Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor: Mechanisms of increased morbidity and mortality of SARS-CoV-2 infection in individuals with diabetes: what this means for an effective management strategy

Dear Sir,

A diagnosis of diabetes has been a key indicator of the severity of COVID-19, and in this regard, the virus has relentlessly highlighted our global Achilles heel of metabolic dysfunction, and points to a prime opportunity to fight back.

That fight, however, is not going to be won with Clorox, Purell, masks, or anti-IL-6 drugs. The fight will only be won through a serious commitment to improving everyone's foundational metabolic health, starting with the lowest hanging evidence-based fruit: dietary and lifestyle interventions. Unfortunately, the overwhelming thrust of the literature published to date on COVID-19 and diabetes has emphasized medications as the lynchpin of glycemic control; this focus is important but too narrow in the face of the large body of research supporting nutritional and behavioral interventions to rapidly improve glucose levels and inflammation [1].

It's an epidemiologic and biologic fact that acquired disorders of glucose metabolism are mostly preventable [2], and often reversible [3], with healthy living strategies. With that, our war against SARS-CoV-2 must soon shift to focus on supporting Americans in getting to a healthy weight [4], improving glycemic control, and restoring insulin sensitivity. Recent published models suggest that we may be moving in the wrong direction, predicting that glycemic control will severely worsen due to social isolation and lockdown, with an estimated 3.68% increase in HbA1c over 45 days for individuals with diabetes during this pandemic [5]. These models highlight the imperative need to support patients with clear, evidence based dietary and lifestyle strategies for glycemic control that they can implement at home.

Examining the multifarious mechanisms through which SARS-CoV-2 increases morbidity in people with diabetes shows us that the relationship is complex, and is a testament to the fact that we are misplacing our resources attempting to fast-track targeted therapeutics, which may chip away at some detrimental inflammation in infected patients, but do little to foundationally improve metabolic and immune resilience against this pandemic or future ones.

This commentary reviews the numerous biologic mechanisms that have been presented in recent literature that may explain why people with diabetes fare worse with COVID-19 than those without. Some of these mechanisms are related to general immune dysfunction, while others are specifically related to this virus. Together, they highlight the multi-system impact of hyperglycemia and metabolic dysfunction on the body's readiness to face infectious disease.

In a 2011 study looking at 21 patients with type 2 diabetes and 21 healthy volunteers, it was found that there was a significant negative correlation between fasting glucose and ability of immune cells to perform phagocytosis [6]. Promisingly, when patients with diabetes underwent intensive 5 day interventions to improve their blood glucose control under monitored conditions, phagocytosis ability improved [6].

Both diabetes [7] and even short bouts of hyperglycemia [8] can acutely alter immune cells' ability to function properly through multiple mechanisms [9]. First, high glucose alters chemotaxis and subsequent phagocytosis. What's more, high glucose levels may prevent a normal respiratory burst, the process by which immune cells kill pathogens by releasing toxic chemicals [9].

Additionally, in the setting of hyperglycemia, glucose can increasingly glycate antibodies, which may reduce their functionality and impair complement fixation [10]. With this information in mind, it seems sensible to focus on minimizing hyperglycemia in order to enhance our immune cells' ability to function properly.

Both diabetes and obesity can lead to a pro-inflammatory state in the body, with circulation of excess cytokines that keep the immune system in “threat” mode. These cytokines, including IL-6 and TNFα, have been found to be elevated in the patients that show severe disease in COVID-19 [11,12], and are associated with increased disease severity [13]. Monoclonal antibody IL-6 inhibitors (normally used in autoimmune diseases like rheumatoid arthritis) are being tested as therapeutics to mitigate immune-mediated morbidity in COVID-19 patients [14]. TNFα, IL-1 and IL-6 are, at baseline, more active in the setting of diabetes and obesity, and it has been posited that infection with SARS-CoV-2 may serve to amplify an already primed cytokine response in patients with these conditions, thus exacerbating the cytokine storm that appears to be driving the multiorgan failure seen in COVID-19 [15].

