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Previews

Glucose or Insulin, Which Is the Culprit in Patients with COVID-19 and Diabetes?

Marc Y. Donath[1,*]
[1]University Hospital Basel, Basel, Switzerland
*Correspondence: marc.donath@usb.ch
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Patients with a metabolic syndrome (overweight, diabetes, hypertension, and dyslipidemia) have a particularly bad outcome if infected with SARS-CoV-2. Yu et al. (2020) suggest that insulin therapy itself may promote fatality in patients with COVID-19 and diabetes.

Several comorbidities have emerged as risk factors for severe COVID-19 development, including type 2 diabetes, increased body weight, hypertension, and dyslipidemia. These illnesses characterize the metabolic syndrome. Thereby, increased glucose concentrations may be responsible for the reported poor outcome. Indeed, in a large retrospective study from Wuhan, type 2 diabetes was associated with a higher death rate due to COVID-19, though the death rate was lower with better controlled blood glucose (Zhu et al., 2020). This would advocate for aggressive treatment with glucose-lowering drugs such as insulin. Contradicting this deduction, in a new correlative retrospective paper by Yu et al. (2020), the authors identified insulin treatment as a possible trigger of death rate in COVID-19 patients with diabetes (Yu et al., 2020). Thus, which is the culprit for the worth outcome in patients with COVID-19 and diabetes, hyperglycemia or insulin? Maybe both, and there are still other suspects in these multimorbid patients.

Clinicians reading the paper by Yu et al. (2020) will at first glance think that the mortality imputed to insulin is due to a selection bias. Indeed, among the 689 patients affected by COVID-19 and type 2 diabetes in Tongji Hospital of Wuhan, a retrospective analysis revealed that insulin treatment was associated with a significant increase in mortality. However, baseline characteristics of the patients treated or not with insulin differed in a number of important health measures, including glycated hemoglobin (HbA1c, 8.4% versus 6.9% in the insulin versus non-insulin group, respectively) and C-reactive protein (47.3 versus 15.5 mg/mL in the insulin versus non-insulin group, respectively). To address these issues, the authors made considerable efforts by adjusting the differences using Cox regression and propensity score matching, and performed additional analyses in several subgroups. Even after these analyses, the use of insulin was still associated with a worse clinical outcome.

In light of these robust statistical tests, the data should be taken as a serious warning, even if causality remains unproven. While waiting for prospective studies, understanding the possible underlying mechanisms could add to the credibility of the hypothesis put forward by the authors. An analysis in a subgroup of patients who did not experience hypoglycemia during hospitalization revealed that insulin treatment in this subgroup was still associated with an increased fatality. Thus, insulin-induced hypoglycemia is an unlikely reason for the possible deleterious effects of insulin. The authors propose an alternative explanation involving inflammation. Indeed, while initially no differences in indicators of systemic inflammation were observed, the IL-1β-dependent CRP and IL-6 were elevated in the insulin compared to the non-insulin group. These results suggest that insulin treatment may have aggravated the injury of some organs by promoting inflammation. This is supported by the observation that insulin may stimulate pro-IL-1β maturation via the NLRP3 inflammasome in activated macrophages (Dror et al., 2017) (Figure 1). Importantly, SARS-CoV-2 seems also to activate the NLRP3 inflammasome (Siu et al., 2019) and thus may exacerbate the insulin effect.

Does this mechanism designate insulin as the culprit for a poor outcome in patients with type 2 diabetes affected by COVID-19? The putative responsibility of insulin does not innocent metabolic stress, i.e., hyperglycemia and dyslipidemia. Indeed, increased glucose concentration and free fatty acids may also induce IL-1β (Maedler et al., 2002), and activation of the innate immune system by IL-1 is ostensible in most patients with type 2 diabetes. This sterile inflammation contributes to the pathogenesis of diabetes and its complications, including impaired insulin secretion and sensitivity, cardiovascular diseases, and heart failure (Donath et al., 2019a). Consequently, blockade of IL-1β may improve glycemia (Donath et al., 2019b), cardiovascular complications (Ridker et al., 2017), and heart failure (Abbate et al., 2010). Thus, glucose may also synergize with SARS-CoV-2 and contribute to a deleterious hyperinflammation in diabetic patients affected by COVID-19. Furthermore, beyond directly inducing NLRP3, hyperglycemia may favor SARS-CoV-2 infection. Indeed, Codo et al. show that elevated glucose levels promote SARS-CoV-2 replication in monocytes (Codo et al., 2020). This involves glycolysis with subsequent reactive oxygen species production and cytokine release including IL-1β.

