Does glycemic control rescue type 2 diabetes patients from COVID-19-related deaths?

Coronavirus SARS-CoV-2, which induced the novel coronavirus disease 2019 (COVID-19), mainly invades the respiratory tract and lungs. Severe cases infected by SARS-CoV-2 progress to acute respiratory distress syndrome, septic shock and multiple organ dysfunction syndrome, which lead to death in some patients. Diabetes is the second most frequent comorbidity, next to cardiovascular disease, of adult inpatients who have died from COVID-19 in Wuhan, China.

Guo et al. investigated COVID-19 patients with diabetes, but no other comorbidities, who were admitted to Wuhan Union Hospital, Wuhan, China (n = 24). They found higher risks of increased severity of pneumonia and mortality with increased inflammatory responses, including higher levels of interleukin-6 and coagulation index, D-dimer, than in COVID-19 patients without other comorbidities, including diabetes (n = 26; Table 1).

Chen et al. compared the clinical and laboratory characteristics between groups with and without diabetes in a retrospective study involving 904 patients with COVID-19 (136 with diabetes, mostly type 2 diabetes) aged 15–99 years who were admitted to the Central Hospital of Wuhan, Wuhan, China. Laboratory data characteristics among those with confirmed COVID-19 with diabetes included a higher number of neutrophils, elevated levels of D-dimer and urea, and lower albumin than among those with confirmed COVID-19 without diabetes. Diabetes was the second most frequent comorbidity among all COVID-19 patients in that study. Comorbidities with the highest frequencies among all patients included hypertension (30.2%), diabetes (15.0%), cardiovascular disease (10.1%), nervous system disease (5.8%), chronic kidney disease (4.7%) and chronic lung disease (2.4%). Comorbidities with a high odds ratio of poor prognosis risk were nervous system disease (odds ratio [OR] 7.63, P < 0.001), chronic kidney disease (OR 7.23, P < 0.001), cardiovascular disease (OR 3.63, P < 0.001), hypertension (OR 2.50, P < 0.001), chronic lung disease (OR 2.48, P = 0.060) and diabetes (OR 2.21, P < 0.001). Multivariable regression showed that older age, lower albumin, elevated C-reactive protein and elevated glucose were independent risk factors for mortality among all COVID-19 patients. In COVID-19 patients with diabetes, older age (adjusted OR 1.09, P = 0.001) and elevated C-reactive protein (adjusted OR 1.12, P = 0.043) were independent risk factors for mortality. Insulin use was associated with poor prognosis (OR 3.58, P = 0.009). However, we need to evaluate the association of the high use of insulin with poor prognosis very cautiously, as diabetes patients with severe infection preferably used insulin in the hospital. In fact, none of the glucose-lowering medications (metformin, insulin, α-glucosidase inhibitor, secretagogues or dipeptidyl peptidase-4 inhibitors) were associated with inhospital death.

In a larger-scale retrospective study, Zhu et al. reported the association of blood glucose control and outcomes in type 2 diabetes patients with COVID-19. They carried out a retrospective, longitudinal, multicenter study from a cohort of 7,337 COVID-19 patients aged 18–75 years with (952 participants) or without (6,385 participants) diabetes in hospitals in China. COVID-19 patients with type 2 diabetes had significantly increased medical interventions and mortality risk. After adjusting for age, sex, indicators of the severity of COVID-19 and hospital site on admission, the hazard ratio of all-cause mortality in the type 2 diabetes group was 1.49 (P = 0.005). The adjusted hazard ratios of the occurrence of acute respiratory distress syndrome, acute kidney injury and septic shock in the type 2 diabetes group were 1.44 (P < 0.001), 3.01 (P < 0.001) and 1.95 (P = 0.009), respectively.

Next, the authors divided the type 2 diabetes group into two further groups: the well-controlled blood glucose (BG) group (median BG 6.4 mmol/L, glycemic variability range 3.9–10.0 mmol/L) and poorly-controlled BG group (median BG 10.9 mmol/L, lowest blood glucose ≥3.9 mmol/L and highest 2-h postprandial glucose >10.0 mmol/L). They found that the necessity of medical interventions and the mortality risk of patients with COVID-19 was increased by poor glycemic control among type 2 diabetes patients. In contrast, well-controlled BG correlated with improved survival rates for COVID-19 patients with type 2 diabetes accompanied by higher lymphocyte counts, lower neutrophil counts, and lower serum levels of interleukin-6, C-reactive protein and lactate dehydrogenase (Figure 1). The adjusted hazard ratio, including comorbidities, of all causes of mortality in patients from the well-controlled BG group was 0.13 (P < 0.001).

Although it is well known that better glycemic control decreases diabetic complications in type 2 diabetes patients, the
mechanism by which poor glycemic control is associated with the increased mortality risk of diabetes patients with COVID-19 is still unclear. The impairment of immune defense by poor glycemic control will be the probable first-line mechanism. In addition, Ackermann et al.5 recently published a noteworthy study that showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes, in the lungs of patients who died from COVID-19-associated respiratory failure. They found that alveolar capillary microthrombi were ninefold higher in patients with COVID-19 than those of patients who died from influenza. Inherently, the pathogenesis of diabetic complications—both micro- and microvascular complications—is vascular disorder, and high glucose impairs the function of vascular endothelial cells. Poorly-controlled BG-related vascular endothelial dysfunction might be involved in the increased mortality of diabetes patients with COVID-19. As the sample size of that study was small, further larger-scale studies are expected to explore the mechanism of the aggravation in COVID-19.

COVID-19 patients with diabetes have been reported to have higher mortality compared with non-diabetic COVID-19 patients; however, recent investigations showed the importance of better glycemic control to avoid death from COVID-19. To date, multiple variance analysis has shown that there are no significant differences in the mortality of diabetes patients with COVID-19 taking different glucose-lowering agents.

**DISCLOSURE**

The author declares no conflict of interest.

Keiko Naruse*
Department of Internal Medicine, School of Dentistry, Aichi Gakuin University, Nagoya, Japan
REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA 2020; 323: 1239.

2. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020; 31: e3319.

3. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care 2020; 43: 1399–1407.

4. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020; 1: 30238–30232.

5. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endotheliitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2015432

Doi: 10.1111/jdi.13320