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Review Article

Unraveling the Nexus: Post-COVID Hyperglycaemia and Diabetes-A Comprehensive Review of the Intricate Interplay and Implications for Glycemic Control

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ABSTRACT

The global impact of Severe Acute Respiratory Syndrome Coronavirus-2 (SARSCOV2) is profound, with Coronavirus Disease 2019 (COVID-19) presenting a clinical spectrum that leads to multi-systemic failure, particularly affecting the pancreas and resulting in diabetes and cardiovascular co-morbidities. Diabetes, the more life-threatening manifestation of COVID-19, is associated with a 30% higher fatality rate. This review aims to explore the intricate relationship between Hyperglycaemia and hyper inflammation in individuals with post-COVID diabetes, emphasizing the risks of recurring hyperglycaemia and distinguishing it from conventional diabetes. Methodologically, data synthesis and extraction were conducted based on diabetes mellitus and recent studies on the impact of coronavirus, especially SARS, on the pancreas, utilizing articles from the Pubmed search engine. Hospitalized COVID-19 patients show a higher likelihood of concurrent conditions, including diabetes mellitus and cardiovascular diseases. Factors contributing to post-COVID diabetes include age, co-morbidities, pre-diabetic status, pre-existing micro-angiopathic disease burden, stress and direct links to elevated blood levels induced by cytokine storms or hyperinflammation from the diabetogenic virus. In conclusion, this study highlights the potential disruptions in glucose production and metabolism following COVID-19 infection. The recommendation is for individuals who have experienced COVID-19 to undergo rigorous glycemic screening approximately a month post-infection. The findings underscore the importance of monitoring and addressing alterations in glucose homeostasis as part of post-COVID-19 care. Further research and clinical observation are essential to enhance our understanding of the intricate relationship between COVID-19 and glycemic control. The key message emphasizes the comprehensive review of the interplay between SARS-CoV-2 infection and the heightened risk of diabetes, advocating for vigilant post-infection glycemic screening and revealing potential disruptions in glucose metabolism.

Key words: Hyperglycaemia, Hyperinflammation, Diabetes Mellitus, Post Covid, Severe acute respiratory syndrome coronavirus-2.

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INTRODUCTION

The Corona virus disease 2019 (COVID-19) epidemic has caused catastrophic damage to humanity during the last century. Given how rapidly this dreadful virus is propagating, it is inevitable. On the other hand, eventually, a large population is affected. The clinical spectrum of Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) infections may encompass innocuous infections, respiratory disease and failure of several organs indicating an important trigger known as a "cytokine storm" that further complicates long COVID-19 development by causing hypoxia and atypical pneumonia, as well as fatal outcomes.[1] Hospitalized COVID-19 subjects are disproportionately more likely to have co-morbid disorders such as Diabetes Mellitus (DM) and Cardiovascular Diseases (CVD).[2] Diabetes has a high morbidity and mortality rate and is a metabolic disease that can be life-threatening. Individuals with COVID-19 had an average calculated prevalence of DM of roughly 20% of the entire group, as reported in prior data sources and both an increasingly severe type of COVID-19 and an increase in mortality.[3]

A meta-review of 13 trials including 3027 COVID-19 subjects also found a causal association between diabetes and an approximately 4-fold higher risk of fatal disease and major illness.[4] Multiple research investigations have demonstrated a connection between COVID-19 and hyperglycaemia in people

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regardless of pre-existing diabetes during a pandemic.[5] Age, being overweight and high blood sugar levels, which are the main mediators of developing DM and outcomes in COVID-19, were revealed to be the key predictors of the risk associated with DM, followed by greater amounts of soluble urokinase Plasminogen Activator Receptor (suPAR). The earlier one serves as a helpful biomarker whose concentrations show the level of immunological activation and predicts mortality and morbidity for chronic illnesses, including cancer and cardiovascular disease.[6] This article highlights interplay between hyperglycaemia and hyperinflammation in post-covid diabetic patients, as well as the risks of post-covid hyperglycaemia's potential recurrence and how it differs from conventional diabetes.

