Does COVID-19 Warn Us to Revisit Virus-Induced Diabetes?

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Abstract

Diabetes is among the most frequently reported comorbidities in patients with coronavirus disease 2019 (COVID-19) and it represents a strong risk factor for developing severe, critical and fatal forms of COVID-19. The association between diabetes and worse outcome in viral infections is not unexpected, as hyperglycemia is detrimental to the control of viremia and inflammation, and very often linked to accelerated morbidity and mortality in a majority of patients. Understanding the pathophysiological mechanisms underlying the impact of diabetes on COVID-19 progression is now under critical scrutiny in several ongoing investigations, with the ultimate aim of maximizing therapeutic outcomes. On the other hand, there is a new school of thought that COVID-19 and its devastating ravage on multiple organs could be causally linked to new-onset of non-communicable diseases, particularly diabetes. Although this was a topic discussed during earlier human virus exposures, this editorial makes a humble effort to consolidate this new school of thought in the context of COVID-19, supported by very recent literature.

Introduction

It is clearly conceived from several studies worldwide that diabetes is a significant risk factor for coronavirus disease 2019 (COVID-19) progression and several adverse endpoints, including mortality. The associations of diabetes with a variety of viruses/virus infections have been reported previously. The worldwide pandemic of COVID-19, seen in multiple races, ethnicities, age groups, and various co-morbidities, has also prompted study on whether COVID-19 infection could be causally linked to new-onset of non-communicable diseases, particularly diabetes. Although this was a topic discussed during earlier human virus exposures, this editorial makes a humble effort to consolidate this new school of thought in the context of COVID-19, supported by very recent literature.

Diabetes is a Strong Risk Factor for COVID-19 Severity

Several studies have emphasized that individuals with co-morbidities, including diabetes and cardiovascular and pulmonary diseases, have a demonstrated higher risk for severe cases of COVID-19, as well as a higher risk of mortality.1–3 Higher susceptibility of diabetic patients to virus infection was also recognized earlier. In patients with severe acute respiratory syndrome (SARS), pre-existing type 2 diabetes (T2D) was shown to be independently associated with poor outcomes.4 Alqahtani et al.5 have also reported that T2D was the primary comorbidity associated with severe or lethal Middle East respiratory syndrome-coronavirus infections. A very recent multi-centric study6 reported that diabetes status increased the need for medical interventions during COVID-19 as well as increased the mortality risk of patients with COVID-19. That study also reported that good glycemic control correlated with improved outcomes in infected patients and emphasized the need for management of optimal glycemic control.

Several aspects of SARS-CoV-2 pathogenesis and potential implications for clinical management of patients with COVID-19 and diabetes as well as metabolic syndrome were also covered in recent reviews.7,8 Sardu et al.9 have also discussed the clinical and preclinical evidence supporting the hypothesis that the endothelium could be a key target organ in COVID-19, as endothelial dysfunction is linked to several co-morbidities, including diabetes and its severity. Thus, the current COVID-19 pandemic is forcing us to reconsider the ways in which effective diabetes management can be delivered during these challenging times.

Is COVID-19 a Trigger for Diabetes?

COVID-19 continues to teach us a lot of new lessons. The threatening new lesson is that there is a bidirectional relationship between COVID-19 and diabetes. Emerging evidence suggests that the coronavirus might trigger diabetes.10 Very recently, new-onset
diabetes and severe metabolic complications of preexisting diabe-
tes, including diabetic ketoacidosis and hyperosmolarity, have been
reported in patients with COVID-19.11-13 These studies war-
rant that patients with elevated blood sugar and no history of dia-
betes should be evaluated for the possibility of new-onset diabetes
mellitus and diabetic ketoacidosis, especially in the setting of con-
comitant COVID-19 infection.

COVID-19 Warrants a Revisit on Virus-Induced Diabetes

Viruses and type 1 diabetes

Despite the fact that mechanistic explanations for how exactly vi-
ruses may influence type 1 diabetes (T1D) etiology are still not
clearly understood, viruses are considered major environmental
candidates for involvement in the ontology of T1D.14 Although it
is difficult to establish a cause-and-effect relationship between
viral infection and diabetes in humans, preclinical animal mod-
els have provided support of such. Using BioBreeding Diabetes-
Resistant and the LEW1.WR1 rat models, β cell inflammation and
diabetes with many similarities to the human disease have been
shown to be induced by infection with the parvovirus Kilham rat
virus.15 Preclinical support also comes from mouse models for
virus-induced T1D, including: (a) acceleration of disease onset in
prediabetic nonobese diabetic mice following coxsackievirus in-
fec tion; and (b) diabetes induction by lymphocytic choriomeningi-
tis virus infection of transgenic mice expressing viral neo-antigens
under control of the rat insulin promoter.16

