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RESEARCH ARTICLE

SARS-CoV-2 (COVID-19) Morbidity and Chronic Disease (Type II Diabetes –T2D) and Pancreatic Carcinoma: Clinco-epidemiologic Perspective

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ABSTRACT

Purpose: Viral infections had been historically observed in chronic disease development and complications including although not limited to hepatitis C, influenza A, cytomegalovirus (CMV), Epstein bar virus (EBV), HIV and herpes simplex. Epidemiologic data had implicated CMV, herpes simplex and hepatitis C in type II diabetes (T2D). With the observed increased incidence T2D in COVID-19 among children and adults, this review aimed to examine scientific literature on immune and endocrine systems dysregulation in T2D and pancreatic neoplasm.
Materials & Method: A qualitative systematic review (QSR) was utilized in assessing the immune system deregulation and endocrine system involvement in chronic disease development such as T2D. The PubMed was the main search engine in studies identification with several search terms such as "SARS-CoV-2 and T2D", "COVID-19 and T2D", SARS-CoV-2 and insulin resistant", etc.
Results: Viral pathogens such as CMV, influenza A, and herpes simplex and hepatitis C infections have been implicated in decreased insulin sensitivity (IS) and increased insulin resistant (IR). Similarly, these pathogenic microbes increased the T2D incidence and complications. SARS-CoV-2 a COVID-19 causative pathogen had been observed in increased risk and incidence of T2D among children and adults. While data are not currently available on the precise mechanistic process, SARS-CoV-2 viral infection in T2D incidence may be explained by excess pro-inflammatory cytokines elaboration (cytokine storm) resulting in increased IR and decreased IS, leading to glucose intolerance and T2D. Further COVID-19 may increase pancreatic neoplasm in populations with increased incidence of COVID-19, due to pancreatic beta cells and insulin receptors dysregulation and cellular dysfunctionality as abnormal cellular proliferation.
Conclusions/Recommendation: SARS-CoV-2 a causative pathogen in COVID-19 morbidity is associated with increased incidence of T2D, which is explained in part by immune and endocrine system integration dysregulation, resulting in cytokine storm, decreased IS and increased IR, implying glucose intolerance and T2D. Additionally this pathogenic microbe may result in increasing incidence of pancreatic neoplasm, a malignant neoplasm with the worst prognosis and excess mortality due to late stage at diagnosis and marginalized biomarkers of susceptibility and morbidity.
Keywords: COVID-19; SARS-CoV-2; Type II Diabetes; Increased Insulin resistance; Decreased Insulin Sensitivity

Introduction

The current (second week in January, 2022) weekly moving average of COVID-19 incidence (709,633, implying 76% increase a week ago); hospitalization (141,385, (37%) and mortality incidence, 1,615 (29%)), and the vaccination prevalence of 62.5% is indicative of the need to examine COVID-19 complications and long term effect upon treatment and recovery. Viral pathogenic microbes infectivity and clinical manifestations, historically and currently had been observed with chronic diseases, following treatment and recovery [1,2]. SARS-CoV-2, a causative pathogen in pediatric COVID-19 as well as adult sub-population had been identified with increasing type II diabetes (T2D), however the precise mechanism of this clinical condition is not fully understood, requiring molecular assessment as well as clinical guidelines and therapeutics. Since this pathogen especially the delta variant had been observed with multiple organ compromization due to marginalized perfusion in some patients, the implication of increased incidence in T2D among children infected with this viral pathogen may be due in part to decreased availability of the beta cells and insulin receptors in the pancreas, required for insulin binding and the glucose transformation to glycogen for hepatic storage and subsequent utilization for metabolic activities.

Currently, non-experimental epidemiologic studies have implicated diabetes as cellular glucotoxicity in pancreatic neoplasm and with the increasing incidence of T2D among children plus the increasing incidence in T2D associated with COVID-19, pancreatic neoplasm incidence [3 – 5]. This malignancy is the only neoplasm with lower prevalence relative to incidence in any setting. However, this low prevalence is due to lack of appropriate and reliable biomarker and late stage at diagnosis.