If both insulin and hyperglycemia are to blame, it puts the clinician in a difficult dilemma for the treatment of these vulnerable patients. Alternative

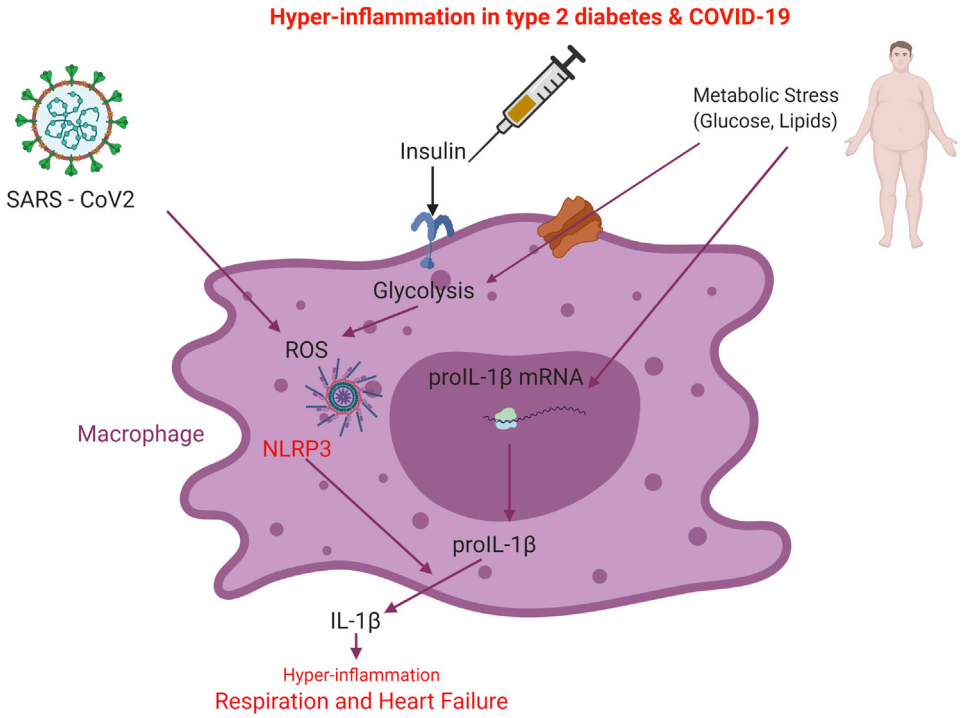

Figure 1. Putative Mechanisms Leading to Cytokine Storm in Patients with COVID-19 and Diabetes
Glucose, lipids, and insulin may potentiate SARS-CoV-2 activation of the NLRP3 inflammasome via glucose metabolism and reactive oxygen species production. This will lead to splicing of pro-IL-1β to IL-1β with subsequent hyper-inflammation inducing respiratory and heart failure.

treatment to insulin should be considered. Yu et al. performed additional analysis and compared insulin with other anti-diabetic treatment in COVID-19 patients. Insulin-treated patients had a significantly higher fatality than those with any other anti-diabetic treatment. Strongly arguing for a deleterious effect of insulin, even patients treated with insulin alone had a higher fatality compared to patients treated with insulin combined with other anti-diabetic drugs, despite higher baseline levels of glucose and HbA1c in the latter group. However, these drugs (metformin, α-glucosidase inhibitors, sulfonylureas, and dipeptidyl peptidase-4 inhibitors) are not very attractive alternatives to insulin in critically ill patients. Indeed, metformin increases the risk of lactic acidosis, α-glucosidase inhibitors and dipeptidyl peptidase-4 inhibitors may not be effective enough to lower glycemia, and sulfonylureas put patients at risk of hypoglycemia. An elegant alternative is sodium/glucose cotransporter 2 inhibitors (SGLT2i), which prevent the reabsorption of glucose in the kidneys, therefore facilitating glucose excretion in the urine. This reduces glycemia without promoting inflammation, since the glucose is eliminated from the body instead of being forced into entering tissues. However, these theoretical thoughts must be corroborated by clinical studies, keeping in mind that SGLT2i may lead to ketoacidosis. Although this untoward effect is rare, it occurs more often in fasting patients with strongly reduced insulin production or action, as observed in some COVID-19 patients with diabetes.

