabetes in the COVID-19 Era

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People with diabetes compared with people without exhibit worse prognosis if affected by coronavirus disease 2019 (COVID-19) induced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly when compromising metabolic control and concomitant cardiovascular disorders are present. This Perspective seeks to explore newly occurring cardio-renal-pulmonary organ damage induced or aggravated by the disease process of COVID-19 and its implications for the cardiovascular risk management of people with diabetes, especially taking into account potential interactions with mechanisms of cellular intrusion of SARS-CoV-2. Severe infection with SARS-CoV-2 can precipitate myocardial infarction, myocarditis, heart failure, and arrhythmias as well as an acute respiratory distress syndrome and renal failure. They may evolve along with multiorgan failure directly due to SARS-CoV-2–infected endothelial cells and resulting endotheliitis. This complex pathology may bear challenges for the use of most diabetes medications in terms of emerging contraindications that need close monitoring of all people with diabetes diagnosed with SARS-CoV-2 infection. Whenever possible, continuous glucose monitoring should be implemented to ensure stable metabolic compensation. Patients in the intensive care unit requiring therapy for glycemic control should be handled solely by intravenous insulin using exact dosing with a perfusion device. Although not only ACE inhibitors and angiotensin 2 receptor blockers but also SGLT2 inhibitors, GLP-1 receptor agonists, pioglitazone, and probably insulin seem to increase the number of ACE2 receptors on the cells utilized by SARS-CoV-2 for penetration, no evidence presently exists that shows this might be harmful in terms of acquiring or worsening COVID-19. In conclusion, COVID-19 and related cardio-renal-pulmonary damage can profoundly affect cardiovascular risk management of people with diabetes.

Besides older age and male sex, diabetes in conjunction with other classic cardiovascular (CV) risk factors such as hypertension, obesity, and smoking has been found associated with adverse outcome in the coronavirus disease 2019 (COVID-19), a severe disease induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in studies from China, Europe, and the U.S. (1–5). Putting all evidence together, it is unfortunately not surprising that during the SARS-CoV-2 pandemic, people with diabetes have a worse prognosis, in particular those with poor metabolic control (1–4).

However, while it is still unclear whether people with diabetes are more prone to be infected by SARS-CoV-2 than people without diabetes (1–4,6), there is no doubt that when infected, they are more prone to have serious complications

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or to die (1–6). This finding may suggest that, more than diabetes itself, the problem might be related to the level of the metabolic control and the presence of comorbidities, particularly cardiovascular disease (CVD). Therefore, it is easy to understand why the prevention/management of CVD in COVID-19 is considered a key issue today (7).

CV Risk Management in People With Diabetes and COVID-19

Figure 1 suggests a diagnostic and management algorithm for dealing with diabetes and related cardiometabolic challenges in COVID-19. Importantly, the algorithm advises in the presence of diabetes and other cardiometabolic risk factors to assess the extent of concomitant pulmonary, cardiac, and renal status, together with the evaluation of related cardiometabolic biomarkers. If any organ damage is found, this may be preexisting and aggravated but also induced by COVID-19 (8)

Severe infection with SARS-CoV-2 can precipitate myocardial infarction, myocarditis, heart failure, and arrhythmias as well as an acute respiratory distress syndrome (ARDS) (8). Direct vascular-endothelial (9), myocardial, pericardial, and in particular extensive pulmonary infection; systemic proinflammatory stimulation (cytokine storm); hypercoagulability; increased sympathetic stimulation; and hypoxia in the context of ARDS (yet contrasted by a higher oxygen demand) can build up to rather complex disease processes and mosaics (8).

Renal failure is frequently seen in patients with multiorgan failure and may be due to infected endothelial cells and endotheliitis of the glomerular capillary loops directly caused by SARS-CoV-2 (9).

Most of the listed complications in Fig. 1 and the related biomarkers, especially high C-reactive protein, hs-troponin, brain natriuretic peptide (BNP)/N-terminal prohormone BNT (NT-proBNP), and D-dimer, have been shown to be associated with a more severe, if not fatal, outcome of COVID-19 (1–5,10–12).