This qualitative systematic review (QSR) attempts to examine viral pathogens (inflammatory process and immunologic response) associated with chronic disease manifestations such as T2D and the implication of COVID-19 in increasing T2D among children, especially pre-diabetics, as well as possible mechanism of this implication (immunologic and endocrinologic mechanistic interaction) . Further, this QSR although inconclusive with respect to inference since scientific evidence discovery remains dynamic and not static, attempts to provide a clinico-epidemiologic recommendation in T2D incidence reduction affiliated with COVID-19 pandemic in pediatric and adult environment.

Materials & Method

A Qualitative systematic review (QSR) was used to assess published scientific literature on the implication of viral pathogens in chronic disease with specific focus on Insulin sensitivity (IS), Insulin resistant (IR) and T2D. Additionally SARS-CoV-2 and T2D remained a focus although marginalized data in this pathway in T2D incidence. This process involved the identification of peer reviewed studies based on sample size, objective, research question, design, analysis and inference. The search strategy involved: "viral microbes and chronic disease", SARS-Cov-2 and chronic disease", viral pathogens and insulin resistance", "SARS-CoV-2 and insulin resistance" The inclusion criteria reflected only studies with full body text and not abstract as well as studies in English and Italian languages only. Studies with sample size < 10 on non-experimental epidemiologic design were not considered in the evidence synthesis in this QSR.

Results: Qualitative Systematic Review (QSR) Evidence Synopsis (ES)

The QSR design in evidence synthesis requires the observation of findings considered to be accurate based of the research questions, design, analysis and inference. The current result reflects the summary, synopsis and synthesis of the observed studies utilized in this QSR as a brief scientific report for an objective dissemination.

Viral Pathogens, Chronic Diseases (T2D) and Malignant Neoplasia

Immuno-epidemiologic data have historically and till date implicated viral infections such as influenza A, herpes simplex, hepatitis C, CMV, etc in diabetes mellitus as well as Epstein bar virus in infectious mononucleolosis and chronic diseases [6 – 8]. The viral implications in T2D is explained in part by aberrant insulin sensitivity (IS) resulting in insulin resistant (IR). Epidemiologic data have implicated marginalized IS in hepatocellular carcinoma, implying increasing incidence of this malignant neoplasm among patients with T2D [9 – 12].

The inert and adaptive human immune system responsiveness in viral infection involves pro-inflammatory mediators and cytokines as cell

signals such as interleukin (IL) beta - (IL-1β), IL-6, IL-8 and interferon gama (IFNγ) as well as tumor necrotic factor (TNF). The elaboration of these mediators in viral infections impairs IS, resulting in IR and glucose intolerance. Specifically, IL-6 had been implicated in suppressor cytokine signaling activation, resulting in marginalized IS. Further, INFγ elaboration from the natural killer cells (NKC) following viral infection had been observed in insulin receptor expression downregulation as well as IL-1β as a pro-inflammatory cytokine from macrophage, as antigen processing cells (APC) in collaboration with MHC-I in helper T-cell (CD4) activation and cytokines elaboration. Consequently, these cellular signals elaborations in these viral infections facilitate cytokine storm, resulting in < IS, and > IR and T2D incidence.

SARS-Cov-2, T2D and Malignant Neoplasia (Hepatocellular and Pancreatic neoplasia)

While there are no specific data on SARS-CoV-2 mechanism in marginalized IS and increased IR, T2D had been observed among pediatric patients with COVID-19 as well as adult patients. The observed increased incidence of T2D is explained in part by IS, IR, beta cells and receptors downregulation as well as the elaborated pro-inflammatory cytokines [13,14].

Whereas viral infection requires IFN gama elaboration, SARS-CoV-2 was associated with marginalized elaboration among patients with severe manifestations. The observed IFN gama adverse elaboration resulted in exponential transmission, severe inflammatory response, pneumonia, cytokine dysregulation, as well as pulmonary edema, neurologic dysfunction and hypercoagulopathy. T2D patients infected with SARS-CoV-2 with severe clinical features were characterized with excess mortality relative to non-T2D patients. The increase in hyperglycemic index among diabetic patients with COVID-19 reflects glucose dysregulation mediated by impaired immune responsiveness, enhancing cytokine storm [15 – 20].

The observed incidence of T2D in the pediatric COVID-19 population is explained in part by pro-inflammatory mediators and cytokines as cell signals such as interleukin (IL) beta -(IL- 1β), IL-6 and interferon gama (IFNγ) as well as tumor necrotic factor (TNF) elaborations. With these inflammatory mediators in SARS-CoV-2 infections and COVID-19 morbidity, there remains impaired IS, resulting in IR and glucose intolerance, with T2D as a chronic disease.

