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Understanding the Mechanisms through Which COVID-19 Impacts the Maternal Immune System and its Effect on Childhood Diabetes Development

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Abstract: *There is limited but emerging evidence about the impact of COVID-19 on people with diabetes. COVID-19 pneumonia is a novel illness rapidly spreading globally, causing disabilities and fatalities. Over the past 2 years, the pandemic's indirect effects on healthcare delivery have become prominent, along with the lingering impacts on those directly infected. Diabetes is a recognized risk factor that increases COVID-19 severity and mortality, as well as complications like acute respiratory distress syndrome and multi-organ failure. Diabetic patients are highly affected due to increased viral cell entry and decreased immunity. Several hypotheses explaining the increased COVID-19 incidence and severity in diabetics were recently proposed in detail. Meanwhile, 20-50% of COVID-19 patients without prior diabetes developed new hyperglycemia or diabetes, suggesting two-way interactions between COVID-19 and diabetes. Further review is required to confirm diabetes as a COVID-19 complication. Diabetes and related complications in COVID-19 patients are primarily due to the acute illness from SARS-CoV-2 infection, releasing glucocorticoids, catecholamines, and pro-inflammatory cytokines known to drive hyperglycemia. This review briefly examines potential mechanisms linking COVID-19 and diabetes, and presents clinical recommendations for better disease management.*

Keywords: *COVID-19, Immune System, SARS-CoV-2, diabetes, Childhood.*

1. Introduction

COVID-19 is an epidemic caused by the SARS-CoV-2 virus [1]. SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus infecting humans and animals. Earlier coronavirus outbreaks were SARS-CoV in 2002-2003 with 10% mortality [2] and MERS-CoV in 2012 with 36% mortality [2]. Coronaviruses have four structural proteins – spike (S), membrane (M), nucleocapsid (N), and envelope (E) [3]. The S protein enables virus attachment and cell entry via its S1 and S2 subunits [3]. The host cell receptor for SARS-CoV and SARS-CoV-2 is ACE-2, while MERS-CoV uses DPP4 [4]. ACE-2 is expressed in the upper respiratory tract, endothelium, kidney, heart, intestine, and pancreas [5]. Endosome cathepsin-L proteases and alkalinity allow viral genome release into the cytosol. The virus replicates and forms mature virions in target cells, prompting apoptosis and pro-inflammatory cytokine activation. T helper cells regulate antigen activity and immunity via interferon-gamma [6]. Th17 cells activate macrophages and mobilize neutrophils through interleukins like IL-17, IL-21, and IL-22. Lymphocyte apoptosis from immune cell infection causes lymphocytopenia [8]. High inflammatory cytokines like IL-6, TNF, CXCL10, and CCL2 cause a "cytokine storm" inhibiting innate immunity. This hyperinflammation induces endothelial HAS2 and hyaluronan synthesis in alveolar cells and fibroblasts. Hyaluronan accumulates fluid around alveolar cells, impairing gas exchange, causing hypoxia and multi-organ failure [7].

There are multiple potential pathways by which maternal SARS-CoV-2 infection could impact fetal brain development: (i) through maternal immune activation (MIA) during key neurodevelopmental windows; (ii) by direct fetal infection of neurological tissues via transplacental viral transmission; or (iii) through compromised placental function resulting in adverse pregnancy outcomes associated with increased neurologic injury risk (e.g. fetal growth restriction, preterm birth, abruption). This review presents emerging evidence on prenatal SARS-CoV-2 exposure effects on offspring neurodevelopment, explores potential mechanisms of how it may impact the fetal brain, and discusses virus and host factors influencing risk. It also discusses the need for cellular models to best study SARS-CoV-2's effects on the developing brain, and to identify at-risk individuals who may benefit from early intervention or therapeutics [8].

Pregnancy causes numerous physiologic changes, including immune alterations. The hormonal changes impact various organ systems [14]. Perhaps the most far-reaching change is progesterone-mediated smooth muscle relaxation, decreasing systemic vascular resistance (SVR) and blood pressure. Venous return and cardiac output increase dramatically - up to 60% in the first trimester - to meet metabolic demands. Decreased SVR causes renal vasodilation and a 50% increase in glomerular filtration rate (GFR). To compensate for decreased SVR and blood pressure, the renin-angiotensin-aldosterone system is continuously stimulated, markedly increasing aldosterone. Decreased gastrointestinal tone causes reflux, delayed gastric emptying, increased water reabsorption, and constipation [15]. Liver metabolism increases, along with decreased lipoprotein lipase activity, raising plasma triglycerides and cholesterol. Although LDL and HDL both increase, LDL rises more markedly, increasing the total cholesterol ratio. Human placental lactogen increases lipolysis and free fatty acids, inducing a diabetogenic state with islet cell hyperplasia and increased insulin secretion. Patients are typically insulin sensitive in the first trimester, become insulin resistant in the second, and maintain resistance until term. Placental corticotropin-releasing hormone causes a three-fold increase in plasma cortisol, resulting in a hypercortisol state [9].

