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Mini Review

Prognostic factors in patients with diabetes hospitalized for COVID-19: Findings from the CORONADO study and other recent reports

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ABSTRACT

Diabetes mellitus is challenging in the context of the COVID-19 pandemic. The prevalence of diabetes patients hospitalized in intensive care units for COVID-19 is two- to threefold higher, and the mortality rate at least double, than that of non-diabetes patients. As the population with diabetes is highly heterogeneous, it is of major interest to determine the risk factors of progression to a more serious life-threatening COVID-19 infection. This brief review discusses the main findings of CORONADO, a prospective observational study in France that specifically addressed this issue as well as related observations from other countries, mainly China and the US. Some prognostic factors beyond old age have been identified: for example, an increased body mass index is a major risk factor for requiring respiratory assistance. Indeed, obesity combines several risk factors, including impaired respiratory mechanics, the presence of other comorbidities and inappropriate inflammatory responses, partly due to ectopic fat deposits. While previous diabetic microvascular (renal) and macrovascular complications also increase risk of death, the quality of past glucose control had no independent influence on hospitalized diabetes patient outcomes, but whether the quality of glucose control might modulate risk of COVID-19 in non-hospitalized diabetes patients is still unknown. In addition, no negative signs regarding the use of RAAS blockers and DPP-4 inhibitors and outcomes of COVID-19 could be identified. Hyperglycaemia at the time of hospital admission is associated with poor outcomes, but it may simply be considered a marker of severity of the infection. Thus, the impact of glucose control during hospitalization on outcomes related to COVID-19, which was not investigated in the CORONADO study, is certainly deserving of specific investigation.

Introduction

The prevalence of diabetes in patients with COVID-19 (Coronavirus Disease 2019), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has varied across countries, ranging from 5–20% in China, 17% in Lombardy in Italy and 33% in the US [1–4]. Diabetes can modulate host–viral interactions and host–immune responses *via* several mechanisms that could also lead to poorer outcomes (see Muniyappa and Gubbi for a review [5]). Of major clinical importance, all studies have so far reported a two- to threefold higher prevalence of diabetes in patients with severe infections requiring admission to intensive care units (ICU) and invasive ventilation compared with those with less severe infection, as well as an increased mortality rate in patients with diabetes (Table 1) [6–14].

However, diabetes patients constitute a highly heterogeneous population in terms of type of diabetes, duration of disease, quality of glucose control, presence of diabetic complications, interference of comorbidities such as obesity and hypertension, and type of glucose-lowering therapy, among others. Which of these different factors could be playing a significant role in the final prognosis of diabetes patients hospitalized because of COVID-19 is virtually unknown in the absence of large prospective studies to address this crucial question.

In fact, the available data in the literature are rather scarce, and some reports have only considered prognostic factors based on theoretical grounds [15]. One small retrospective single-centre observational study in China analyzed the clinical characteristics and outcomes of 48 severe COVID-19 patients with diabetes [16], and found that survivors of COVID-19 with diabetes did not differ

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Table 1
Risk of poor clinical outcomes and death in diabetes patients with COVID-19 infection.

References	Studies (n) (n of patients)	Poor composite outcomes HR/OR (95% CI)	Death HR/OR (95%CI)% CI)
Observational studies			
Zhou et al., 2020 [6]	One, Wuhan, China (191)	NA	2.85 (1.35–6.05)
Guan et al., 2020 [7]	One, nationwide, China (1500)	1.59 (1.03–2.45)[a]	NA
Meta-analyses			
Li et al., 2020 [8]	Three (1278)	2.21 (0.88–5.57)[b]	NA
Roncon et al., 2020 [9]	Four (1380/354)	2.79 (1.85–4.22)[b]	3.21 (1.82–5.64)
Fadini et al., 2020 [10]	Six, China (1687)	2.26 (1.47–3.49)[c]	NA
Yang et al., 2020 [11]	Seven (1576)	2.09 (0.89–4.82)[c]	NA
Zheng et al., 2020 [12]	11 (2570)	3.68 (2.68–5.03)[d]	NA
Huang et al., 2020 [13]	30 (6452)	2.38 (1.88–3.03)[e]	2.12 (1.44–3.11)
Wang et al., 2020 [14]	31 (6104)	2.61 (2.05–3.33)[c]	NA