While chronic hepatitis C infection had been implicated in hepatocellular carcinoma, the high hyperglycemic index in COVID-19 may result in hyperinsulinemia and glucose intolerance. With this molecular alteration, the beta cells of the pancreas reflect insulin dysregulation and the subsequent impairment in the DNA replication, RNA transcription and mRNA translation, resulting in impaired gene expression, abnormal protein synthesis and cellular dysfunctionality. Whereas the exact pathway to pancreatic neoplasm incidence or development from COVID-19 is not fully understood, this condition may result in increased incidence of pancreatic neoplasm in future.

Conclusions/Recommendations

Historical data on viral implication in chronic disease namely T2D clearly observed immunologic and endocrinologic interaction dysregulation. SARS-CoV-2 and COVID-19 remain a predisposition to T2D, while high hyperglycemic index remains to adversely affect the beta cells in the pancreas and the insulin receptors, leading to pancreatic neoplasm, a unique malignancy, with incidence rate higher than the prevalence proportion, due to late stage at diagnosis driven by inadequate and accurate biomarker currently.

The findings from this QRS although inconclusive, since all scientific evidence discovery are driven by uncertainties (random error quantification), is indicative of the need for the scientific community and public health experts globally to:

(1) Advocate SARS-CoV-2 testing, tracing and tracking for diagnosis and treatment of COVID-19 patients in preventing T2D incidence.
(2) Encourage all vaccine eligible Americans to be fully vaccinated, implying first and booster shots of Pfizer and Moderna for community herd immunity enhancement and marginalized transmissions.
(3) Encourage the utilization of the pending FDA approval of the antiviral agent in symptoms management and immune system enhancement of patients with early COVID-19 symptoms manifestations.
(4) Recommend the healthcare system blood glucose level assessment for all patients with COVID-19 and SARS-CoV-2 sero-positivity.

(5) Encourage physical and social distancing outside and indoors if feasible.
(6) Require vaccinated and unvaccinated (ineligible individuals) to wear face mask such as N-95 in any gathering including place of worship, since, God, Divine or Supernatural being works with the human society and not for the human society.
(7) Advocate indoor air quality and ventilation in all settings for CO2 marginalization and O2 enhancement.
(8) Encourage all seropositive individuals in any setting to be tested negative prior to community interaction and return to work including the healthcare system. Such initiative protects non-COVID-19 patients from SARS-CoV-2 transmissibility and infection from the healthcare facility or hospital.

With the T2D in this pandemic remaining global in terms of increasing incidence, the industrialized nation should allocate adequate and appropriate vaccines to the under developed nations in the world, as well as provide resources for the training of healthcare providers in these countries, thus appropriately delivering these vaccines to the poor and the undeserved in these global communities. The adherence to these observations and recommendations will allow for lower incidence of COVID-19-related T2D and the long-term effect of pancreatic neoplasm. While these recommendations remain inconclusive, the WHO and CDC should apply scientific data which are dynamic and not static in addressing TD2 and potential pancreatic malignant neoplasm in COVID-19 pandemic.

Dedication: This QSR is dedicated to **Palmer Beasley, MD, MPH,** former Dean and Professor emeritus, University of Texas -School of Public Health (in memoriam), who dedicated his career in the evaluation of chronic hepatic disease in hepatocellular carcinoma.

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Conflict of Interest: All authors have declared no conflict of interest.