Hematologic changes also occur - plasma volume and erythrocyte volume increase, but plasma increases more, decreasing hematocrit and causing dilution anemia. Increased venous stasis heightens thromboembolism risk [17]. Maternal immune adaptations provide protection while avoiding detrimental fetal immune response. Although the mechanism is unclear, research supports cooperation between maternal and fetal immunity rather than broad maternal suppression [10].

Obesity causes chronic systemic inflammation, increasing comorbidities like fatty liver disease, retinopathy, cardiovascular disease, nephropathy, and autoimmunity. It confers insulin resistance, often causing type 2 diabetes mellitus (T2DM). Chronic inflammation is seen in insulin target tissues and is key to the T2DM disease state. Pro-inflammatory macrophage recruitment and activation drive this inflammation, along with other immune markers like tumor necrosis factor-α (TNF-α), which is overexpressed in adipose tissue and activates inflammatory signaling molecules like JNK and IKKβ [20]. Other adipokines like interleukin 1β (IL-1β) and leptin also contribute to the chronic inflammatory response. The immune system's role in T2DM is so intertwined with glucose changes that scientists coined the term "immunometabolism" [11].

A quarter of pregnancy complications - gestational diabetes, hypertension, preterm labor, macrosomia - associate with maternal obesity. Excess adipose tissue causes deleterious effects on metabolic, vascular, and inflammatory pathways affecting outcomes [24]. Obesity and diabetes mellitus, separately and combined, are high-risk pregnancy criteria, with their comorbidity significantly increasing complications [12].

2. COVID-19 and Diabetes

Recent multi-center studies have shown COVID-19 severity is much higher in diabetes patients. This is partly due to: (a) insulin resistance; (b) hyperglycemia promoting pro-inflammatory cytokines and advanced glycation end products (AGEs); (c) oxidative stress; (d) adhesion molecule production mediating tissue inflammation; and (e) a robust pro-inflammatory response. Abnormally delayed-type hypersensitivity reactions, complement activation dysfunction, inhibited lymphocyte

proliferation to stimuli, and impaired macrophage/neutrophil functions occur in diabetes [28]. Hyperglycemic pulmonary epithelial cells had augmented viral infection and replication, indicating hyperglycemia's role in enhancing viral infections in vivo. SARS-CoV-2 binds ACE-2 receptors expressed in the pancreas, adipose tissue, and intestine. Therefore, SARS-CoV-2 infection may cause glucose metabolism alterations and augment COVID-19 severity [13].

3. COVID-19 and Renin–Angiotensin System on Diabetes

Renin-angiotensin system (RAS) blockers may enhance COVID-19 by increasing ACE2 expression. Since SARS-CoV-2 uses ACE2 for host cell entry, RAS-blockers could further spread the virus in diabetics. ACE-2 is highly expressed in the upper respiratory tract, lungs, alveolar epithelial cells, endothelium, kidney, heart, neurons, intestines, immune cells, pancreas, and vascular endothelium. SARS-CoV-2 replication spreads mature virions which elicit interleukin production, lymphocyte apoptosis, and innate immunity inhibition upon immune exposure. The resulting cytokine storm causes hyperinflammation and multi-organ failure [34]. Some studies show RAS blockade could reduce COVID-19 severity in hypertension [14]. Another study pointed out SARS-CoV-2-ACE2 interaction dysregulates the host viral response. ACE2 regulates angiotensin II (Ang II) production, and by destroying ACE2, SARS-CoV-2 enables unrestricted Ang II development. However, Ang II's injury response role depends on ACE2 metabolizing it to Ang-(1-7). Ang-(1-7) has opposing effects to Ang II-AT1R. SARS-CoV-2-induced ACE2 degradation thus removes control of Ang II's pro-inflammatory and tissue damaging activities. Therefore, COVID-19 pathogenesis stems from the host response to SARS-CoV-2 [15].