HR: hazard ratio; OR: odds ratio; CI: confidence interval; NA: not available
[a] Intensive care unit (ICU), ventilation or death.
[b] ICU admission.
[c] severe COVID-19 infection.
[d] mortality/critical events.
[e] mortality, severe COVID-19 infection, acute respiratory distress syndrome (ARDS), need for ICU care, disease progression.

significantly from non-survivors with diabetes in prevalence of associated comorbidities, including hypertension, cardiovascular disease (CVD) and chronic pulmonary disease. Indeed, survival was independent of overall glycaemic control, as assessed by glycated haemoglobin (HbA_{1c}) on hospitalization. However, given the very small number of patients, this analysis has to be interpreted with caution. In the largest series of 5700 patients hospitalized with COVID-19 in New York City in the US, it was only mentioned in passing that, of the patients who died, those with diabetes were more likely to have received invasive mechanical ventilation or care in the ICU compared with those without diabetes, with no further information provided regarding the characteristics of those diabetes patients [17].

One key question is whether diabetes is a risk factor for COVID-19 infection and poorer outcomes because of the deleterious role of hyperglycaemia on immune responses and defence against infections [18], the multiple complications associated with diabetes, especially CVD and/or renal disorders, and the comorbidities frequently encountered, such as obesity, hypertension and obstructive sleep apnoea, in the type 2 diabetes (T2D) patient population [19]. Furthermore, the potential interference of certain medications frequently prescribed for diabetes patients are also worthy of attention [19,20]: renin–angiotensin–aldosterone system (RAAS) blockers have been suspected to facilitate intracellular penetration of SARS-CoV-2 [21]; and dipeptidyl peptidase (DPP)-4 inhibitors can interfere with the immune response [22].

Thus, identifying the risk factors of progression to serious life-threatening COVID-19 infection is a key step that would allow preventative strategies in the diabetes population to limit the incidence of traumatic outcomes, such as the need for tracheal intubation for mechanical ventilation or death.

Findings from CORONADO

The CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcomes) study was a large-scale nationwide (68 French centres) observational study of patients with diabetes hospitalized for COVID-19 carried out in March 2020 [23]. Its main objective was to identify the clinical and biological characteristics associated with disease severity and mortality in patients with diabetes in hospital because of COVID-19. The primary outcome combined tracheal intubation for mechanical ventilation and/or death within 7 days of hospital admission. Individual components of the primary outcome were considered a pre-specified secondary outcome, as was also hospital discharge by day 7.

An intermediate analysis recently published in *Diabetologia* [23] focused on 1317 participants (admitted during 10–31 March 2020 at 53 centres) who were predominantly T2D patients (88.5%), with a gender distribution of 35% female vs. 65% male. Their mean age was 69.8 years and median body mass index (BMI) was 28.4 kg/m^2. Microvascular (including chronic kidney disease) and macrovascular complications were found in 46.8% and 40.8% of patients, respectively, and a medical history of hypertension was identified in 77.2% (57.1% were using RAAS inhibitors). Their mean glycated haemoglobin (HbA_{1c}) level was 8.1 ± 1.9% (65 ± 21 mmol/mol), and their routine glucose-lowering medications mostly comprised metformin (56.6%), insulin therapy (38.3%) and DPP-4 inhibitors (21.6%).

The composite primary outcome was noted in 29.0% of participants, while 10.6% died and 18% were discharged by day 7. Whereas, on univariate analyses, several characteristics at admission were significantly associated with the primary outcome (higher BMI, male gender and previous treatment with RAAS blockers, the latter two of only borderline significance), on multivariable analyses, only BMI remained positively associated with the primary outcome [odds ratio (OR): 1.28; 95% confidence interval (CI): 1.10–1.47]. Of note, however, this association was largely driven by tracheal intubation rather than death. Moreover, the increased risk of the primary outcome appeared to be less in patients with grade-3 obesity (BMI $\geq$ 40 kg/m^2) than in those who were overweight (25–29.9 kg/m^2) or with grade 1–2 obesity (BMI 30–39.9 kg/m^2).