Whether glucose, insulin, or other factors explain the high level of mortality observed in patients with COVID-19 and type 2 diabetes remains unclear. It is difficult to fight an enemy whose identity is nebulous. In today's emergency, clinicians have no choice but to make an educated guess. The retrospective study by Yu et al. may guide their challenging choice until prospective studies provide more robust data.

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Adipocyte Microenvironment: Everybody in the Neighborhood Talks about the Temperature

Farnaz Shamsi,[1] Yu-Hua Tseng,[1] and C. Ronald Kahn[1,*]
[1]Joslin Diabetes Center, Section on Integrative Physiology and Metabolism, Harvard Medical School, Boston, MA, USA
*Correspondence: c.ronald.kahn@joslin.harvard.edu
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Adipose tissue is composed of a variety of cells distributed in different depots and playing various metabolic roles. In a recent issue of *Nature*, Sun et al. (2020) use snRNA-seq and functional studies to identify a population of adipocytes that can suppress the thermogenic activity of neighboring adipocytes by secretion of acetate.

Adipocytes are a major hub for energy balance and fuel metabolism in the body. Inter- and intra-depot heterogeneity of adipocytes offers a wide range of functional diversity enabling short- and long-term regulation of energy storage and dissipation. White adipocytes store energy in the form of triglycerides in lipid droplets and are found in discrete white adipose tissue (WAT) depots, as well as dispersed in other tissues throughout the body. Excess WAT is associated with insulin resistance and metabolic syndrome. Brown and beige adipocytes, on the other hand, are specialized to burn energy and generate heat. Classical brown adipocytes are present in a distinct brown adipose tissue (BAT) depot, while beige/brite adipocytes appear intermixed in WAT depots, where they are induced or activated in response to certain environmental cues, such as chronic cold exposure, exercise training, or pharmacologic treatment with the β-adrenergic receptor activators. In general, increased brown/beige fat is associated with improved metabolic health.

Previous studies using lineage tracing and clonal isolation of adipocyte progenitors have revealed developmental and functional diversity of adipocytes within the brown or white adipose depots (Lee et al., 2019; Min et al., 2019). In their recent paper, Sun et al. have uncovered a new adipocyte subtype that is present in both WAT and BAT that can negatively regulate the thermogenic activity of neighboring adipocytes (Sun et al., 2020). To identify these cells, Sun et al. employed a novel variation of single-nucleus RNA sequencing (snRNA-seq) using murine adipocytes expressing a fluorescent nuclear label. This identified a population of CYP2E1+/ALDH1A1+ adipocytes that represent about 10% of adipocytes in interscapular BAT and 20% of adipocytes in subcutaneous WAT in mice. snRNA-seq of human BAT and WAT demonstrated the presence of similar adipocytes in human adipose tissue. Importantly, they found that the frequency of CYP2E1+/ALDH1A1+ adipocytes in mice decreases upon cold exposure and increases in thermoneutrality, suggesting they may play a negative role in thermogenesis and metabolism.

Previous studies have reported a role for ALDH1A1 (aldehyde dehydrogenase 1 family member A1) in the regulation of adipose thermogenesis and metabolism (Kiefer et al., 2012; Ziouzenkova et al., 2007). ALDH1A1 is a cytosolic enzyme that catalyzes the conversion of retinaldehyde to retinoic acid. Mice lacking *Aldh1a1* display enhanced energy expenditure and are protected against diet-induced obesity and insulin resistance (Ziouzenkova et al., 2007). *Aldh1a1* deficiency in WAT leads to accumulation of retinaldehyde, which activates the retinoic acid receptor and recruits the coactivator PGC-1α to the UCP1 regulatory region (Kiefer et al., 2012). To address the functional role of CYP2E1+/ALDH1A1+ adipocytes in BAT thermogenesis, Sun et al. used a combination of *in vivo* and *in vitro* gain- and loss-of-function studies. Consistent with the above studies, knockdown of *Aldh1a1* in adipocytes resulted in an elevated level of UCP1, the key thermogenic protein, leading to increased BAT glucose uptake and enhanced oxygen consumption upon cold exposure. Conversely, overexpression of *Aldh1a1*