It also appears that certain “helpful” immune cells (certain subsets of CD4+ and CD8+ T cells) that coordinate the immune response are decreased in concentration in the blood of people with diabetes who have COVID-19, and there is a higher proportion of pro-inflammatory immune cells (i.e. Th17 cells) [4]. SARS-CoV-2 may infect circulating immune cells and cause increased cell death of these more helpful immune cells, leading to lymphocytopenia, which is associated with worse severity of COVID-19 [4]. The death of CD4+ and CD8+ T cells relieves inhibition and effective modulation of the innate immune system, causing an exaggerated deluge of inflammatory cytokines, resulting in a cytokine storm. Specifically, recent reports have shown that there are reduced numbers of memory T lymphocytes, Treg subtypes, and helper T cells in patients with severe COVID-19 [15]. In short COVID-19 generates an uncoordinated and aggressive immune response, specifically in those with diabetes, and this immune response causes intense damage to organs. The baseline pro-inflammatory state found in diabetes and obesity may serve to exacerbate this.

A theorized potential link between diabetes and COVID-19 mortality lay in hemoglobin [16]. Because of higher circulating glucose levels, patients with diabetes will have a higher percentage of glycated hemoglobin. SARS-CoV-2 surface proteins seem to bind to and potentially impair the heme molecule within red blood cells, causing separation of iron from the molecule to form a porphyrin [16]. This results in red

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blood cells carrying less oxygen and carbon dioxide, and thereby can generate cell death and intense inflammation in the lungs. Because patients with diabetes and older people have more glycated hemoglobin, they may be preferentially affected by SARS-CoV-2 binding and dissociation of iron from heme to form porphyrins [16].

SARS-CoV-2 is able to enter human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in lung tissue, cardiac tissue, endothelial cells of blood vessels, the kidney, intestinal cells, hepatocytes, and pancreas cells [4], and which appears to have increased levels on the cells of people with diabetes, potentially thereby facilitating increased opportunity for the virus to infect cells [17].

The ACE2 receptor may be increased in patients taking specific medications, including GLP-1 agonists, thiazolidinediones, ACE inhibitors, statins, and angiotensin II type-1 receptor blockers (ARBs), all of which are frequently taken by individuals with diabetes [4].

Aside from medications potentially increasing risk of COVID-19 via increasing levels of ACE2, there also may be an additional virus-specific mechanism. It is known that a diabetic state is associated with higher levels of plasmin(ogen), a protease enzyme that can cleave furin sites in COVID-19 S proteins and allow the virus to have easier infectivity [18]. According to a paper published recently in *Physiologic Reviews*, "the cleavage of the new furin sites in the S protein of the [COVID-19] virus by plasmin … may enhance its infectivity by expediting entry, fusion, duplication, and release in respiratory cells. Elevated plasmin (ogen) and furin levels are a common feature in COVID-19 patients with underlying medical conditions, and could be an independent factor for risk stratification of patients with COVID-19 [4,18]." For the virus to infect, the S1 region of its spike fusion protein is cut and released by proteases, allowing the virus to be absorbed into the cell. In short, proteases normally elevated in diabetes may be facilitating viral entry into human cells [4].

It is known that elevated blood glucose levels can directly increase glucose concentrations in airway secretions, and in the case of influenza, the process of exposing lung cells to elevated glucose significantly increased viral infection and replication [19]. Together, this suggests that high blood glucose may increase the replication ability of the virus, although this has not been fully established in COVID-19.

Furthermore, diabetes is associated with structural changes to lung tissue including collapse of portions of the lung and altered permeability of the blood vessels in the lung [19]. This impact of diabetes on lung physiology and structure, in conjunction with the propensity of COVID-19 to infect lung tissue cells, may be contributing to increased mortality.