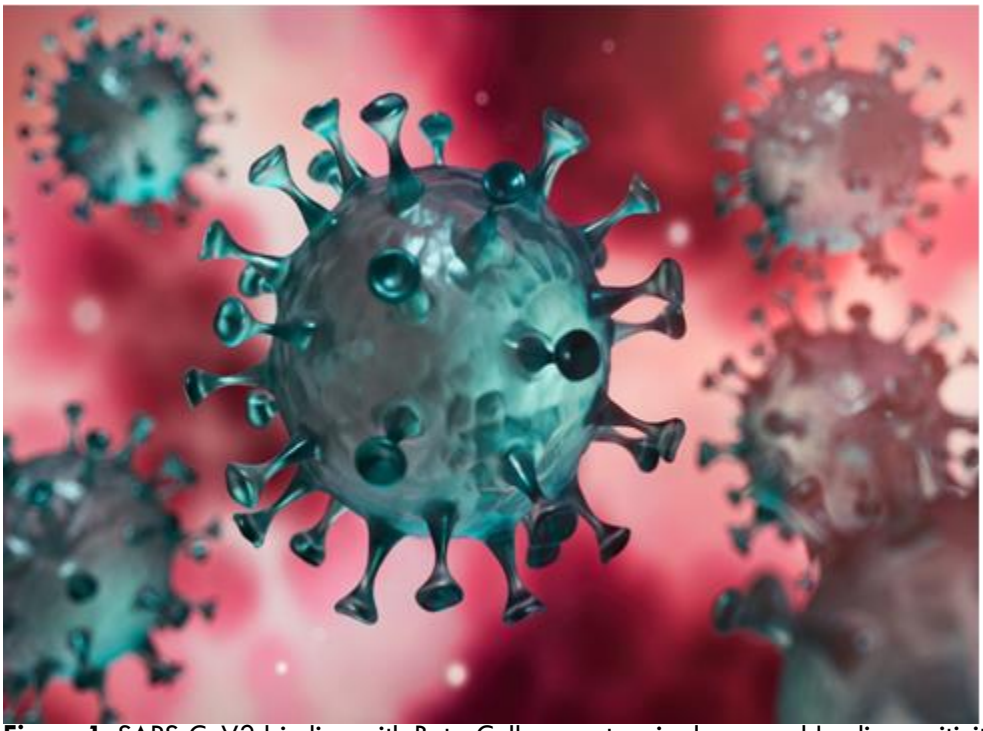

Figure 1. SARS-CoV2 binding with Beta Cells receptors in decreased Insulin sensitivity and increased insulin resistance.