Therefore, it is crucial to evaluate the extent of organ damage in people with diabetes and other cardiometabolic conditions if infected by SARS-CoV-2. Also, it has turned out that the classic CV risk management in patients with SARS-CoV-2 infections and COVID-19 is much more complicated and partially burdened by still unresolved issues and uncertainties (7). For example, increased levels of D-dimer (13), BNP/NT-proBNP (14), troponin (15), and inflammatory cytokines (16) have been reported to be present in diabetes, independent of any concomitant infection. This may imply that the use of these biomarkers to follow the evolution of COVID-19 in people with diabetes needs a careful evaluation.

The management of hypertension is a key issue, particularly in presence of diabetes and COVID-19. Hypertension is the most frequent comorbidity in people with a worse prognosis for COVID-19 (1–6). The issue about the management

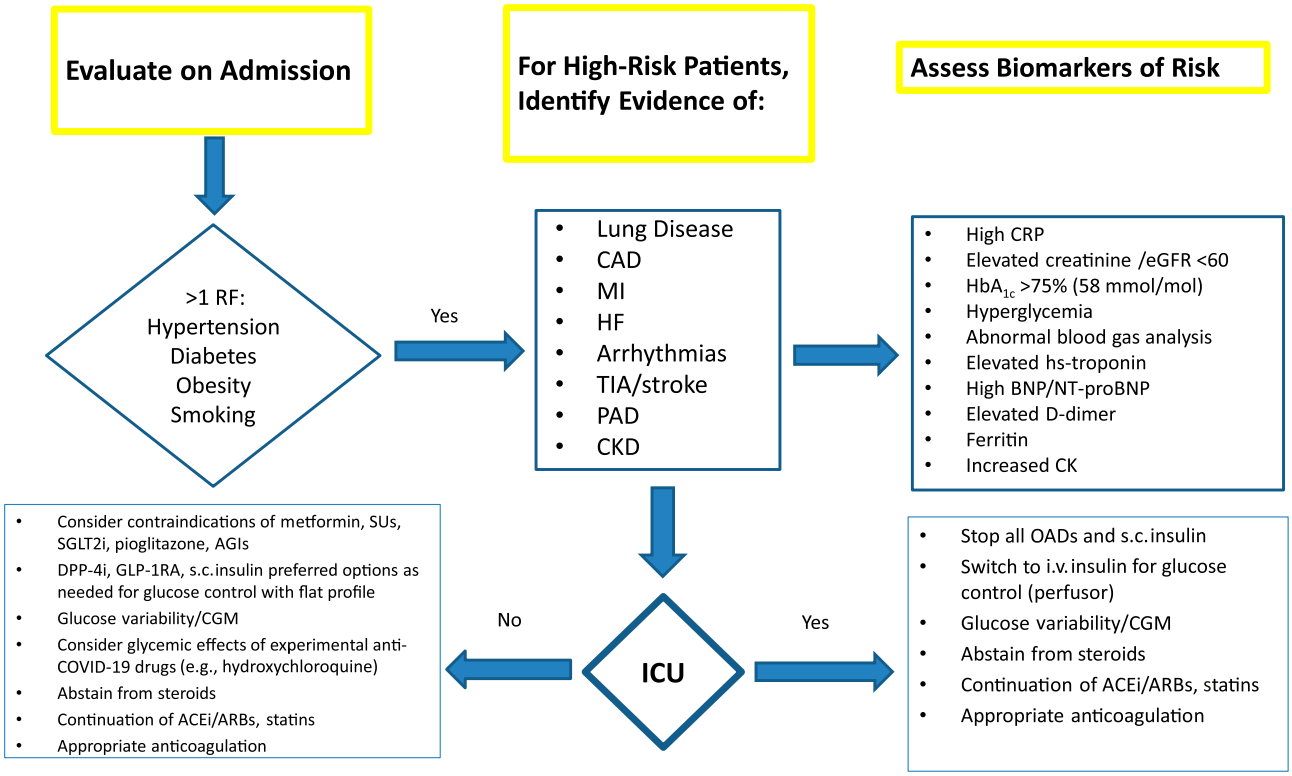

Figure 1—Hospitalized people with diabetes and COVID-19: a possible flowchart for the management based on the assessment of the related cardiometabolic status and CV risk factors predicting adverse outcomes. What is suggested in the flowchart is speculative but based on emerging understanding of the underlying mechanisms, and it provides the authors' current suggestions. AGI, α-glucosidase inhibitor; ACEi, ACE inhibitors; CKD, chronic kidney disease; CAD, coronary artery disease; CGM, continuous glucose monitoring; CRP, C-reactive protein; CK, creatine kinase; DPP-4i, DPP-4 inhibitors; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; OADs, oral antidiabetic drugs; PAD, peripheral artery disease; RF, risk factor; SGLT2i, SGLT2 inhibitors; TIA, transient ischemic attack.

of blood pressure is related to the possible effect of ACE inhibitors and angiotensin receptor blockers (ARBs) in favoring a worse COVID-19 outcome, particularly in diabetes (17). The problem was raised by the evidence that because SARS-CoV-2 utilizes ACE2 receptor to enter into host cells, particularly pneumocytes (18), and because both ACE inhibitors and ARBs can increase ACE2 expression (17), these drugs can potentially indirectly facilitate the penetration of the virus into the cells.

Quite understandably, the debate over the use of ACE inhibitors and ARBs in COVID-19 generated serious fears in the millions of people treated with these compounds. The prompt positioning of several scientific societies and also of the European Medicines Agency made a very important clarification, pointing out that no evidence was available to justify stopping the use of these drugs, which have been demonstrated to save millions of lives (19). Therefore, the recent data, showing not only the safety of both ACE inhibitor and ARB use in COVID-19 but also a potential benefit of these drugs, are very relevant (20).

