Commentary *Highlight Article*

Pre-diabetes and COVID-19, could we be missing the silent killer?

Aubrey Mbulelo Sosibo and Andile Khathi

College of Health Sciences, University of Kwa-Zulu Natal, Westville 3629, South Africa
Corresponding author: Aubrey Mbulelo Sosibo. Email: sosibo.aubrey3@gmail.com

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Impact statement

It is widely accepted that type 2 diabetes patients infected with COVID-19 tend to experience more severe COVID-19 complications. However, investigations about the association between pre-diabetes and COVID-19 are almost unchartered. If this association is left unattended, then the potential of missing a silent killer will persist. Therefore, using pieces of evidence from recent literature, we address why pre-diabetes and COVID-19 can be a deadly combination. We see it plausible that similar COVID-19 induced complications observed in individuals with type 2 diabetes may also occur in people with pre-diabetes. We see this correspondence invoking further discussions and investigations that will ultimately play a significant role in how COVID-19 infected patients with pre-diabetes are managed.

Pre-diabetes (or intermediate hyperglycemia) is a state in which the blood glucose concentration is above normal but not high enough to diagnose type 2 diabetes.[1] But whether pre-diabetes should concern us during and after the coronavirus disease 2019 (COVID-19) pandemic is an exigent question.

The onset of pre-diabetes is triggered by the reduction in insulin sensitivity and diminished pancreatic beta-cell function, which causes glycemic dysregulation.[1] This impaired regulation of glucose concentrations causes moderate hyperglycemia and is associated with chronic microvascular and macrovascular complications, cognitive dysfunction, as well as blood pressure changes.[1,2] Nevertheless, the body can maintain this intermediate hyperglycemic state over a prolonged period through compensatory mechanisms by stimulating the pancreatic beta cells to secrete more insulin and reduce insulin clearance by the liver.[3] However, these compensatory mechanisms can reach a point of exhaustion, resulting in a more severe hyperglycemic state that eventually leads to type 2 diabetes. Literature suggests that exposure to COVID-19 causes direct injury to the insulin-secreting beta-cells of the pancreas.[4] Therefore, it is plausible that exposure to COVID-19 in pre-diabetes people will be detrimental, especially on these compensatory mechanisms.

The infection with the severe acute respiratory syndrome coronavirus 2 initiates COVID-19.[5] The severity of the COVID-19 symptoms is increased by the existence of comorbidities, such as diabetes mellitus. This is also accompanied by data that states that COVID-19 has a higher fatality rate in people with pre-existing type 2 diabetes than in those without.[6] The COVID-19 infection appears to have a cytopathogenic effect like the previous severe acute respiratory syndrome coronavirus (SARS-CoV) infection in 2003, whereby multiple tissues such as the pancreas are injured. The literature generated from the SARS-CoV pandemic showed that the infection induced injury on the islets of Langerhans.[7] The outcome was explained by the elevated expression of the SARS-CoV receptor, angiotensin-converting enzyme 2 in the islets of Langerhans.[7] Results from a study by Wang and colleagues indicates that patients with COVID-19 pneumonia are likely to display mild pancreatic injury.[8] We postulate that the COVID-19 induced injury to the pancreatic beta-cell islets will exacerbate insulin resistance significantly in individuals with pre-diabetes, which, in turn, will lead to hyperglycemia. Furthermore, some researchers have suggested that COVID-19 infection may subsequently trigger new cases of type 2 diabetes.[4] If this happens to be correct, then people with pre-diabetes are at most risk not only for the onset of type 2 diabetes but for severe illness from COVID-19.

Studies show that many hospitalized patients who developed moderate or severe COVID-19 illness had pre-diabetes based on their HbA1c or impaired fasting glucose (IFG).[9,10] Strikingly, one of them recorded that 24% of patients with moderate-severe COVID-19 had pre-diabetes.[9] Elevated IFG was shown to be able to predict for 28-day mortality independently in admitted patients without diabetes.[10] Additionally, type 2 diabetes is proven to independently suppress immune responses by generating advanced glycation end-products and the subsequent constant inflammation.[11] Other experimental and observational studies have shown that pre-diabetes is associated with elevated C-reactive protein and interleukin-6.[11,12] These biochemical markers contribute significantly to the cytokine storm development, which has been detected in

severe cases of COVID-19 infected patients. Taken together, these observations suggest that pre-diabetes could be a silent-killer in the fight against COVID-19 as it is not traditionally viewed as comorbidity.

We, therefore, propose that pre-diabetes be treated as a comorbidity for COVID-19. We further suggest that all COVID-19 infected patients be screened for pre-diabetes so as to reduce the risk of fatality and improve clinical care. There is currently no therapeutic drug approved for pre-diabetes management. However, glucose-lowering treatments such as metformin are recommended for patients with type 2 diabetes, and more recently, people considered to be at a high risk of developing diabetes. Rising blood glucose levels have been observed during hospitalization in COVID-19 infected patients.[13] However, it remains unknown whether metformin administration will attenuate glucose levels in COVID-19 infected patients with pre-diabetes. Therefore, we recommend that scientific trials be conducted to assess drugs like metformin and other anti-diabetic drugs to investigate their effects on blood sugar control and the resultant clinical outcomes of COVID-19 infection in people with pre-diabetes. However, since the patients have pre-diabetes, we recommend that the trials start with low metformin doses.

In conclusion, the prognosis of COVID-19 in hospitalized patients with pre-diabetes is yet to be established due to the minimal data currently available. However, we are confident that the current information presented in this commentary can assist researchers in endocrinology and virology, as well as those caring for COVID-19 patients with pre-diabetes.

AUTHORS' CONTRIBUTIONS

Both AMS and AK contributed significantly to the writing of the manuscript. AMS wrote the first draft, and AK reviewed it and made necessary changes.

DECLARATION OF CONFLICTING INTERESTS

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ORCID ID

Aubrey Mbulelo Sosibo https://orcid.org/0000-0002-9617-5715

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