



Journal of Medical Sciences

ISSN 1682-4474

science
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Commentary

COVID-19, Immunity and Pre-Diabetes: Are We Missing Another Target Area to Be Explored?

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Abstract

COVID-19 has been reported to cause mild illness and recovery observed in a short period. Type 2 diabetes, an explored condition, have been reported to be diagnosed from the long-lasting asymptomatic condition called pre-diabetes. Furthermore, pre-diabetic subjects with COVID-19 has never been explored due to a silent condition of the pre-diabetes stage.

Key words: COVID-19, Immunity, pre-diabetes, lymphocyte, nuclear factor-kappa- β , normoglycemia, CD4⁺ T-cell

Citation: Mzimela, N.C. and A. Khathi, 2022. COVID-19, Immunity and pre-diabetes: Are we missing another target area to be explored? J. Med. Sci., 22: 154-157.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

In December, 2019 the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has been reported to cause Coronavirus (COVID-19) emerged in Wuhan and has since spread globally¹. According to World Health Organisation (WHO), in June 2020, the disease saw accelerated growth in Africa which contributed to 54 countries in Africa experiencing death and new cases due to COVID-19¹. COVID-19 has been reported to only cause relatively mild illness in younger and healthier subjects. However, in older people patients and those with existing medical conditions, COVID-19 has been reported to have severe effects which can even result in death. These medical conditions include, but are not limited to, cardiovascular disease, chronic respiratory disease, cancer and diabetes². Additionally, COVID-19 was reported in older men displaying co-morbidities that contribute to a weaker-functioning immune system^{2,3}. In one of the conditions mentioned, type 2 diabetes (T2D) was shown to lead to a dysregulated immune system which is due to abnormalities caused by hyperglycaemia⁴. According to research done by Liu and co-workers, patients with overt type 2 diabetes and COVID-19 were found to display the lowest lymphocyte count⁵. These participants showed decreased lymphocyte count which included B-lymphocytes and T-lymphocytes⁵. However, there is a paucity of information on the state of the immune system in pre-diabetic subjects who have COVID-19.

The pre-diabetic state is an asymptomatic, intermediate stage between normoglycemia and overt T2D which is characterised by blood glucose concentrations above normal but not high enough to be classified as T2D⁴. Due to pre-diabetes being asymptomatic, people often go undiagnosed even though there is the presence of chronic subclinical inflammation⁶. A recent study posited that pre-diabetic patients who contract COVID-19 might account for the high number of people who experience severe COVID-19 symptoms without any reported comorbidities⁷. Results obtained from a study conducted in 2020 indicated that more than two-thirds of patients with COVID-19 that did not recover from the disease were subjects with either type 1 or type 2 diabetes⁸. This shows that having diabetes and COVID-19 is a risk that can contribute to increased mortality globally. However, it is of value to evaluate the effects of COVID-19 in pre-diabetic subjects as an immunity target area since hyperglycaemia is not yet chronic at this stage. It is of great value to focus on the pre-diabetic state as it has been neglected although studies show that complications that are observed in T2D begin during prediabetes. A recent study indicated that hyperglycaemic patients with COVID-19 are connected to poor outcomes compared to normoglycemic

subjects⁹. A retrospective observational study done by Bode and co-workers indicated that COVID-19 subjects with uncontrolled hyperglycaemia are the contributors of high mortality rate compared to those patients without diabetes⁶. Hyperglycaemia has been reported to cause activation of nuclear factor-kappa- β (NF- κ B) through activation of inhibitor kappa- β . This activation causes phosphorylation of serine residue of an insulin signalling pathway, therefore causing downregulation of the pathway. This downregulation results in insulin resistance and translocation of NF- κ B from the cytoplasm to a nucleus where it activates the gene expression by binding to nearby DNA binding sites resulting in changes in the cell function which include inducing inflammatory signalling or immune response. Maybe targets of the mechanisms that contribute to chronic inflammation and suppressing the immune system might provide an answer to certain undiscovered traits of COVID-19 by investigating immune states of hyperglycaemia-COVID-19 and pre-diabetes-COVID-19 combinations.

