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Commentary

Does diabetes risk after SARS-CoV-2 infection depend on the viral variant?

Rohita Rangu [a,b], Pandora L. Wander [a,c], Sakeneh Zraika [a,b,*]

[a] Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, United States
[b] Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington, Seattle, WA 98195, United States
[c] Division of General Internal Medicine, Department of Medicine, University of Washington, Seattle, WA 98195, United States

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ABSTRACT

SARS-CoV-2 infection is associated with an elevated risk of new-onset diabetes. With infections forecast to rise in the coming months, this may exacerbate an existing public health crisis by increasing rates of diabetes worldwide. Much remains to be learned about a causal link between SARS-CoV-2 and incident diabetes. This is complicated by the rapid evolution of new SARS-CoV-2 variants that may have differential effects on development of diabetes. It is possible that some variants confer an increased risk, while others carry little to no risk. Distinguishing between these possibilities could be key in preventing or screening for new-onset diabetes, and could inform care of at-risk individuals with recent SARS-CoV-2 infection.

1. The connection between COVID-19 and diabetes

Clinical characteristics of new-onset diabetes after SARS-CoV-2 infection remain poorly characterized, largely owing to a reliance on electronic health record data in early epidemiological studies and thus, a lack of rigorous assessment of autoimmunity and/or β-cell function prior to SARS-CoV-2 infection and at diabetes diagnosis. Based on existing evidence, COVID-19 seems to be consistently associated with an increased risk of type 2 diabetes (T2D) but not type 1 diabetes (T1D). For example, Al-Aly found that SARS-CoV-2 infection was associated with a 40% higher risk of T2D but not T1D in U.S. veterans [1]; however, due to the use of diagnostic codes, misclassification of diabetes sub-type may have occurred. Further, SARS-CoV-2 infection does not often correlate with the presence of islet autoantibodies [2–5]. That said, studies in which islet autoantibodies were measured have generally been small and/or used cross-sectional designs. Therefore, uncertainty remains about the relationship between SARS-CoV-2 infection and diabetes subtype.

Impaired insulin secretion from pancreatic islet β cells is a critical determinant of diabetes development. Despite little evidence that SARS-CoV-2 triggers an autoimmune response to islets, it is suggested that the pathogenesis of new-onset diabetes in infected individuals includes early β-cell injury [6]. This may occur via direct SARS-CoV-2 invasion of β cells [6], as in human islets that display impaired insulin secretion upon infection with wild-type (WT) SARS-CoV-2 *in vitro* [7]. Alternatively, indirect β-cell injury may occur due to the exaggerated systemic pro-inflammatory cytokine response, which can induce endoplasmic reticulum stress in β cells [7] and impair their function/survival. Infected islet endothelial cells may also impact β-cell health, perhaps by altering secretion of paracrine factors known to support β-cell function/survival.

SARS-CoV-2 infection can also induce insulin resistance [8], the latter a metabolic derangement commonly triggered by pro-inflammatory cytokines [9]. Insulin resistance can predispose individuals to diabetes by contributing to hyperglycemia, compensatory hyperinsulinemia, and ultimately β-cell failure. Corticosteroid treatment, which improves clinical outcomes in hospitalized individuals with COVID-19 who require supplemental oxygen, may also induce insulin resistance. Although one study did not find dexamethasone to cause clinically significant changes in blood glucose among COVID-19-positive individuals without diabetes [10], this possibility needs further study.

2. Evolution of SARS-CoV-2: Are some variants more damaging than others?

SARS-CoV-2 variants differ in their phenotypic characteristics and the degree to which they induce acute symptoms. The Delta (B.1.617.2) variant produces higher infection loads than WT SARS-CoV-2 and the Omicron (B.1.1.529) [11] and Alpha (B.1.1.7) variants [12]. It also

Abbreviations: ACE2, angiotensin-converting enzyme 2; PASC, post-acute sequelae of COVID-19; T1D, type 1 diabetes; T2D, type 2 diabetes; WT, wild-type.

* Corresponding author: 1660 South Columbian Way (151), Seattle, WA 98108, United States.
E-mail address: zraikas@uw.edu (S. Zraika).

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displays increased transmissibility compared to Alpha [13]. The risk of severe COVID-19 is greater with the Alpha, Beta (B.1.351), Gamma (P.1) and Delta variants than with WT SARS-CoV-2, as measured by hospitalization, ICU admission and/or death [14]. Furthermore, the Beta and Gamma variants are more able to evade vaccine-mediated immunity than the Delta variant [15]. Similarly, the BA.1 Omicron subvariant exhibits an enhanced ability to evade immunity when compared to Delta [16], likely explaining the marked increase in reinfection rates after emergence of Omicron. However, an early subvariant of Omicron has ~2-fold lower case fatality ratio than Delta [17]. As acute COVID-19 severity is positively correlated with the risk of diabetes after SARS-CoV-2 infection [18], the propensity of a variant to induce severe acute disease may be a determinant of diabetes development.