It was also noteworthy that age, history of microvascular and macrovascular complications, decreased estimated glomerular filtration rate (eGFR) and comorbidities such as treated obstructive sleep apnoea were all independently associated with risk of death by day 7 (OR: 2.14–2.80). Age played a major role (OR: 14) when diabetes patients > 75 years of age were compared with diabetes patients < 55 years of age. Previous long-term glucose control, as assessed by HbA_{1c} measurement, was not significantly associated with the primary outcome, unlike early clinical (dyspnoea) and biological [elevated C-reactive protein (CRP)] markers of more severe disease. In fact, in age- and gender-adjusted non-linear models, plasma glucose concentrations at admission were significantly and positively associated with both the primary outcome and death by day 7. However, the negative impact of admission ambient glucose concentrations was no longer significant on multivariate analysis. It is also worth noting that diabetes-related disorders with severe hyperglycaemia, including ketosis and ketoacidosis, and also hypoglycaemic events were reported at the time of admission.

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In conclusion, the CORONADO study confirmed the severity of the prognosis for COVID-19 infection in people with diabetes, as 20.3% of the study population required tracheal intubation for mechanical ventilation, and the mortality rate was 10.6% as early as 7 days after admission. On multivariate analysis, an increased BMI (already starting in the overweight range) was the only independent prognostic factor of COVID-19 severity, as assessed by the composite primary outcome in this large cohort of diabetes patients. Of major importance, however, having a history of vascular diabetes complications and treated obstructive sleep apnoea significantly increased the risk of death. In contrast, parameters of previous or admission glucose control and routine pharmacological therapies, including RAAS blockers and DPP-4 inhibitors, were not independently associated with such a prognosis.

Unanswered questions

At this time, CORONADO is the largest published observational study specifically focused on the characteristics of diabetes patients hospitalized for COVID-19 infection. It was designed to address three main objectives:

- to characterize the phenotype of patients with diabetes hospitalized for COVID-19;
- to determine the prevalence of poor prognoses using a primary outcome combining death and tracheal intubation for mechanical ventilation within the first 7 days of hospital admission; and
- to identify any prognostic factors associated with early severity of COVID-19 in this specific in-patient diabetes population, a key step towards implementing preventative strategies to reduce the risk of life-threatening outcomes.

However, numerous factors may interfere with the relationship between COVID-19 infection and poor outcomes in patients with diabetes (Fig. 1). The present discussion focuses only on the three that merit particular interest and which mostly concern patients with T2D, who represented 88.5% of patients included in the CORONADO study [23]. The number of patients with type 1 diabetes (T1D) was deemed too small from which to draw any definite conclusions in this patient subgroup.

Role of diabetic complications and glucose control

Although vascular diabetic complications did not significantly influence the composite primary outcome, they were significantly associated with death in the CORONADO cohort [23]. This is not surprising, as it is well established that both CVD and renal impairment are associated with higher death rates in the diabetes population in both long-term and acute conditions, such as those encountered with severe COVID-19 infection [14]. In addition, besides causing severe pneumonia, it is well known that the SARS-CoV-2 coronavirus can induce cardiovascular complications [8,24] and acute renal injury [25,26], making it highly plausible that these detrimental complications are likely to be more frequent and severe in such predisposed patients.

One question of interest is the potential role of glucose control on outcomes related to COVID-19 in patients with diabetes. This crucial point should be analyzed according to three separate periods:

- prior to admission (assessed by HbA_{1c} measurement);
- at the time of hospital admission (indicated by concomitant plasma glucose concentrations); and
- during the hospital stay (Fig. 1).

An important message of the present results of CORONADO is that previous glucose control has no significant impact on severity of COVID-19 in people with diabetes who require hospitalization. Indeed, HbA_{1c} levels were associated with neither the composite