4. COVID-19 and Insulin Resistance

Insulin resistance has serious health effects on vasculature, heart, brain, and kidneys. COVID-19 causes insulin resistance in patients, resulting in chronic metabolic abnormalities not present pre-infection. Insulin is a pancreatic hormone activating glucose transportation to muscle and adipose. Insulin resistance stems from decreased tissue insulin sensitivity and inadequate pancreatic secretion for blood glucose regulation. ACE-2 converts angiotensin-2, a vasoconstrictor, pro-fibrotic, and pro-inflammatory molecule, into vasodilatory angiotensin 1–7. SARS-CoV-2 infection decreases ACE2 expression, increasing Ang II activity and insulin resistance [41]. Increased immunological response also occurs with SARS-CoV-2 infection. Reports state SARS-CoV-2 damages pancreatic beta cells, with significantly increased fasting glucose in infected individuals not receiving glucocorticoids versus non-SARS pneumonia patients [16]. Viral infection destroys pancreatic beta cells and disturbs blood glucose homeostasis in T2DM patients. These glucose metabolism alterations and pancreatic SARS-CoV-2 infections may initiate T2DM or type 1 diabetes onset [45]. One study showed a ~40% diabetes increase in SARS-CoV-2 infected individuals, though the reasons are not fully known [17].

5. COVID-19 Mediated Inflammatory Responses Pertaining to Diabetes

Cytokine storm is a major disturbance in COVID-19 patients. Diabetic male mice showed altered CD4 T helper cell counts and elevated IL17α [18]. In a MERS model, diabetic mice had fewer inflammatory macrophages, CD4 T cells, and very low CCl2 and CXCl10 versus controls. COVID-19 patients have not only low CD4 and CD8 cells but increased pro-inflammatory cytokines [19]. DM patients also show abnormal antiviral interferon response, delayed Th1/Th17 activation, and increased inflammation [20]. Mild COVID-19 induces a pro-inflammatory response with high inflammatory cytokines and IP10, decreasing insulin sensitivity. DM suppresses neutrophil chemotaxis, phagocytosis, and intracellular microbial killing. Thus, diabetes patients show initial Th1 cell-mediated immunity activation delay, adaptive immunity abnormalities, and a late hyperinflammatory response [21].

6. Conclusions

The percentage of diabetics is very high among SARS-CoV-2 infected patients. Currently, about 15% of COVID-19 patients have diabetes. Diabetics have very high COVID-19 risk. Though the pathophysiological and molecular mechanisms linking the diseases are not fully understood, evidence shows diabetes plays an important role in COVID-19 infection and affects severity. One

possibility for increased COVID-19 severity in diabetics is deregulated immune cells causing poor SARS-CoV-2 responses, co-existing conditions like obesity, hypertension, and cardiovascular disease, altered ACE-2 receptor expression, and endothelial dysfunction. Diabetics are highly recommended to adhere to treatment recommendations for SARS-CoV-2 infection, regularly monitor blood glucose, and follow appropriate COVID-19 behaviors. Treating SARS-CoV-2 infected diabetics differs from the general population, requiring special care. Caution is needed when recommending commonly prescribed anti-diabetic drugs like biguanides, SGLT2 inhibitors, DPP-4 inhibitors, sulfonylureas, and insulin, as reports show these could exacerbate COVID-19 conditions. However, controversies persist regarding using these agents in SARS-CoV-2 infected diabetics, as some studies report potential benefits while others show detrimental outcomes. Further research is therefore needed to suggest appropriate treatment and dietary regimens for individuals with coexisting diabetes and COVID-19.

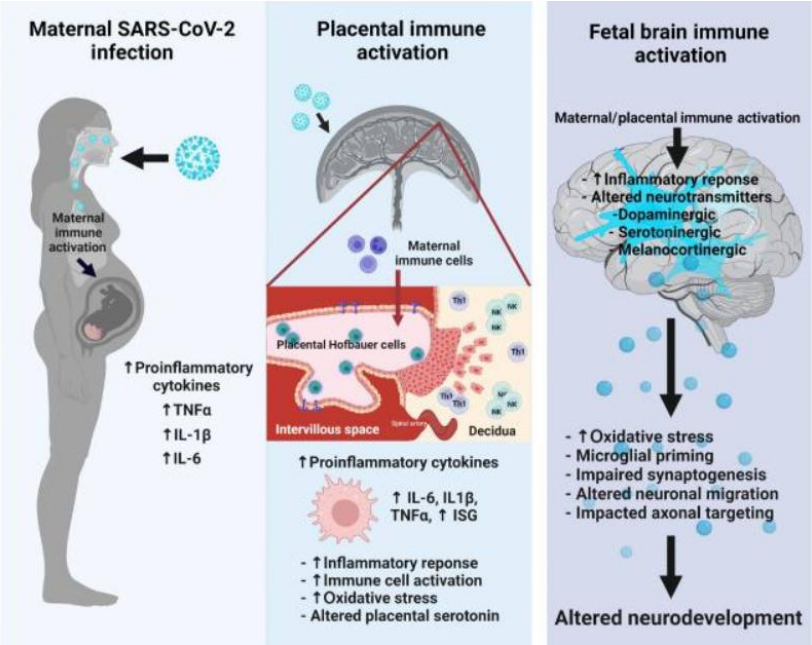

Fig (1) the mechanisms through which COVID-19 Impacts the maternal Immune system and its effect on childhood Diabetes development