In this context, it seems mandatory to also clarify similar pending issues for a number of glucose-lowering drugs (21).

The management of CV risk in diabetes has been recently addressed by the European Society of Cardiology Guidelines developed in collaboration with the European Association for the Study of Diabetes (22) and by the American Diabetes Association and European Association for the Study of Diabetes Consensus Report, "Management of Hyperglycemia in Type 2 Diabetes, 2018" (23). Both are clearly underlining the urgent need to prioritize particularly glucagon-like-peptide 1 receptor agonists (GLP-1RAs) and sodium–glucose transporter 2 (SGLT2) inhibitors in the management of CV risk in diabetes, independently of glycemic control and/or a history of a CV event (22,23).

However, exendin-4 increases cardiac ACE2 expression in rats (24), while liraglutide increases ACE2 expression in cardiac and pulmonary cells in type 1 diabetic rats (25). Even if the evidence is not available yet, it is realistic to believe that this could be a GLP-1RA class effect. Similarly, the promotion of ACE2 activity by SGLT2 inhibitors has been proposed as a plausible mechanism of renal and CV protection with this class of drugs (26,27).

In addition, it is worth mentioning that pioglitazone (28) and metformin (29) have also been shown to upregulate ACE2. Furthermore, although no direct effect on ACE2 has been reported, insulin treatment has been shown to attenuate renal A disintegrin and metalloproteinase 17 (ADAM-17) expression in diabetic mice (30). In normal physiology, ADAM-17 cleaves ACE2, thereby inactivating the enzyme (30). Whether the same phenomenon is replicated in human pneumocytes is not known. On the other hand, it should be noted that pioglitazone (31), SGLT2 inhibitors (32), GLP-1RAs (33), and also insulin (34) have shown anti-inflammatory activities, which might be very helpful for patients with COVID-19.

Finally, the use of dipeptidyl peptidase 4 (DPP-4) inhibitors in the present scenario deserves detailed discussion. DPP-4 inhibitors target the enzymatic activity of DPP-4, a glycoprotein expressed ubiquitously in many tissues, including immune cells. DPP-4 activates T cells and upregulates CD86 expression and the NF-κβ pathway, thereby promoting inflammation (35). Hence, inhibition of DPP-4 has given rise to concerns regarding a possible increase in the risk of infections (35). Some meta-analyses have identified an increased risk of nasopharyngitis and urinary tract infection, while others have negated this finding (35). Although SARS-CoV-2 does not require DPP-4, the potential anti-inflammatory role of DPP-4 inhibitors raises questions as to whether DPP-4 modulation might help offset the cytokine-mediated acute respiratory complications of COVID-19 (35).