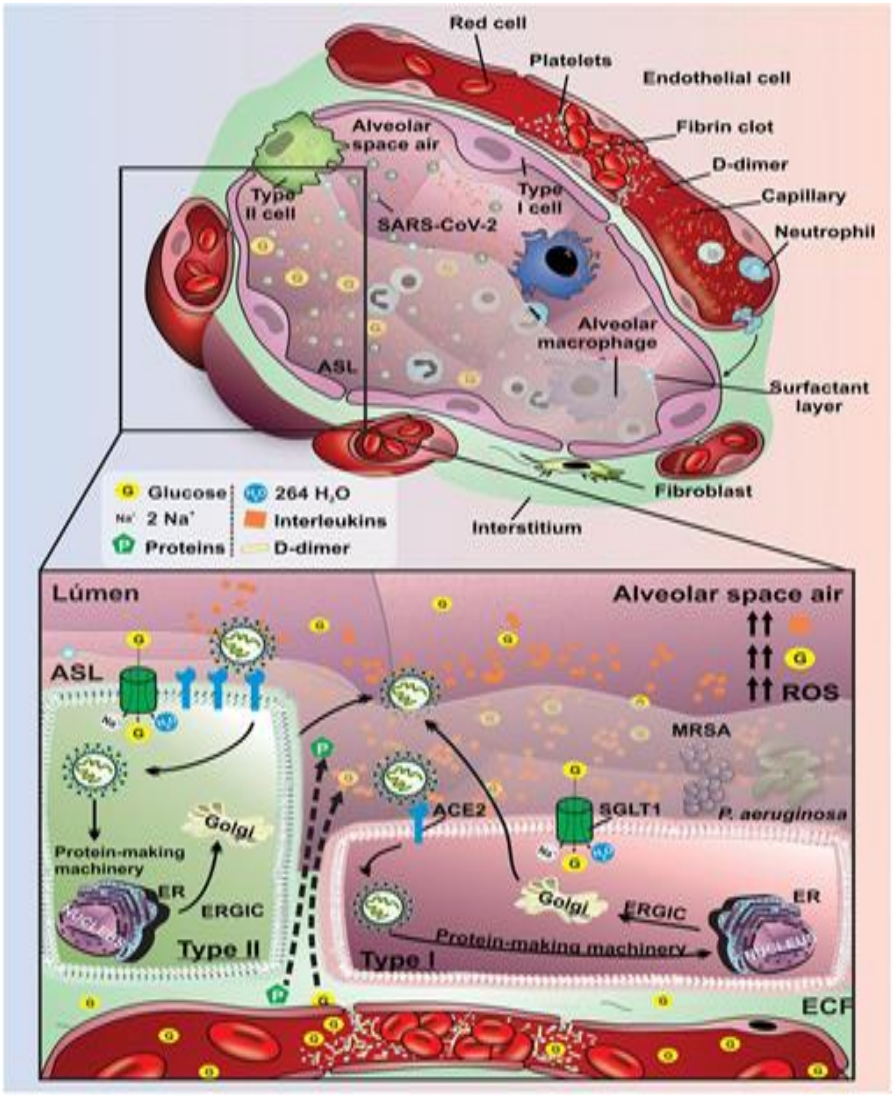

Figure 2: Immune and endocrine system integration in glucose intolerance and T2D.

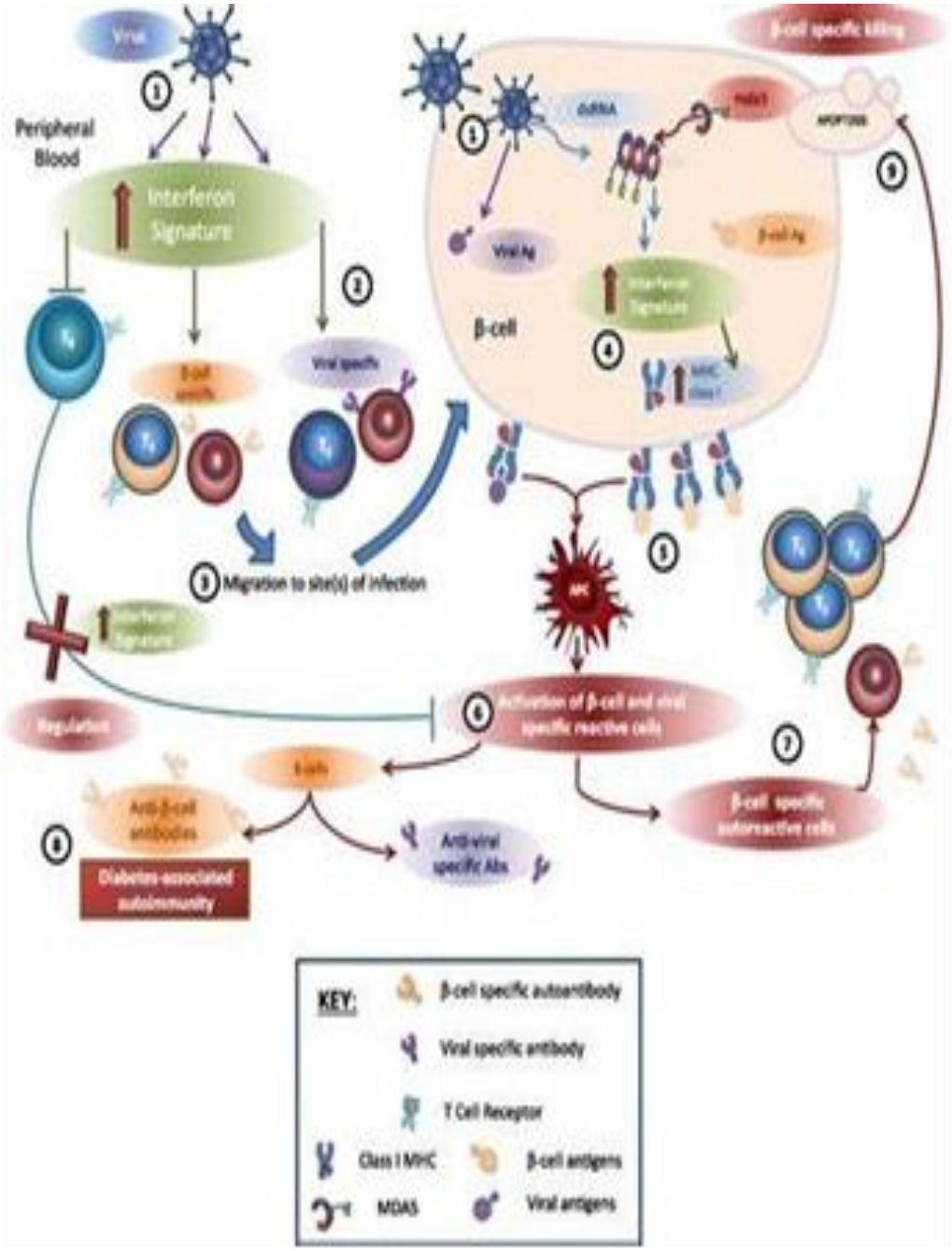

Figure 3: Viral involvement within the peripheral blood and interferon activation inducing beta cells down regulation and glucose intolerance, enhancing T2D incidence.

