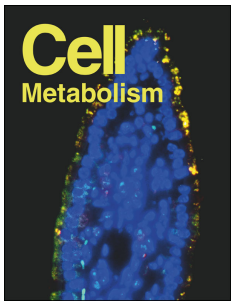

Glucose or insulin, which is the culprit in patients with covid-19 and diabetes?

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Glucose or insulin, which is the culprit in patients with covid-19 and diabetes?

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Patients with a metabolic syndrome (overweight, diabetes, hypertension, dyslipidemia) have a particularly bad outcome if infected with SARS-CoV2. In this issue of *Cell Metabolism*, Yu and colleagues 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) in this issue of *Cell Metabolism*, the authors identified insulin treatment as a possible trigger of death rate in COVID-19 patients with diabetes (Yu, 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) (Yu, 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 characteristic 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, 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 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 difference 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) (Fig. 1). Importantly, SARS-CoV2 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 glycaemia (Donath et al., 2019b), cardiovascular complications (Ridker et al., 2017), and heart failure (Abbate et al., 2010). Thus, glucose may also synergize with SARS-CoV2 and participate to a deleterious hyper-inflammation in diabetic patients affected by COVID-19. Furthermore, beyond directly inducing NLRP3, hyperglycemia may favor SARS-CoV2 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 ROS 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 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 treatment had a significant 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 critical 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 glycaemia 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 glycaemia 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.

Figure caption:
Putative mechanisms leading to cytokine storm in patients with covid-19 and diabetes
Glucose, lipids and insulin may potentiate SARS-CoV2 activation of the NLRP3 inflammasome via glucose metabolism and ROS production. This will lead to splicing of pro-IL-1β to IL-1β with subsequent hyper-inflammation inducing respiratory and heart failure

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