Another aspect to consider involves optimal management of hyperglycemia. Hyperglycemia seems to increase the risk of infection by SARS-CoV-2 (36) and to worsen the prognosis of COVID-19 (37). Optimal glycemic control must be considered an important target of diabetes management, particularly during COVID-19 (15). A recent opinion is that starting the management of diabetes with a combination therapy is more effective than starting with monotherapy (23,38). In this endeavor, it seems helpful for the time being (see Fig. 1) to strictly consider the contraindications of diabetes medications (37,38), as those may evolve along with a more severe disease process and progression of COVID-19.

Hypoxia increases the risk of lactic acidosis and limits the use of metformin. Rapidly occurring kidney failure likewise prohibits the use of metformin; it also prohibits use of most sulfonylureas (SUs) and DPP-4 inhibitors as well as SGLT2 inhibitors and α-glucosidase inhibitors. Moreover, the risk of diabetic ketoacidosis and hypovolemic events with SGLT2 inhibitors will be increased under these circumstances. Developing heart failure challenges the use of pioglitazone, and severe hypoglycemia may complicate the treatment with SUs. Hence, continuous glucose monitoring may become a key issue (39,40), especially in patients with more severe SARS-CoV-2 infection, together with monitoring of renal function, blood gases including pH and oxygen saturation, and signals for emerging heart failure, coagulation, and progressive inflammation (Fig. 1). Preferred options as needed for glucose control with low glucose variability comprise DPP-4 inhibitors in the absence of contraindications, GLP-1RAs, and subcutaneous insulin (Fig. 1). Also, experimental anti–COVID-19 drugs such as hydroxychloroquine, lopinavir/ritonavir, and atazanavir may affect glucose control, with hydroxychloroquine increasing the risk of hypoglycemia, while others may exhibit diffuse drug-drug interactions with diabetes medications, both in terms of increased but also decreased exposure with the resulting related impact on glycemia (41,42). Moreover, several GLP-1RAs may reduce the exposure to atazanavir (42). In aggregate, careful consideration and glycemic monitoring seem mandatory when experimental anti–COVID-19 drugs are used in people with diabetes.

Management of Hyperglycemia and CV Risk in People With Diabetes During Hospitalization in ICU for COVID-19

Mounting evidence is showing that hyperglycemia at the presentation in the hospital for COVID-19, even in people without diabetes, is linked to a higher risk of admission to the intensive care unit (ICU) and a worse prognosis (37,43). This, somehow, is not surprising because it is well known that acute hyperglycemia during the stay in ICU is accompanied by a dramatic increase of inflammation, which in turn can precipitate an acute CV event (44).

Figure 1 also deals with COVID-19 patients with diabetes requiring intensive care including respiratory support or external oxygenation. Concerning diabetes management, a key issue is how glycemia is managed during hospitalization for COVID-19 in ICU. Unfortunately, it is not surprising that patients suffering from COVID-19 with hyperglycemia may have a higher risk of a poorer outcome compared with those with euglycemia (37,43,45,46). We also have to keep in mind that diabetes management is not easy to handle in severely sick people. Therefore, when facing high glucose levels due to severe infection per se, it is required that patients are switched to insulin. Insulin treatment might not always be safely managed in such situations, unless it is administered intravenously via an exact dosing perfusion device to avoid subcutaneous absorption irregularities in critically ill patients (47). For this reason, appropriate glycemic management during the COVID-19 pandemic has been a big challenge (48,49).