Mechanism of Hyperinflammation by SARS

Angiotensin Converting Enzyme 2 (ACE2) is a Renin-Angiotensin-Aldosterone System (RAAS) component that adds to SARS-CoV-2's pathogenicity. A homolog of Angiotensin Converting Enzyme (ACE), ACE2 is also a recognized cellular receptor needed for SARS-CoV and SARS-CoV-2 infection and balances the consequences of Angiotensin II (Ang II). Angiotensin Receptor Blockers (ARB) and Angiotensin Converting Enzyme 1 (ACE I) may up-regulate ACE2 and aid the migration of SARS-CoV-2 inside the cells, predisposing individuals towards the illness and worsening COVID-19.[7] The findings of Fang *et al.*, revealed that patients who were taking ACEIs or ARBs exhibited a higher concentration of ACE2 receptors in their lungs, which may have contributed to their post-covid complications or severe symptoms. Heart, pancreatic cells, enterocytes, kidney tubular epithelium and endothelial cells, all express ACE2 that has been isolated from type I and II alveolar epithelial cells.[8-11] When the cellular virus fuses to ACE2 and enters through an endosomal pathway, proximal serine proteases like TMPRSS2 that are involved in S protein priming and spike protease fragmentation, like Furin, form the spike fusion peptide.[12,13] The SARS-CoV-2 virus's genome breaks free into the cytosol, then replicates further to produce mature viruses and further propagation, as a result of the pH imbalance of the endosomal milieu and the existence of proteases such as cathepsin-L.

Apoptosis or necrosis of infected cells provokes inflammatory reactions characterized by the production of cytokines that are pro-inflammatory or chemokines, which attract inflammatory cells. Through the production of Interferon-gamma (IFN-γ), CD4 T helper (Th1) mediates antigen transmission and protects against intracellular infections like COVID-19. Th17 cells generate Interleukin-17 (IL-17), IL-21 and IL-22, which in turn promote neutrophil and macrophage magnetism.[14] SARS-CoV-2 produces lymphocytopenia by infecting immune cells in circulation and increasing lymphocyte (CD3, CD4 and CD8 T cell) apoptosis. A "cytokine storm"-the expulsion of enormous quantities of inflammatory cytokines-arises when lower T cell performance frees the innate immune system from its restraint. A cytokine storm of IL-6 and lactate dehydrogenase blood levels both independently can predict the seriousness of COVID-19.[15] It was hypothesised that this action may accelerate the spread of COVID-19 in individuals with diabetes mellitus by raising oxidative stress, which may destroy proteins, lipids and DNA and affect the body's framework and activity. Clinically, cytokines and chemokines, which are indicators of inflammation, are found to be excessive in patients with severe COVID-19.

Hyperglycaemia by SARS

The primary underlying factor leading to the development of Type 2 Diabetes Mellitus (Type 2 DM) is the incapacity of pancreatic beta-cells to secrete enough insulin when insulin sensitivity is decreased.[16] The pancreas may experience direct or indirect effects from viral infections. The coronavirus's adherence to the ACE2 receptor in the epithelial cells of the islets of the pancreas, as well as several additional variables (like TMPRSS2, TMPRSS4, NRP-1, CD209L and SR-B1) necessary for effective SARS-CoV-2 entry, are all contributory to acute hyperglycaemia associated with coronavirus infection.[17] The presence of ACE2 within the endocrine pancreas and its precise location together lead to concern that coronaviruses may specifically affect islets, possibly causing hyperglycaemia.[18] Findings from human pancreatic tissues showed the presence of ACE2 in blood vessels and pancreatic duct epithelial and they concluded that pancreatic endocrine cell infection with SARS-CoV-2 is unlikely to serve as the chief triggering factor of diabetes.[19] COVID-19-associated hyperglycaemia could be caused by viral adipocyte infection, which would lead to secondary insulin resistance and diminished secretion of the glucoregulatory hormone adiponectin. *In vitro* and animal findings have demonstrated that adipocytes may contract SARS-CoV-2 and this is correlated to a reduction in the expression of adinopectin.