3. How might different SARS-CoV-2 variants impact diabetes development?

The extent of β-cell damage induced by SARS-CoV-2 may be governed by mutations that impact the virus' properties. For instance, mutations affecting receptor affinity may modulate viral entry into β cells and subsequent cellular derangement. The SARS-CoV-2-spike D614G mutation that exists in most variants but not WT, increases infectivity by allowing enhanced binding to the angiotensin-converting enzyme 2 (ACE2) receptor [19]. Another example is the N501Y mutation in the spike protein of the Omicron variant, which increases ACE2 affinity and reduces neutralization by monoclonal antibodies [20]. As ACE2 expression has not been unequivocally demonstrated in the β cell, an alternative receptor for SARS-CoV-2 in β cells is the highly expressed CD147 [21]. CD147 inhibition reduced entry of the Alpha and Delta variants into epithelial cells to a greater extent than the Beta and Gamma variants [22]. This suggests that the Alpha and Delta variants may utilize CD147 to enter cells. Should CD147 be a predominant route for SARS-CoV-2 entry into β cells, variants utilizing CD147 may have higher rates of β-cell infection, plausibly increasing the risk of diabetes development.

Some variants may modulate immune responses. In mice, the BA.1 Omicron subvariant was associated with less cytokine release than the Beta variant [23] and induced less extensive lung inflammation than the Beta [23] and Delta [24] variants. ORF3a mutations, which are present in the Beta, Gamma, and Delta but not Alpha and Omicron variants, are associated with worsened inflammatory responses and post-acute sequelae of COVID-19 (PASC) [25]. Furthermore, maintenance of higher infection loads, as would be observed with the Delta variant [11,12], is correlated with an increased risk of an exaggerated immune response with high levels of circulating cytokines [26]. Higher circulating cytokine concentrations may thus induce β-cell stress and diminish insulin secretion.

4. Gaps in knowledge, opportunities, and challenges for future work

Studies are beginning to elucidate the differential effects of SARS-CoV-2 variants on PASC [27]; however, little is known about effects on diabetes development. More study is needed to determine invasion mechanisms of SARS-CoV-2 variants in β cells, and the extent of β-cell damage by different strains. Such investigations could include *in vitro* studies, or morphological and transcriptome or proteome analyses of autopsy pancreas samples from individuals infected with different SARS-CoV-2 variants. Further, differential effects on insulin secretion and sensitivity *in vivo* can be studied. New-onset diabetes development and progression should also be monitored in individuals after SARS-CoV-2 infection by different variants. Large databases like the CoviDIAB registry and national databases of the US Department of Veterans Affairs may facilitate such longitudinal studies.

Several challenges exist in studying SARS-CoV-2 variants and new-onset diabetes. Most importantly, the causal variant of infection is not identified for many individuals. Additionally, longitudinal metabolic testing is needed to characterize new-onset diabetes, which can be burdensome to conduct and is not routinely performed in individuals with COVID-19. Also, SARS-CoV-2 infection is associated with increased burden of metabolic complications related to lipid metabolism and obesity [1] – these promote insulin resistance and impair insulin secretion independent of SARS-CoV-2 infection. Thus, assigning a direct cause-effect relationship between SARS-CoV-2 infection and new-onset diabetes may be confounded by such factors, which could differ by variant of infection. Lastly, risk of diabetes after SARS-CoV-2 infection is increased in several population subgroups such as individuals that are over 65 years of age, male, and Black [18]. There is also a graded increase in risk with a body mass index of >25 and ≤ 30 kg/m^2 and of >30 kg/m^2 [18]. These characteristics must be controlled for when evaluating the impact of SARS-CoV-2 variants on new-onset diabetes.

5. Concluding remarks

Differing properties of SARS-CoV-2 variants may damage the β cell to different extents. Some variants may carry a greater risk of diabetes development in infected individuals, though additional research is needed to assess the validity of and mechanisms underlying this theory. Given the potential public health impacts of a post-COVID diabetes epidemic, the results of these investigations are urgently needed to inform diabetes risk assessments and preemptive screening strategies.

Author contributions

R.R. and S.Z. conceived the idea for the manuscript. R.R., P.L.W. and S.Z. wrote the manuscript. P.L.W. and S.Z. edited the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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