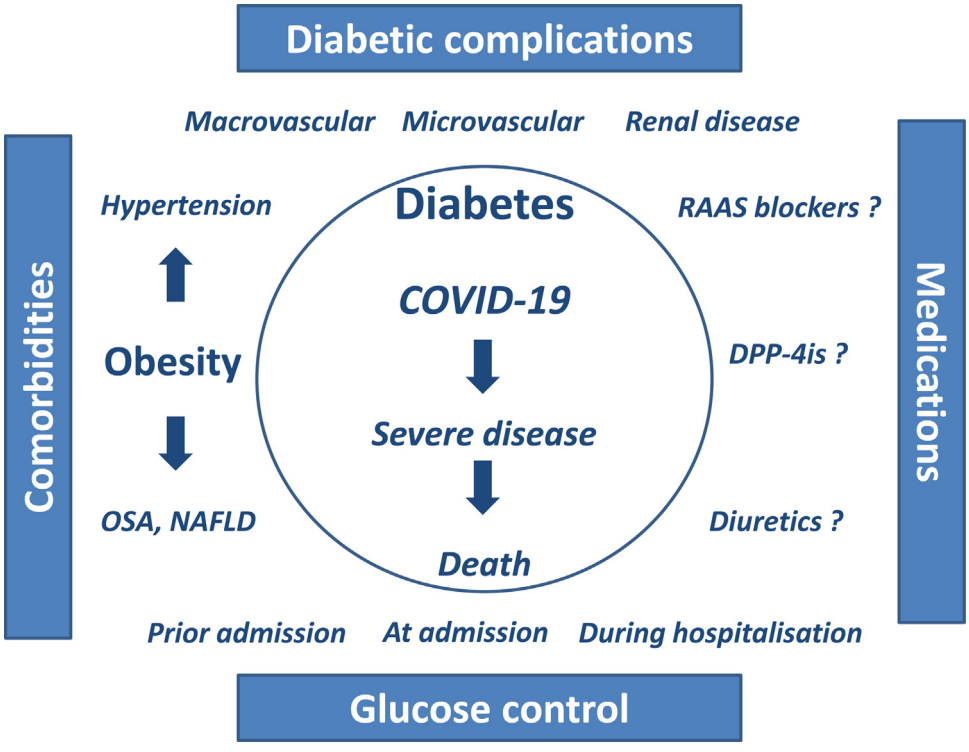

Fig. 1. Factors that may have an impact on outcomes of COVID-19 (Coronavirus Disease 2019) infection in patients with diabetes as per the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study and others. RAAS: renin–angiotensin–aldosterone system; DPP-4is: dipeptidyl peptidase-4 inhibitors; OSA: obstructive sleep apnoea; NAFLD: non-alcoholic fatty liver disease.

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primary outcome nor the death rate [23]. Such results may seem surprising as chronic hyperglycaemia has long been known to damp down the immunological defences of diabetes patients [18,27]. However, caution is still required, as HbA_{1c} measurements were missing in about one-third of the studied population. Thus, it would appear to be most prudent to wait for the final analysis of CORONADO in an even larger cohort before drawing any definite conclusions as to the role of patients' past glucose control on final outcomes. Moreover, as CORONADO was focused on hospitalized patients with diabetes, it is still not known whether poor glucose control might favour the occurrence of less severe COVID-19 infection in diabetes patients not requiring hospitalization.

Similarly, while plasma glucose concentration at admission was not significantly correlated with the primary outcome on multivariate analysis, in age- and gender-adjusted non-linear models, admission plasma glucose concentrations were significantly and positively associated with both the primary outcome and death by day 7. Nevertheless, this observation relied upon only one glucose measurement, which was not performed under standardized conditions across all study patients (for example, venous vs. capillary glucose, fasting vs. postprandial, variable time delay from last administration of glucose-lowering medication, especially insulin ...). Thus, here again, caution is required in the interpretation of these data. It may be speculated that, at least in some patients, acute hyperglycaemia at admission could be linked to disease severity and stressful conditions, especially if hypoxia and respiratory distress (dyspnoea at hospital admission was associated with the primary outcome) were already present. Thus, plasma glucose at admission could be considered an early marker of disease severity.

Also of potential interest, it was previously reported that the SARS coronavirus may be able to enter pancreatic islets through its ACE2 receptor, thereby causing damage to beta cells and leading to acute diabetes [28]. However, whether or not there is a reverse causality relationship between COVID-19 infection and acute hyperglycaemia remains speculative, as this question cannot be answered by any observational study (such as CORONADO).