According to the report by Tay and co-workers, it takes a few days for the body to produce antibodies that are specific for targeting coronavirus while neutralizing antibody activity reached the peak around 14 days¹⁰. It also depends on the strength of the immune system to detect whether it can keep infection immune memory that will be able to protect a host in future exposure to COVID-19. Hong Kong scientists reported a COVID-19 subject that had recovered from a virus that was re-infected more than 4 months later¹¹. This case indicates that the immune system role can be the answer to some of the questionable responses caused by COVID-19 infection. Additionally, a study in China reported that some recovering COVID-19 subjects displayed very low neutralising antibodies which are responsible for binding or sticking to corona, therefore, blocking it from infecting other cells in the human body¹². In response to COVID-19 infection, a human immune system produces/secretes SARS-CoV-2-specific antibodies, CD4⁺ T cells and CD8⁺ T cells¹³. This implies that SARS-CoV-2 specific CD4⁺ T-cell and responses by CD8⁺ T-cell can be responsible for controlling and primary resolution of infections caused by SARS-CoV-2 in COVID-19 patients¹³. Therefore, it is of importance to explore the immunity against COVID-19 that is induced by SARS-CoV-2 infection by targeting the response of antibodies, memory B-cell, T-cell memory and CD4⁺ T-cell. A report by Sherina and co-workers indicated that COVID-19 immune involves antibodies, T-cells and B-cells¹⁴. These 3 elements have been reported to be the key protectors of COVID-19 patients from being infected for at least 8 months¹⁴. This could be due to the memory of the robust immune memory of survivors of COVID-19^{1,14}. The ability of white blood

cells (specifically T-cells and B-cells) have been reported to have recollection powers^{1,14}. These 3 elements combined enable the immune system to have the ability to recognise and re-attack invading COVID-19, therefore preventing it from re-infecting the recovered human being¹³. This study has measured these 3 elements from 119 COVID-19 recovered subject's blood samples and the study extended to 8 months post-infection^{3,14}. Additionally, a study done by Qin and co-workers using 44 COVID-19 patients, reported that severe COVID-19 patients had significantly decreased concentration of B cells, T cells and natural killer (NK) cells even below normal levels⁵. In this study, they further explore an analysis of different T-cells sub-types in COVID-19 patients, which were both helper T(Th)cells (CD3⁺, CD4⁺) and suppressor T-cells (CD3⁺, CD8⁺)⁵. Severe COVID-19 patients displayed reduced Th cells and suppressor T-cell concentration¹¹. However, the ratio of Th and suppressor (Th/Ts) observed was still at a normal rate⁵. This study report then indicated that severe COVID-19 infection might cause damage to certain types of immune cells such as lymphocytes, suppressing the immune system⁵. In addition to decreased lymphocytes, the neutrophils were reported to be more increased in patients with severe COVID-19 indicating a life-threatening condition of COVID-19⁵. Severe COVID-19 subjects have also been reported to have increased pro-inflammatory cytokines such as TNF- α , IL-1 and IL-6 with chemokine IL-8 also reported¹¹. Bearing in mind that the immune system dysregulation contributes to chronic inflammation this exacerbates the progression of the disease instead of leading to recovery. However, the state of immune memory was only targeted to COVID-19 infected subjects, shifting from the state of hyperglycaemia.

An interesting study by Liu and co-workers indicated that patients with severe COVID-19 and diabetes tend to experience severe COVID-19 compared to those without diabetes⁵. Additionally, the state of immunity reported that patients with COVID-19 and diabetes had decreased lymphocyte count and their subsets especially CD4⁺, CD8⁺ T and B cells such as B(CD19⁺)⁵. The diabetic state can delay the production of antibodies by decreasing the level of B (CD19⁺) circulating which then results in delaying the removal of the COVID-19 virus, worsening its prognosis. However, these observations were made in overt type 2 diabetes, COVID-19 infected subjects. The complications of pre-diabetic COVID-19 infected patients still lack answers, which might be another answer to the solution of the cloud of the COVID-19 pandemic.

It is an undeniable fact that some infected subjects are living in an environment that exposes them to high-calorie diets and sedentary lifestyles. These two factors expose the human subject to be more prone to the development of

pre-diabetes without even noticing as it is asymptomatic. This then raises concern if the researchers are missing another target to explore since most people who are infected with COVID-19 do not even know whether they are pre-diabetic or not. This could exacerbate the development of a weak immune system due to acute hyperglycaemia and which could be further worsened by abnormalities caused by COVID-19.

CONCLUSION

We strongly believe that more research needs to investigate the immune state in prediabetes-COVID-19 patients. This could help improve COVID-19 management strategies as this could decrease the risk of adverse effects.

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