Apart from the animal work, the limited human studies im-
ply that viral infection may trigger T1D. Studies that measured
enterovirus RNA or viral protein found a significant association
between enterovirus infection and T1D-related autoimmunity and
clinical T1D.17 In the past, greater incidences of fasting glycemia
and acute-onset diabetes have been reported among patients with
SARS coronavirus 1 pneumonia.18 Several studies, including ones
on identical twins, suggest that environmental factors such as vi-
ruses and other pathogens may be critical triggers, either through
direct cytolytic effect and gradual beta cell destruction or by by-
stander activation of the immune system.19

Viruses and type 2 diabetes

While the development of type 2 diabetes (T2D) involves com-
plex and heterogeneous processes, virus infection has also been
implicated. Several studies have demonstrated the prevalence of
T2D among persons with hepatitis, suggesting a two-way connec-
tion between diabetes and hepatitis C virus.20,21 An independent
effect of hepatitis C virus—related cirrhosis on increasing T2D in-
cidence has also been reported.22 In the context of an association
of virus infection with T2D and Alzheimer’s disease,23 there is also
demand for identification of a single or a panel of likely blood-
based viral biomarkers for early diagnosis of diabetes as well as
Alzheimer’s disease. In a recent multi-omics longitudinal study,24
which followed the changes that occurred during respiratory viral
infections, an impaired immune response to respiratory viral in-
fec tions was demonstrated in insulin-resistant individuals and this
attests a potential contribution of respiratory viral infections to the
increased risk of T2D development.

In the context of COVID-19, we conceive the hypothesis that
COVID-19 consequences on multiple organs, for example, hepatic
manifestations as well as amyloid-associated β cell dysfunction
may drive new-onset T2D. Cases of liver damage or dysfunction
(mainly characterized by moderately elevated serum aspartate
aminotransferase levels) have been reported among patients with
COVID-19.25 It is suggested that COVID-19 may predispose in-
dividuals to increased risk for unrecognized underlying liver dis-
 ease, especially nonalcoholic fatty liver disease26 as well as other
hepatic consequences of COVID-19 infection;27 these are, in turn,
strong risk factors for T2D. Considering that fatty liver is an early
instigator of T2D and alteration in hepatic glucose homeostasis is one
of the hallmarks of T2D, there is increasing attention being paid
to following-up of COVID-19 patients for hepatic manifestations.

It is now well conceived that β cell dysfunction is linked to
differential activation of innate immune pathways by distinct islet
amyloid polypeptide (IAPP) aggregates.28 While a study29 recently
found respiratory syncytial virus and herpes simplex virus type 1
to accumulate a rich and distinctive protein corona in different bio-
 logical fluids, it is interesting to note that the study also demon-
strated that viruses bind amyloidogenic peptides in their corona
and catalyze amyloid formation via surface-assisted heterogeneous
nucleation. Very recently, using a vaccine based on virus-like
particles coupled to IAPP peptides (that induce specific antibod-
ies against aggregated IAPP), it was demonstrated in vivo that the
codeveloped IAPP deposition, decreased pro-inflammatory
cytokines, and delayed onset of hyperglycemia.30 These collective
findings emphasize that the mechanistic convergence between vi-
ral and amyloid pathologies should be studied in-depth in the con-
text of T2D and Alzheimer’s disease.

Diabetogenic effect of COVID-19?

There is now a new school of thought, hypothesized by Rubino et
al.33 that there might be a potential diabetogenic effect of COV-
ID-19. However, the following questions remain: a) Are the al-
terations of glucose metabolism that occur with a sudden onset in
severe COVID-19 persistent or transient? b) Will it remit when the
infection resolves? c) How frequent is the phenomenon of new-on-
set diabetes, and is it a classical type 1 or type 2 diabetes, or a sub-
stratified new type of diabetes? and d) Do these patients remain at
higher risk for diabetic ketoacidosis and other complications?

Other interesting questions I propose are: a) If hyperglycemia
in COVID-19 patients is transient, will it pose a potential risk for
later T2D development in a subset of patients, like the phenom-
emon that is very well established in gestational diabetes mellitus?
b) Will COVID-19 infection exploit individuals with prediabetes
for early development of T2D?