One important aspect not considered at all in the CORONADO study was the management of diabetes and quality of glucose control during hospitalization (from admission to day 7). Attention to good glucose control was recently recommended [29] and demonstrated in a large study of 7337 cases of COVID-19 (of which 952 had preexisting T2D) [30]. In that retrospective observational study from China, patients with well-controlled blood glucose (range: 3.9–10.0 mmol/L) during hospitalization experienced markedly lower mortality compared with those with poorly controlled blood glucose [upper limit of glycaemic variability: $>$ 10.0 mmol/L; adjusted hazard ratio (HR): 0.14, 95% CI: 0.03–0.60; $P = 0.008$]. Previous studies done before the COVID-19 pandemic had shown that the quality of glucose control during hospitalization in ICUs for an acute event (cardiovascular surgery, myocardial infarction ...) could influence the final outcome, although controversial results were reported concerning optimal target levels of glycaemia [31,32]. Nevertheless, there is some consensus for maintaining blood glucose concentrations at 4–10 mmol/L in diabetes patients hospitalized in ICUs as well as in those now with COVID-19 [33].

However, even if the impact of glucose control during the hospitalization of diabetes patients with COVID-19 has yet to be prospectively investigated, the need for diabetes care customized for ICUs has been strongly suggested to help healthcare providers who are already overwhelmed by the dramatic pandemic situation and the need to support other vital functions, thereby potentially exposing patients with diabetes to poorer management of their specific disease [34]. Likewise, it has also been suggested that individualized care strategies, novel therapeutic regimens and the use of modern diabetes technology might help to reduce the clinical inertia hampering proper diabetes management in ICUs, a situation that could lead to poor glucose control and potentially worse outcomes for patients with diabetes and COVID-19 infection [35].

In fact, diabetes patients with COVID-19 have to control their glucose levels in a situation with more variable, and often decreased, food intakes, while also being confronted with a severe infection generally accompanied by fever and a cytokine-mediated insulin-resistant state. In addition, as already mentioned, it is also possible that the SARS coronavirus can penetrate into pancreatic islets and damage beta cells, thereby aggravating the course of diabetes and triggering acute hyperglycaemia [28]. Thus, COVID-19 represents a double threat to patients with diabetes. The difficulty of controlling diabetes in such a setting has been confirmed by, on the one hand, the rather large number of ketoacidosis episodes already reported [36] and, on the other hand, the episodes of hypoglycaemia most probably due to an unanticipated lack of food, two metabolic adverse events reported at hospital admission in the CORONADO cohort [23].

Role of antihypertensive and antidiabetic medications

Many patients with diabetes are treated with RAAS blockers as either antihypertensive agents or for nephroprotection. In the CORONADO study, 57.1% of the diabetes cohort received such pharmacotherapy. Yet, there has been some controversy in the literature over the possible negative, neutral or even positive impact of RAAS blockers on risk associated with these medications when administered to COVID-19 patients [20,37,38]. However, CORONADO has provided reassuring results, as RAAS blockers were not associated with the primary outcome according to multivariable analysis [23]; these observations are in agreement with the results of other studies [21,39,40] and support the recommendation not to stop RAAS blockers in diabetes patients possibly exposed to SARS-CoV-2 infection [41]. Also, as discussed by the authors, the negative impact of diuretics reported in the study could be attributed to the more severe baseline condition of patients suffering from heart failure or more severe hypertension.

The final question is whether or not glucose-lowering medications could differentially affect the risk of COVID-19 infection and more severe outcomes [42,43], although there are still many uncertainties in seeking answers [19]. A similar concern as that discussed with RAAS blockers has been raised over the use of DPP-4 inhibitors [20,22], although no worse signs were reported among the 21.6% of patients treated with such agents in the CORONADO cohort. The increased risk associated with insulin was probably due to the fact that the use of this pharmacotherapy reflects more advanced diabetes disease in patients who are often older and more frail [44]. The possible protective role of metformin has been proposed based on theoretical grounds, and the pleiotropic effects of the compound have yet to be investigated in clinical practice [45]. Of note in CORONADO, however, fewer of the people who died were using metformin. It has also been hypothesized that dapagliflozin (not available in France until only recently) can prevent the severe course of COVID-19 infection by preventing the lowering of cytosolic pH and reducing the viral load [46]. A large international randomized controlled trial is currently underway to investigate the potential role of dapagliflozin in both diabetes and non-diabetes patients with COVID-19 (Dapagliflozin in Respiratory Failure in Patients with COVID-19; ClinicalTrials.gov identifier: NCT04350593). In ICUs, the proper use of insulin therapy is, without question, the mainstay therapy [33]. Nevertheless, in view of the major interest raised by COVID-19 in the diabetes population, it is anticipated that dedicated observational studies, and possibly randomized controlled trials, will be designed

