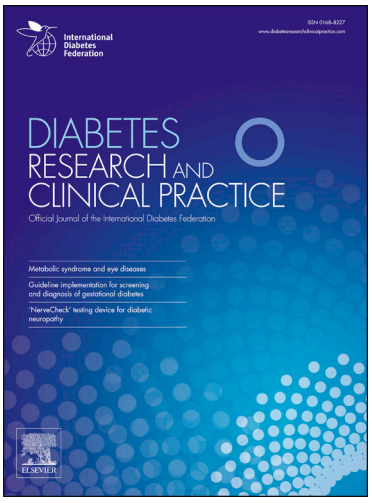
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proofs



Letter to the Editor

COVID 19 and low-glucose levels : is there a link ?

Francesco Piarulli, Annunziata Lapolla

PII: S0168-8227(20)30535-0
DOI: https://doi.org/10.1016/j.diabres.2020.108283
Reference: DIAB 108283

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 29 May 2020
Accepted Date: 19 June 2020

Please cite this article as: F. Piarulli, A. Lapolla, COVID 19 and low-glucose levels : is there a link ?, *Diabetes Research and Clinical Practice* (2020), doi: https://doi.org/10.1016/j.diabres.2020.108283

COVID 19 and low-glucose levels : is there a link ?

Francesco Piarulli, MD

DPT Medicine Padova University

Annunziata Lapolla, MD

DPT Medicine Padova University

The COVID-19 pandemic is claiming many victims among those infected worldwide. Patients' prognosis depends primarily, but not exclusively on their viral load. The response of the host's immune system is partly responsible, either by default (in immunocompromised patients) or, paradoxically, by excess - when a destructive "cytokine storm" occurs in the lung as a result of an exaggerated mobilization of the host's immune cells. This cytokine storm seems to be the most serious prognostic factor because it aggravates the inflammatory, thrombophilic state, leading to a disseminated intravascular coagulation (DIC) - a situation difficult to control and potentially fatal. There is no clear scientific evidence as yet to indicate what triggers a cytokine storm.

A highly contagious virus like influenza A, which causes annual flu epidemics all over the world, has been known to trigger such cytokine storms too, leading to inflammation, the need for hospitalization, and even death. The mechanisms behind such cytokine storms, that make some individuals suffer more from the flu than others, remain unclear, however. A study on influenza A virus infection in mice showed that glucose metabolism was a driving force behind the onset of the often fatal inflammatory response known as a cytokine storm. Mice treated with glucosamine produced significantly higher levels of inflammatory cytokines and chemokines than mice not given glucosamine. When researchers analyzed blood glucose levels in patients diagnosed with influenza A and healthy controls, they found that the hexosamine biosynthetic pathway, by means of which a

small portion of glucose is metabolized, plays an essential part in cytokine storms triggered by the influenza virus. These findings may partly explain why diabetics are at greater risk of serious complications and death from influenza and other infections. Preliminary data indicate that this appears to be the case for COVID-19 as well (1). Both hyper and hypoglycemia are independent predictor of hospital mortality in critically ill individuals, independent of severity of illness, diabetes diagnosis or length of stay in the Intensive Care Unit (ICU) (2,3).

Patients' metabolic conditions could therefore have a crucial role in determining the release of certain proinflammatory cytokines, such as interleukin 1-beta (IL-1β). An in vitro study of ours conducted some time ago showed that monocytes from patients with type 2 diabetes and normal controls overproduced IL-1β when tested in a low-glucose milieu (4). This happened already in basal conditions, but even more in the presence of a known proinflammatory factor, lipopolysaccharide (LPS), the structure of which contains glucosamine (a picture similar to the experiment conducted by Wang et al). The same did not happen under normal and high-glucose conditions, not even in the presence of LPS. On the other hand, monocytes retained their anti-inflammatory capacity by overproducing anti-inflammatory cytokines like interleukin 10 (IL-10) in response to LPS, but only in the presence of normal glucose concentrations.

It has been reported that hypoglycemic conditions induce an upregulation of the GLUT 3 glucose transporter in the plasma membrane of the monocyte-macrophage [5], and that LPS amplifies GLUT 3 overexpression [6]. GLUT 3 upregulation is a self-regulating mechanism to ensure an adequate glucose supply to the cells, and thus protect monocytes against the harmful effects of low glucose levels, thus amplifying inflammatory cell activation in the presence of LPS. Wright et al. showed that acute hypoglycemia induced by hyperinsulinemic clamping led to an increase in CD40 expression (an inflammatory activation index) on monocytes in type 1 diabetic patients [7].

In vivo hypoglycemia may induce an increase in counter-regulatory hormonal adrenergic activity as well, resulting in further inflammatory stress [8].

Hypoglycemia therefore, besides representing a risk factor of cardiovascular and total mortality (for all causes) in diabetic patients, could represent a trigger mechanism for the "cytokine storm" during COVID-19 disease [9].

In the light of these experimental data, we recommend pursuing optimal glycemic control, avoiding both hyper and hypoglycemia, to prevent or mitigateany cytokine storms, and thus improve the otherwise dismal prognosis for both diabetic and not diabetic patients admitted to semi-intensive or ICU with COVID-19.

Conflict of interest: The authors declare no conflict of interest.

Funding: The authors received no funding from an external source.

1. Q. Wang, P. Fang, R. He, et al. *O*-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5. *Sci. Adv.* 15 APR 2020; **6**:eaaz7086
2. Falciglia M, Freyberg RW, Almenoff PL, et al. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009;37:3001-9.
3. Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc* 2010;85:217-24.
4. Piarulli F, Sartore G, Sechi A, et al. Low Glucose Concentrations Induce a Similar Inflammatory Response in Monocytes from Type 2 Diabetic Patients and Healthy Subjects. *Oxid Med Cell Longev*. 2017; 2017:9185272. doi:10.1155/2017/9185272
5. E. T. Korgun, R. Demir, P. Sedlmayr et al., Sustained hypoglycemia affects glucose transporter expression of human blood leukocytes. *Blood Cells, Molecules & Diseases*, 2002; 28 (2),152–159.

6. I. A. Simpson, D. Dwyer, D. Malide, et al. The facilitative glucose transporter GLUT3: 20 years of distinction. *American Journal of Physiology: Endocrinology and Metabolism.* 2008; 295(2), E242–E253.

7. R. J. Wright, D. E. Newby, D. Stirling, et al. Effects of acute insulin-induced hypoglycemia on indices of inflammation: putative mechanism for aggravating vascular disease in diabetes. *Diabetes Care*, 2010; 33(7), 1591–1597.

8. Wright R. J., Frier B. M. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? *Diabetes Metabolism Research and Review*. 2008;24(5):353–363.

9. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein H. C., Miller M. E., et al. Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine*. 2008;358(24):358, 2545–2559.