Research published April 18th, 2020 found that patients exposed to highest amount of environmental nitrogen dioxide (NO_2) had increased risk of death from COVID-19, and that long-term exposure to this pollutant may be one of the most important contributors to fatality by compounding lung inflammation [20]. Additionally, exposure to this trace-gas also has been linked to development of diabetes and many other chronic diseases, and is a potent driver of cytokine release and inflammatory cascades [20]. Minimizing exposure to environmental pollutants may serve a role in quelling the underlying pro-inflammatory state that characterizes metabolic disease and COVID-19 associated cytokine storms, however more research needs to be done to confirm this. Other environmental toxins, including persistent organic pollutants (POPs) found in air, water, and food generated from pesticides and industrial chemicals, are also strongly implicated in the pathogenesis of metabolic syndrome; promoting "clean living," toxin-avoidant strategies for patients as simple as emphasizing organic foods, home air purification, and non-toxic home supplies could be considered, although the clinical utility of these measures in the acute setting is unknown [21].

It is not just diabetes that is making COVID-19 more deadly; it's also possible that COVID-19 is making diabetes worse [11]. It is known that SARS-CoV-2 can infect endocrine pancreas cells via their expression of ACE2 receptors. As such, it's possible that pancreatic damage from the virus and resultant impairment in beta-cell insulin secretion could worsen preexisting diabetes or even predispose to new cases of diabetes in non-diabetic subjects. This could make hyperglycemia worse in the short term (and thus lead to a more severe COVID-19 disease course), and also trigger the emergence of increased rates of autoimmune diabetes, whereby the body coordinates an immune response to the damaged pancreas, with physiology akin to type 1 diabetes.

Given this complexity, it is clear that a piecemeal pharmaceutical approach is misguided; foundationally improving metabolic health is key to resilience against this pandemic and those we will inevitably face in the future. It is important to remember that influenza and other bacterial and viral illnesses also discriminate against people with diabetes, with these individuals being six times more likely to need hospitalization during influenza epidemics than people without diabetes [22]. We must commit to evidence based dietary and lifestyle strategies that prevent and reverse disease, which have been shown to be highly effective (some studies showing reversal of diabetes in as little as 10 weeks of coaching and nutritional interventions) [23]. Strategies that involve optimization of nutrition, exercise [24], sleep hygiene [25], stress management [26], and toxin exposure [27] all play a role in management of metabolic disease, and yet have been largely missing from existing literature on management of diabetes in the setting of COVID-19.

Importantly, the standard Western diet is a known driver of a similar pro-inflammatory signature to that seen in severe COVID-19 physiology, and consuming healthy foods can have a rapid anti-inflammatory effect [1]. Consuming fresh, fiber-rich, whole foods could serve to mitigate some of the overwhelming immune response that appears to be compounded in patients with COVID-19 who have diabetes and obesity, and must be a central focus included in any clinical recommendations made to patients or healthcare systems during this pandemic [28]. Wang, et al. recently put forth "Five No" rules for diabetes management during COVID-19 which included "no going out, no gatherings, no sedentariness, no stop on medications, no anxiety [29]." What is starkly missing is the clear, simple, and strong recommendation for no added sugar or ultrarefined carbohydrates, both of which are known drivers of postprandial hyperglycemia and inflammation. As a medical community, we must not miss the opportunity to serve patients with straightforward, evidence-based nutritional and lifestyle strategies to assist in glycemic control.

Incorporating more emphasis on these strategies could result in a silver lining of the COVID-19 tragedy being that we reverse the tide of the American chronic disease epidemic. If there's anything this COVID-19 pandemic has demonstrated, it's that if there is a collective will, action can happen. We must focus some of that collective will, in the form of practice habits, research efforts, and policy recommendations, on a central factor that will lead to a healthier and more prosperous future: foundational metabolic health.

Declaration of competing interest

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