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in the near future to investigate the various positive and/or negative influences of the available glucose-lowering agents in patients with T2D when exposed to SARS-CoV-2 coronavirus [47].

Role of obesity

The frequent concurrence of both diabetes and obesity may confound, or at least complicate, identification of the independent role of either condition on its own. The negative effects of obesity on the severity of COVID-19 [48] and the need for invasive mechanical ventilation [49,50] have already been reported independently of the presence of diabetes. In addition, the CORONADO study has confirmed the deleterious role of obesity, and even overweight, in life-threatening outcomes in a large diabetic (mainly T2D) population with COVID-19 [23]. On multivariate analyses, BMI remained the only prognostic factor for the composite primary outcome. The negative impact of obesity on outcome was largely driven by its effect on tracheal intubation for mechanical ventilation whereas its effect on mortality was considerably lower. While death is an unequivocal outcome, mechanical ventilation depends on both the physician's decision and patient's acceptance.

It remains unclear as to why obesity aggravates COVID-19 severity and markedly increases the need for tracheal intubation for mechanical ventilation [49], although several underlying mechanisms may be considered. Obese patients have impaired respiratory mechanics resulting from a combination of poor respiratory muscle strength, reduced lung volume, increased airway resistance and impaired gas exchange. In addition, more subtle yet complex interactions may arise between adipose tissue and the immune system [48,51]. For instance, an overexpression of inflammatory adipokines from visceral fat depots can affect the immune response, impair chemotaxis and alter macrophage differentiation [52]. In addition, the inflammatory response of visceral, but also thoracic (epicardial and mediastinal), fat deposits can lead to an upregulation and greater release of inflammatory cytokines such as interleukin (IL)-6 [5]. It has been suggested that adipose tissue in people with obesity may act as a reservoir for more extensive viral spread and increased shedding, immune activation and cytokine amplification [53]. Indeed, it has even been hypothesized that excess fat might lead to the possible presence of ectopic fat deposits in the alveolar interstitial space that is exposed to viral infection. This, in turn, could aggravate the inflammatory infiltrate, a phenomenon that could then contribute to the massive oedema observed in COVID-19 patients who require mechanical ventilation [50].

Moreover, obesity is associated with an increased risk of comorbidities, such as hypertension, renal impairment, obstructive sleep apnoea [54] and non-alcoholic fatty liver disease (NAFLD) [55], all conditions that can aggravate the prognosis [14]. Of particular interest, in the CORONADO cohort, obstructive sleep apnoea was found to be an independent risk factor of early death, as were also elevated levels of aspartate transaminase (AST). While a previous history of NAFLD was not associated with the primary outcome, the elevated AST levels noted at admission may have been a reflection of liver cytolysis directly due to SARS-CoV-2 infection [56] or related to multiple-organ damage secondary to hypoxia, a systemic cytokine storm and/or haemodynamic shock [14,57]. In fact, AST elevation has more frequently been observed in severe forms of COVID-19 infection, especially during hospitalization [56]. In a longitudinal retrospective cohort study of 5771 patients with COVID-19 in China, abnormal AST levels were associated with the highest mortality risk compared with other indicators of liver damage, with an HR of 4.81 with AST levels of 40–120 U/L and an HR of 14.87 when AST was $>$ 120 U/L [58]. In a meta-analysis of 13 studies involving a total of 3027 patients with SARS-CoV-2 infection, AST $>$ 40 U/L was associated with an OR of 4 for critical/fatal COVID-19 [12]. The findings of CORONADO are in line with such observations.