Answering these questions will require frequent monitoring and
follow-up in COVID-19 patients subsequent to their recovery.

Proposing “CoviDIAB” for COVID-19 follow-up

The good news is that brain-storming by an international group of
leading diabetes researchers led to establishment of a global reg-
istry of patients with COVID-19-related diabetes, called “CoviDI-
AB” (covidiab.e-dendrite.com).34 The major goal of the registry
is to determine the extent and phenotype of new-onset diabetes
that is defined by hyperglycemia in confirmed COVID-19 patients
(with negative history of diabetes and normal glycated hemoglobin
level). It is mentioned that the registry will be expanded to include
patients with preexisting diabetes who present with severe acute
metabolic disturbance(s), so as to investigate the epidemiologic
features and pathogenesis of COVID-19-related diabetes and to
gain insights on the optimal management of patients during and after the course of COVID-19. Follow-up on COVID-19 patients for diabetes incidence would also stimulate conduct of experimental biology research using human pluripotent stem cells (hPSCs) and organoids.

In fact, Yang et al. generated a library of hPSC-derived cells/organoids and showed that hPSC-derived hepatic and pancreatic cells are permissive to SARS-CoV-2 infection. This fascinating observation was further validated using adult primary human islets, adult hepatic and cholangiocyte organoids, and a humanized mouse model. Thus, closer monitoring of individuals with high risk for diabetes is the need of the day, to evaluate the contribution of SARS-CoV-2 in previously infected COVID-19 patients regarding progression toward type 1 or type 2 diabetes. It is expected that such hPSC/organoid-based platform can also be used for drug screening, with an aim towards development of prospective antiviral therapeutics.

Future directions

As COVID-19 pandemic continues, there is an imperative need for COVID-19 follow-up studies to track and understand its long-term health consequences. It is important to notice that there are few cases of reactivation of COVID-19 in apparently cured patients and such relapse of COVID-19 could pose a vicious cycle of public health burden. Although preliminary evidences suggest that antibody responses occur in those who have been infected, further studies are needed to differentiate whether these IgG antibodies are protective or not & if protective, how long this protection lasts needs to be evaluated. Earlier follow-up studies done in patients infected with SARS and MERS-CoV did noticed long-term health burden with poor quality of life. Therefore, depending on the individual’s metabolism and immunity, there is also a concern in that your health may never be the same after COVID-19 infection and in this context, several cohort studies are underway to study the long-term health consequences. The proposed ‘CoviDIAB’ study discussed in this review is one such visionary effort with regard to studying the genesis of diabetes and its complications. In fact, COVID-19 follow-up studies should track the occurrence of all non-communicable diseases to better understand the long-term health consequences. Such cohort studies that follow populations over years are the need of the day to trace the pandemic’s physical, mental and social consequences so as to develop and adopt suitable prevention and disease-management strategies.

Conclusions

As more and more studies are being conducted and published, there is increasing attention in studying the bidirectional relationship between COVID-19 and diabetes—nutshell details are illustrated in Figure 1. First, it is now well-conceived that diabetes patients, characterized by their subclinical inflammation and immune-compromised state, are more susceptible/vulnerable to COVID-19 infection. Secondly, COVID-19 infection in diabetic patients aggravates morbidity and may be linked to increased mortality. The biological explanations for this could be virus exploitation of multiple organs, severity due to altered ACE2 activity and Ca\textsuperscript{2+} homeostasis breakdown, preexisting diabetes-induced target organ damage, chronic inflammation, endothelial dysfunction, hyper-coagulable state, activation of renin-angiotensin-aldosterone system (RAAS), dysregulation of sympathetic nervous system; increased oxidative stress, ER stress and senescence.
such as ‘CoviDiAB’, should deliver mechanistic outcomes in this direction.

It appears that understanding how COVID-19-related diabetes develops and the new-biology etiology of this disease would pave the way for stratification of diabetes, perhaps using a special category which I proactively propose as “VIDM” for virus-induced diabetes mellitus. Such stratification of diabetes might require different treatment modalities in the context of personalized/precision medicine. With the alarming pandemic of COVID-19, it’s time for India and other developing countries to join the global registry as well as to start their own COVID-19 registry with much more focus on cohort-specific follow-up investigations.

It is expected that this brief overview would stimulate more brain-storming and discussion on the mechanisms and possibilities of COVID-19-induced diabetes among the researchers, clinicians, government health authorities and patients.

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