This "new-onset" hyperglycaemia might be categorized as "stress-induced" hyperglycaemia, "new-onset DM" in previously undiagnosed diabetes, due to SARS-CoV-2's effects on the pancreatic islets, or "secondary DM" brought on by the use of corticosteroids.[20] The myocardium, vasculature, intestines, kidneys, respiratory system and pancreatic islets all release ACE2. SARS-CoV-2 hooks to ACE2 and acts as a ligand to get into the cells. Mice lacking ACE2 become more prone to β cell collapse. Following the viral complex's endocytosis, ACE2 expression is down-regulated and has two separate functions. It damages β cells and inhibits pancreatic islet cell activity. On the other hand, a decrease in ACE2 activity results in uncontrolled angiotensin II action and obstructs insulin production via decreasing circulation and raising the level of oxidative stress in the pancreatic cell. Coronaviruses may, therefore negatively impact cells in the pancreas and induce hyperglycaemia.[21] Stress-induced hyperglycaemia is a hallmark of relative insulin insufficiency, linked to increased lipid breakdown and elevated levels of free fatty acids in the blood, both of which are present in acute diseases

including myocardial infarction and severe infections.[22] Because of the cytokine outbreak, stress hyperglycaemia in COVID-19 could be considerably worse.[17] Inflammatory indicators like erythrocyte sedimentation rate, C-reactive protein and white blood cells show elevated concentrations in diabetes patients who have just been diagnosed with the disease.[23] Cytokine storm-induced acute inflammation may make insulin resistance worse.[24] As per the study, those with hyperglycaemia had considerably greater amounts of neutrophils, D-dimers and inflammatory markers than people with appropriate glucose levels.[25] There may be more SARS-CoV-2's contribution to the cause of diabetes than mere pancreatic ACE2 expression and β-cell degeneration.[26] In several clinical scenarios, factors resulting in autoimmunity, insulin resistance, or β-cell stress within the skeletal muscle, liver and adipose tissues can lead to newly diagnosed diabetes. Additionally, deprived oxygen supply and swelling brought on by the SARS-CoV-2 infection of the blood vessels of islet results in secondary harm to β cells.[27]

Association of Hyperinflammation and Hyperglycaemia

Stress and inflammation seem to be coupled with each other. Internal or external stress can increase cortisol levels, which can reduce insulin sensitivity and increase hepatic glucose production. Cortisol causes a short-term response to elevated blood glucose levels and is endocrinologically active.[28] Those who are at risk for Type 2 DM exhibit a first phase of insulin resistance that is offset by an increased level of insulin production from the beta cells. The pancreatic operating capacity eventually loses the ability to handle the necessary generation of insulin[29] as the disease gets worse and beta cell shortage develops around the time diabetes is diagnosed as a result of the beta cells' inability to release adequate insulin. Insulitis, an inflammatory condition affecting the pancreatic islets of beta-cell, is thought to be an auto-inflammatory process, which causes a decrease in beta cell count and responsibility.[30] The most prevalent, well-researched and very significant mechanism that is activated in the islets of several Type 2 DM models and results in beta cell failure is inflammasomes/IL-1 beta signaling.[31] Amyloid polypeptides, Free Fatty Acids (FFAs) and endo-cannabinoids are supplemental immune cell types that contribute to islet inflammation in type 2 DM.[32] Type 2 DM is closely linked to immune system activation in terms of both incidence and progression and both innate and adaptive immunity play a role in mediating adipose tissue inflammation. The phenotypic shift of macrophages from predominantly anti-inflammatory M2-type to a greater portion of pro-inflammatory M1-type macrophages is a major determinant in the onset and intensification of islet inflammations.[33] The data indicates that the infiltration of macrophages into adipose tissue follows the induction of both B and T cells.[34]