Taking BMI into account even in a population with diabetes might improve risk stratification, thereby allowing for more effective selection of the diabetes patients who are most likely to require early hospital admission and stricter safety measures to minimize their increased risk of developing more severe complications. However, not all studies reported the same BMI cut-off in association with greater risk of severe complications related to COVID-19. In CORONADO, a higher risk had already been observed in overweight patients with diabetes. However, an increased risk for the primary outcome appeared to be less pronounced in diabetes patients with grade-3 obesity (BMI $\geq$ 40 kg/m^2). The authors considered this observation to be in agreement with the so-called "obesity paradox" previously reported in ICUs in patients exposed to severe respiratory distress syndromes. Nevertheless, researchers in a French study reported higher risks if BMI was $\geq$ 35 kg/m^2 [49], whereas one US study [59] reported an even higher risk if BMI was $\geq$ 40 kg/m^2 as did another large US study [60] in cohorts of COVID-19 patients not specifically focused on diabetes. In fact, it has been suggested that COVID-19 may be a challenge to the "obesity paradox" [61], although more data from patients with morbid obesity (BMI $\geq$ 40 kg/m^2) are as yet required to support this conclusion [48].

Thus, there is clearly a need for more evidence to raise awareness of what BMI score should be considered the cut-off for an increased risk of severe illness as a result of COVID-19 [62]. In addition, whether such a cut-off might differ in patients with and without diabetes also requires further investigation. In any case, given the potentially critical role of body weight and fat mass in determining the severity of pneumonia requiring respiratory assistance, it is important to systematically collect anthropometric information from patients hospitalized with COVID-19 [63]. One noteworthy suggestion is that obesity could shift severe COVID-19 infections towards younger age groups [64,65]. Indeed, it may be speculated that a similar shift occurred in patients with diabetes in the CORONADO cohort (about one-third of whom were aged $<$ 65 years), although direct comparison with a non-diabetes population remains mandatory to confirm such an hypothesis.

Ultimately, if obesity plays a crucial role, then therapeutic actions targeting adipose tissue could help to reduce the burden of COVID-19 disease, including in the large cohort of patients with T2D [51]. Likewise, if adipose tissue related to obesity plays a deleterious role in the excessive immune reaction and inflammation, then diabetes patients with obesity might benefit to a greater extent from a pharmacological therapy that modulates cytokine activity, especially IL-6, and/or the complement system [50]. As such, tocilizumab has been proposed as a therapeutic option for compassionate use in patients with COVID-19 [66]. A recent observation has found that hyperglycaemia, both at admission and during the hospital stay, was associated with higher IL-6 levels and a reduced efficacy of tocilizumab, leading to poorer outcomes in COVID-19 patients regardless of the presence or not of known diabetes [67]. However, further studies are now necessary to confirm this finding.

Conclusion

Diabetes is one of the more important comorbidities linked to the severity of infection by SARS-CoV-2. The CORONADO study was designed to characterize the phenotype of patients with diabetes hospitalized for COVID-19, to determine the prevalence of the need for mechanical ventilation or death and to identify the prognostic factors associated with poorer outcomes. As the first such

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large-scale observational study, it has undoubtedly provided a major piece of the complex puzzle linking diabetes and COVID-19 infection: some prognostic factors have been identified, focusing on BMI in relation to the need for respiratory assistance and the presence of previous diabetes complications associated with risk of death. However, other answers still require further analyses in even larger cohorts, especially in order to reassess the influence of previous glucose control based on larger numbers of HbA_{1c} measurements, which means that the final results of the CORONADO study are awaited with great interest. In addition, the impact of glucose control during hospitalization on outcomes related to COVID-19—which was not investigated in CORONADO—is certainly deserving of specific investigation. Moreover, the results of certain pharmacological therapies currently under investigation to improve the prognosis in high-risk populations, such as diabetes patients, are also likely to be available in the near future.

Disclosure of interest

André J. Scheen declares that he has no competing interest.

Michel Marre worked as a clinical investigator in the CORONADO study and declares no conflicts of interest directly relevant to the content of this manuscript. He is President of the *Fondation Francophone pour la Recherche sur le Diabète* (FFRD), a financial sponsor of the CORONADO study; the FFRD is sponsored by the *Fédération Française des Diabétiques*, Novo Nordisk, MSD, Eli Lilly, Abbott Laboratories and AstraZeneca.

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