7. References

1. Sharma A., Tiwari S., Deb M.K., Marty J.L. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): A global pandemic and treatment strategies. Int. J. Antimicrob. Agents. 2020;56:106054.
2. Rabi F.A., Al Zoubi M.S., Kasasbeh G.A., Salameh D.M., Al-Nasser A.D. SARS-CoV-2 and coronavirus disease 2019: What we know so far. Pathogens. 2020;9:231.
3. Satarker S., Nampoothiri M. Structural proteins in severe acute respiratory syndrome coronavirus-2. Arch. Med. Res. 2020;51:482–491.
4. Pitocco D., Tartaglione L., Viti L., Di Leo M., Pontecorvi A., Caputo S. SARS-CoV-2 and DPP4 inhibition: Is it time to pray for Janus Bifrons? Diabetes Res. Clin. Pract. 2020;163:108162.
5. Hamming I., Timens W., Bulthuis M., Lely A., Navis G.v., van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. A J. Pathol. Soc. Great Br. Irel. 2004;203:631–637.
6. Bosch B.J., Bartelink W., Rottier P.J. Cathepsin L functionally cleaves the severe acute respiratory syndrome coronavirus class I fusion protein upstream of rather than adjacent to the fusion peptide. J. Virol. 2008;82:8887–8890.
7. Amara A., Mercer J. Viral apoptotic mimicry. Nat. Rev. Microbiol. 2015;13:461–469.

8. Azkur A.K., Akdis M., Azkur D., Sokolowska M., van de Veen W., Brüggen M.C., O'Mahony L., Gao Y., Nadeau K., Akdis C.A. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75:1564–1581.
9. Charlton B., Lafferty K.J. The Th1/Th2 balance in autoimmunity. Curr. Opin. Immunol. 1995;7:793–798.
10. Bell T.J., Brand O.J., Morgan D.J., Salek-Ardakani S., Jagger C., Fujimori T., Cholewa L., Tilakaratna V., Östling J., Thomas M. Defective lung function following influenza virus is due to prolonged, reversible hyaluronan synthesis. Matrix Biol. 2019;80:14–28.
11. Xu C., Zia U. Recovery from acute kidney injury with diabetic ketoacidosis following SARS-CoV-2 infection: A case report and literature review. Cureus. 2020;12:e11702.
12. Skyler J.S. Diabetes mellitus: Pathogenesis and treatment strategies. J. Med. Chem. 2004;47:4113–4117.
13. Singh A.K., Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A narrative review. Diabetes Res. Clin. Pract. 2020;165:108266.
14. Al-Sayyar A., Hulme K.D., Thibaut R., Bayry J., Sheedy F.J., Short K.R., Alzaid F. Respiratory Tract Infections in Diabetes–Lessons from Tuberculosis and Influenza to Guide Understanding of COVID-19 Severity. Front. Endocrinol. 2022;13:919223.
15. Mazucanti C.H., Egan J.M. SARS-CoV-2 disease severity and diabetes: Why the connection and what is to be done? Immun. Ageing. 2020;17:21.
16. Wang A., Zhao W., Xu Z., Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res. Clin. Pract. 2020;162:108118
17. Hussain A., Bhowmik B., do Vale Moreira N.C. COVID-19 and diabetes: Knowledge in progress. Diabetes Res. Clin. Pract. 2020;162:108142.
18. Mirabelli M., Chiefari E., Puccio L., Foti D.P., Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. Int. J. Environ. Res. Public Health. 2020;17:3664.
19. Bielka W., Przezak A., Pawlik A. Therapy of type 2 diabetes in patients with SARS-CoV-2 infection. Int. J. Mol. Sci. 2021;22:7605.
20. Nguyen N.N., Ho D.S., Nguyen H.S., Ho D.K.N., Li H.-Y., Lin C.-Y., Chiu H.-Y., Chen Y.-C. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. Metabolism. 2022;131:155196.
21. Sun B., Huang S., Zhou J. Perspectives of antidiabetic drugs in diabetes with coronavirus infections. Front. Pharmacol. 2021;11:592439.