Commentary

Diabetes and sepsis outcomes – it is not all bad news

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Abstract

Patients with diabetes mellitus have an increased risk of developing infections and sepsis. In this issue of *Critical Care* Esper and colleagues report on a large survey, involving 12.5 million sepsis cases, that examined the impact of pre-existing diabetes on organ dysfunction during sepsis. Their main conclusion was that diabetes patients, relative to non-diabetics, were less likely to develop respiratory failure and more likely to develop renal failure during the course of sepsis.

Most physicians recollect cases where patients with diabetes had trivial injuries or infection, but rapidly progressed to life threatening sepsis and death. Although such clinical experiences may suggest that diabetes is associated with more severe infections and poor outcomes, observational studies have shown conflicting results. The interaction between diabetes, a chronic condition, and an acute infection is complex. Most studies suggest that diabetes increases susceptibility to infection. However, its effect on outcomes of infection, especially in the critical care setting, is less clear.

In this issue of *Critical Care*, Esper and colleagues [1] have added to our current understanding of organ dysfunction during severe sepsis by comparing the incidence of different organ dysfunctions in patients with sepsis who did and did not have diabetes. There are several key findings of this study. First, diabetes was associated with higher risk of acute kidney injury (13% versus 7%) and lower risk of acute respiratory failure (9% versus 14%); the latter association, suggesting a protective effect of diabetes, is intriguing and in line with an earlier study showing that diabetes is associated with lower risk of acute lung injury in patients with septic shock [2]. Second, contrary to clinical perception, Esper and colleagues show that diabetes was associated with lower case-fatality (18.5% versus 20.6%), likely due to lower risk of acute respiratory failure, which is often associated with worse survival [3]. These results would suggest that diabetes may have no effect or reduce mortality after infection. Indeed, results of epidemiologic studies to determine the effect of diabetes on short-term mortality after infection are conflicting [4-7].

The current study demonstrates complexities of understanding interaction between diabetes and outcomes of infection. Diabetes is a multifaceted disease and abnormalities include immune dysfunction and metabolic derangements, including hyperglycemia. Furthermore, these patients often have a higher burden of chronic conditions, such as cardiovascular and chronic kidney disease [8], and therapies used in diabetics, such as insulin, statins and thiazolidinediones, together with diabetes associated immune abnormalities [9,10], may influence the host response to infection and outcomes. A clear answer to which factors influence the overall impact of diabetes on sepsis outcomes will require a translational approach using epidemiologic studies combined with animal and *in vitro* models.

The authors address most limitations in the current study. First, lower risk of acute respiratory failure could be confounded by lower risk of developing respiratory tract infection in diabetes, but subgroup analysis in individuals with a respiratory source of infection confirmed findings observed in the overall analysis. Second, the study used an administrative dataset and whether acute respiratory failure was due to acute lung injury could not be determined. Misclassification errors due to inclusion of patients with acute respiratory failure due to congestive heart failure or patients who were intubated due to septic shock without evidence of lung abnormalities may have occurred. Congestive heart failure is likely to be more common in diabetes and would attenuate the difference in the risk of acute lung injury between those with and without diabetes. Finally, administrative datasets and

even well designed observational studies cannot tease out acute and chronic organ dysfunction. For instance, the diagnosis of acute kidney injury is difficult when pre-illness creatinine levels are not routinely available. Thus, the higher risk of acute kidney injury in diabetes could be confounded by higher prevalence of chronic kidney disease. Finally, discrimination between insulin-dependent and non-insulin-dependent diabetes could not be made, and no information was available on glucose levels at and after admission or on the regulation of diabetes prior to the septic episode (for example, by using HbA1c levels).

In summary, these findings by Esper and colleagues advance our current understanding of the interaction between diabetes and infection. Well designed epidemiologic studies and translational approaches are necessary to understand the factors that contribute to sepsis outcomes in diabetics and the mechanisms involved. Unlike most non-infectious illnesses, such as cardiovascular disease and cancer, where diabetes is associated with poor outcomes [11,12], diabetes may confer some protection against acute lung injury in patients with sepsis and may not be associated with higher short-term mortality after infection - indeed it is not all bad news.

Competing interests

The authors declare that they have no competing interests.

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