Due to the stress induced by SARS-CoV-2 infection and to the inappropriate glycemic management during hospitalization, patients may suffer from extreme glycemic excursions (48,49). This means that people with diabetes may experience not only extreme glycemic swings during hospitalization but also peaks of hypoglycemia and hyperglycemia. Hypoglycemia has been shown to potentiate host's innate immune reaction to endotoxins by mobilizing proinflammatory monocytes with negative consequences on CV mortality (50). Furthermore, how recovery from hypoglycemia is achieved might be dangerous: hyperglycemia post-hypoglycemia is also an issue, leading to an enhancement of inflammation (51). Hyperglycemia has been known for decades to make people susceptible to infections per se by increasing the concentration of several toxic intracellular by-products of the glycolytic pathway (52). This means that despite trying to do their best for infected people, COVID-19 units may unintentionally end up making the disease more serious because of glycemic variability (53).

During severe influenza virus infection, pulmonary lesions and mortality are driven by massive cytokine and adhesion molecule release by pulmonary endothelial cells that allows the uncontrolled extravasation of leukocytes in the alveolus, thus severely damaging respiratory function (9). Glucose variability during the hospitalization may amplify these phenomena (53), worsening the prognosis. Also deserving attention is the fact that high glycemic variability is predictive per se of high ICU mortality (54). Therefore, it has already been suggested that the management of glucose variability has to be part of the more comprehensive approach to the management of hyperglycemia today: it seems that this must be urgently applied in ICUs (53).

Even though we understand that in such a critical situation this request is not easy to implement, we believe that the best possible action to prevent a worse outcome is essential in any medical act. Nevertheless, it is quite surprising that recent guidelines specifically developed for the management of people with COVID-19 in ICUs do not consider diabetes and glycemic management at all (55).

As outlined in Fig. 1, the following approach is recommended: intravenous insulin administration, if therapy is required for glycemic control, should be implemented using exact dosing with a perfusion device aiming at a blood glucose target between 140 and 180 mg/dL (7.8–10.0 mmol/L) (56). All other diabetes medications including subcutaneous insulin should be stopped to avoid potential dosing irregularities or serious drug side effects (see the previous paragraph). Continuous glucose monitoring should be applied to enable glucose control with low variability in the intended target range (39,40,56). Use of steroids should probably be avoided (55), as they do not seem overly effective in COVID-19 but rather may severely offset stable glycemic control. Blood pressure control should target a range for systolic blood pressure between 125 and 140 mmHg and for diastolic below 85 mmHg with continuation of ACE inhibitors or ARBs, as currently emphasized by all international authorities and scientific associations as well as very recent data (19,20). Continuation of statin therapy is informed by monitoring creatine kinase in plasma, as profound increases of this muscle enzyme have been described in cases with COVID-19 with concomitant rhabdomyolysis.

The thrombotic risk also deserves particular attention in diabetes. People with diabetes are more prone to thrombotic events (57), and data are showing that during COVID-19, a thrombotic event is a quite frequent complication. There are already specific recommendations (for example, the Mount Sinai COVID-19 Anticoagulation Algorithm [58]) about the management of the thrombotic risk during COVID-19, recommendations which probably have to be implemented as soon as possible in people with diabetes and COVID-19. It is also worth mentioning that good management of hyperglycemia and particularly of any acute increase of glycemia or glucose variability may reduce the risk for a thrombotic event (57).

Finally, the risk for acute heart failure must be considered. A large percentage of people with diabetes have asymptomatic heart failure (14), which can be precipitated during COVID-19. Therefore, special consideration to this aspect seems also very relevant.

CVD, DIABETES, AND COVID-19: PERSPECTIVES

It is likely, unfortunately, that humankind will have to face recurrent phases of SARS-CoV-2 infection in the future. Diabetes increases COVID-19 severity, particularly when CVD is already present (1–8). Therefore, in perspective, there are some actions that probably must be implemented to preserve people with diabetes from the risk related to SARS-CoV-2 infections. Implementing the current guidelines on the prevention of CVD in diabetes appears to be one of these urgent actions, more so than ever in the past.

Emerging as an acute infectious disease, COVID-19 may become a chronic epidemic similar to influenza because of genetic mutation. Therefore, we should be ready for the reemergence of COVID-19. Considering that CVD represents the leading epidemic in diabetes, it is mandatory to set long-term strategies not only aiming to avoid the infection but also to have people with diabetes in the best CV conditions if infected.

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