References

1. O'Connor SM, Taylor CE, Hughes JM. Emerging Infectious Determinants of Chronic Diseases. *Emerging Infectious Diseases*. 2006;12(7):1051-1057. doi:10.3201/eid1207.060037

2. Rasa S, Nora-Krukle Z, Henning N, et al. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Journal of Translational Medicine*. 2018;16(1). doi:10.1186/s12967-018-1644-y

3. Valaiyapathi B, Gower B, Ashraf AP. Pathophysiology of Type 2 Diabetes in Children and Adolescents. *Current Diabetes Reviews*. 2018;14. doi:10.2174/1573399814666180608074510

4. Remedi MS, Emfinger C. Pancreatic β-cell identity in diabetes. *Diabetes, Obesity and Metabolism*. 2016;18:110-116. doi:10.1111/dom.12727

5. Bensellam M, Jonas JC, Laybutt DR. Mechanisms of β-cell dedifferentiation in diabetes: recent findings and future research directions. *The Journal of endocrinology*. 2018;236(2):R109-R143. doi:10.1530/JOE-17-0516

6. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. *Viruses*. 2019;11(8):762. doi:10.3390/v11080762

7. Burrell CJ, Howard CR, Murphy FA. Viral Syndromes. *Fenner and White's Medical Virology*. Published online 2017:537-556. doi:10.1016/B978-0-12-375156-0.00039-4

8. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. *Frontiers in Immunology*. 2021;11. doi:10.3389/fimmu.2020.587380

9. Parikh HM, Elgzyri T, Alibegovic A, et al. Relationship between insulin sensitivity and gene expression in human skeletal muscle. *BMC Endocrine Disorders*. 2021;21(1). doi:10.1186/s12902-021-00687-9

10. Kälsch J, Bechmann LP, Heider D, et al. Normal liver enzymes are correlated with severity of metabolic syndrome in a large population-based cohort. *Scientific Reports*. 2015;5(1). doi:10.1038/srep13058

11. Bose SK. Hepatitis C virus infection and insulin resistance. *World J Diabetes*. 2014;5(1):52. doi:10.4239/wjd.v5.i1.52

12. Bose SK. Hepatitis C virus infection and insulin resistance. *World J Diabetes*. 2014;5(1):52. doi:10.4239/wjd.v5.i1.52

13. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2020;Volume 13:3611-3616. doi:10.2147/dmso.s275898

14. Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism. *Frontiers in Endocrinology*. 2019;10. doi:10.3389/fendo.2019.00703

15. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *Journal of Biomedical Science*. 2016;23(1). doi:10.1186/s12929-016-0303-y

16. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *Journal of Biomedical Science*. 2016;23(1). doi:10.1186/s12929-016-0303-y

17. Al-Kuraishy HM, Al-Gareeb AI, Alblihed M, Guerreiro SG, Cruz-Martins N, Batiha GES. COVID-19 in Relation to Hyperglycemia and Diabetes Mellitus. *Frontiers in Cardiovascular Medicine*. 2021;8:644095. doi:10.3389/fcvm.2021.644095

18. Muniangi-Muhitu H, Akalestou E, Salem V, Misra S, Oliver NS, Rutter GA. Covid-19 and Diabetes: A Complex Bidirectional Relationship. *Frontiers in Endocrinology*. 2020;11. doi:10.3389/fendo.2020.582936

19. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nature Reviews Endocrinology*. Published online November 13, 2020:1-20. doi:10.1038/s41574-020-00435-4

20. Montefusco L, Ben Nasr M, D'Addio F, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nature Metabolism*. 2021;3(6):774-785. doi:10.1038/s42255-021-00407-6