EDITORIAL

Does glycemic control affect outcome of COVID-19?

Diabetes is associated with adverse outcome of coronavirus disease 2019 (COVID-19). In a whole-population study of a UK data set of >60 million persons, approximately 5% had diabetes, but of 23 698 in-hospital COVID-19-related deaths in this population, 33.2% were of people with diabetes, with mortality rates among persons those with type 1 and type 2 diabetes approximately 5-fold and 10-fold greater than that in the nondiabetic population; with adjustment for age and other risk factors, type 1 and type 2 diabetes were associated with near tripling and doubling of mortality rates, respectively.[1]

We define diabetes by the presence of hyperglycemia, but we also know that, even among persons not known to have diabetes, the development of hyperglycemia in the setting of infection, trauma, surgery, or a cardiovascular event is associated with adverse outcome. It is then logical to ask whether the adverse outcome of COVID-19 among persons with diabetes is related to the degree of hyperglycemia and, if so, whether this represents a causal relationship or rather shows that the severity of illness in a given individual with diabetes leads to both higher blood glucose concentration and greater likelihood of mortality. So far, reports from different data sets are somewhat contradictory.

The same whole-population UK data set reported that, compared with those having glycated hemoglobin (HbA1c) 48-53 mmol/mol (6.5-7.0%), COVID-19-related mortality with HbA1c of 86 mmol/mol (10.0%) or more was 2.23 fold greater among persons with type 1 diabetes, and among those with type 2 diabetes, mortality with HbA1c 59-74 (7.6%-8.9%), 75-85 (9.0-9.9), and ≥86 (10.0%) was increased 1.22, 1.36, and 1.61-fold, respectively.[2] A different UK data set of >17 million adult National Health Service patients gave an adjusted mortality hazard ratios of 1.31 and 1.95 among those with diabetes having HbA1c <7.5% and ≥7.5%, respectively.[3]

Specific hospitalized patient data sets, however, do not show that prior glycemic control, as reflected in HbA1c, are associated with different likelihood of adverse outcome among persons with diabetes. In an Iranian hospital, 24 persons with HbA1c 6.5-7 had a similar mortality rate (21%) to that of 93 persons (23%) with HbA1c 8%-11.2%.[4] In analysis of 1317 persons with diabetes hospitalized for COVID-19 in France, the outcome of tracheal intubation or death by day 7 was not associated with HbA1c level on admission, although there was a linear correlation with admission plasma glucose, as well as with body mass index.[5] Another study, of 1279 persons with diabetes hospitalized for COVID-19 in New York, showed no association of mortality with HbA1c on admission, whereas obesity, as well as increasing age and male sex and increasing complexity of outpatient diabetes treatment, were again associated with greater likelihood of adverse outcome.[6]

What can we conclude from the discrepancy between the population and hospital data sets? Conceptually, several sets of mediators of adverse COVID-19 outcome may exist among persons with diabetes (Box 1). There may be a direct risk associated with hyperglycemia. Hyperglycemia may, however, be a marker of stress of illness. The risk seen among persons with diabetes may be because of insulin resistance, inflammation, hypercoagulation, or underlying obesity. And diabetes is associated with cardiovascular disease, chronic kidney disease, dyslipidemia,

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BOX 1   Potential mediators of adverse COVID-19 outcome in diabetes

Hypothesis	Implications
Direct increased risk from hyperglycemia	Goal: normalize glycemia (subhypothesis: adverse outcome proportionate to degree of hyperglycemia)
Hyperglycemia as marker of metabolic stress	Severity of illness rather than glycemia per se causing adverse outcome
Risk because of obesity, insulin resistance, inflammation, or hypercoagulation	Glycemia per se may not directly lead to adverse outcome
Diabetes as marker of associated illnesses	Cardiovascular disease, chronic kidney disease, dyslipidemia, hypertension, etc. rather than glycemia per se as actual mediators

hypertension, and a variety of other conditions, which may mediate adverse outcome.

Certainly, glycemic control matters, and we have learned a great deal about practical approaches to optimizing glycemia during hospitalization with COVID-19.[7] Whether or not glycemia is the direct mediator, the disturbing association of diabetes with adverse outcome of COVID-19 is of great concern and must inform our ongoing approach to the care of our patients.

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