Risk Associated With Post-Covid Diabetes

Except in cases of diabetes, hyperglycaemia (at least two blood sugar readings over 10 mmol/L or 180 mg/dL in any 24 hr with a Glycated Haemoglobin (HbA1C) below 6.5%) is associated with a higher risk of COVID-19 mortality when compared with normoglycemia.[35] In essence, hyperglycemic patients without diabetes experienced more repercussions during their first month in a healthcare facility, which increased their overall mortality rate.[36,37] Approximately twice as many COVID-19 individuals with newly diagnosed diabetes as those with already existing diabetes have a higher chance of mortality from any cause.[38] Traditional hazards include insulin resistance causes the activation of free fatty acids from adipose tissue that increases in type 2 DM. Higher lipogenesis, Reduced Apo lipoprotein B-100 (ApoB) breakdown and higher substrate availability are the three processes behind the increased hepatic synthesis of extremely low-density lipoproteins. These modifications result in a lipid profile with small dense LDL particles, high Triglycerides (TGs), elevated Apo B production and low levels of High-Density Lipoprotein Cholesterol (Low HDL-C).[39]

Due to its propensity for oxidation, this LDL subtype is crucial in the development of atherogenesis. Atherogenic dyslipidemia (Increase of both Fasting and Post-prandial TGs, Low levels of HDL-C and Apo lipoprotein (Apo A), Increase in small dense LDL Particles, Increase of Apo B), which is a more potent prognostic of cardiovascular risk than LDL cholesterol, a low HDL-C or single increased TGs.[40] In addition, more than 60% of those with Type 2 DM have arterial hypertension.[41] It is specifically associated with three things: (1) *elevated renin-angiotensin-aldosterone system* function; (2) *hyperinsulinemia related to increased renal reabsorption of sodium;* and (3) *raised sympathetic tone*.[42] Advancing age, being overweight, as well as the initiation of kidney disease also nurture the development of the worldwide incidence of elevated blood pressure. The risk of CVD is increased by diabetes and hypertension. Hypertension increases the cardiovascular risk in diabetic patients, even though diabetes confirms a cardiovascular risk that is twice as high in males more than three times as high in women.[43,44] It is most important to understand how obesity influences atherogenesis, new procoagulant and prothrombotic cardiac risk variables in Type 2 DM patients since they raise CVD mortality rates in these people.[45] Resistance to insulin and hyperinsulinemia, post-prandial hyperglycaemia, microalbuminuria and hematological and thrombogenic variables are only a few examples of non-traditional risk factors.

Management

Insulin was usually effective in lowering blood glucose levels in COVID-19 patients.[46] Patients were also treated with hydroxychloroquine in prior reports. The latter drug has a reputation for boosting endogenous insulin secretion.[47] Larger than anticipated insulin dose could be required. In COVID-19

patients, frequent intake of dexamethasone owing to novel treatments is also likely to result in hyperglycaemia.[48-54]

CONCLUSION

The 10% of COVID-19 patients who have post-COVID syndrome are apart from those with serious acute COVID-19. According to the majority of preceding research findings, new-onset diabetes develops at far higher rates in many COVID-19 individuals. These challenges lengthen hospital stays and raise treatment costs generally. In conclusion this work reveals that if affected with covid 19, in time there will be fluctuation in glucose production and metabolism, since SARS COV-2 has higher affinity for ACE2 receptor largely present in pancreas. Hence Post infection, patients should undergo a stringent glycaemic screening post one month of infection.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SARSCOV2: Severe Acute Respiratory Syndrome CoronaVirus-2; **COVID-19:** Coronavirus disease 2019 DM Diabetes mellitus; **Type 2 DM:** Type 2 Diabetes Mellitus; **CVD:** Cardiovascular Disease; **SuPAR:** Soluble Urokinase Plasminogen Activator Receptor; **RAAS:** Renin-Angiotensin-Aldosterone System; **ACE:** Angiotensin Converting Enzyme; **ACE 1:** Angiotensin Converting Enzyme 1; **ACE2:** Angiotensin Converting Enzyme 2; **Ang II:** Angiotensin II; **ARB:** Angiotensin Receptor Blockers; **IL-17:** Interleukin-17; **FFAs:** Free Fatty Acids; **ApoB:** Apo lipoprotein B; **ApoA:** Apo lipoprotein A; **Low HDL-C:** Low Levels of High-density Lipoprotein Cholesterol; **TGs:** Triglycerides; **HbA1c:** Glycated haemoglobin.

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