Received: 25 March 2020 | Accepted: 26 March 2020

DOI: 10.1002/dmrr.3321

COMMENTARY

WILEY

Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics

Ernesto Maddaloni | **Raffaella Buzzetti**

Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

Correspondence
Ernesto Maddaloni, Department of Experimental Medicine, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy.
Email: ernesto.maddaloni@uniroma1.it

Abstract

A novel RNA betacoronavirus causing coronavirus disease 2019 (Covid-19) has now been declared pandemic disease by WHO. Guo et al published the first report of biochemical features in patients with diabetes and the further risk that this disease can determine to the progression of Covid-19. Among different cytokines found significantly higher in patients with diabetes compared to those without, Interleukin-6 (IL-6), which is already increased in conditions of chronic inflammation, may play a more deleterious role in Covid-19 infection. Targeting the overexpression of Il-6 effects with a monoclonal antibody against IL-6 receptor or using Janus Kinase inhibitors may be particularly helpful for treatment of Covid-19 pneumonia in diabetes.

KEYWORDS

Covid-19, diabetes, inflammation; IL-6

At the end of 2019, a novel RNA betacoronavirus (currently named SARS-CoV-2) has emerged in Wuhan, China, causing coronavirus disease 2019 (Covid-19). The disease has rapidly spread in several countries (114 with more than 120 000 confirmed cases when this article was written) and by March 11, 2020, the Director-General of the World Health Organization, Tedros Adhanom Ghebreyesus, has declared Covid-19 a pandemic disease. The case fatality ratio of Covid-19 has been initially described in China to be about 1%-2%,[1] but higher percentages are being estimated in other countries, with Italy nowadays experiencing the highest numbers.[2] Differences among countries are unlikely due to viral changes, but more likely due to other reasons including different healthcare systems and actions taken to contain the outbreak (such as early or late lockdown), but also to differences in the prevalence and features of conditions that could interact with Covid-19 to worsen health outcomes, such as mean population age and comorbidities. Therefore, knowledge of the virus behaviour and of risk factors favouring Covid-19 development and progression is crucial to predict what could happen worldwide in the near future. As SARS-CoV-2 is spreading very fast, the acquisition of data from Wuhan, where the local scientific community has already accumulated experience and data about Covid-19, should be even faster. Going in this direction, Diabetes/Metabolism Research and Reviews has now published a study by Guo et al,[3] reporting on the added risk of diabetes to the progression of Covid-19. While results of this study should be read in the light of some limitations such as the low sample size and the large age difference between study groups when patients with other comorbidities were excluded, it still provides relevant insights that could inform about how Covid-19 interacts with preexisting conditions. It is not surprising that diabetes significantly increases the risk of Covid-19 progression. Diabetes is, indeed, already known to worsen outcomes of other similar viral infections such as the 2003 severe acute respiratory syndrome due to SARS-CoV or the H1N1 infection.[4,5] While not surprising, this interaction is, however, alarming considering the high transmission rate of SARS-CoV-2 and the global prevalence of diabetes. With about half a billion people affected, diabetes is the leading noncommunicable and chronic pandemic disease worldwide. Guo et al[3] describe a mortality rate of Covid-19 among people with diabetes and without other comorbidities of about 16%. Therefore, we need to rapidly halt SARS-CoV-2 spreading and to be prepared to the worst-case scenarios by knowing much more about the factors predisposing people with diabetes to Covid-19 progression. Notably, data from Guo et al[3] suggest that the severity of Covid-19 in diabetes may be hidden by an initial milder presentation of SARS-CoV-2 infection, with fewer patients experiencing fever, chill, chest tightness, and shortness of breath. This phenomenon, which resembles the silent symptoms people with diabetes experience also in other conditions such as myocardial infarction, may cause a life-threatening delay in providing the needed care,

finally resulting in poorer prognosis. Based on these results, it is crucial not to underestimate Covid-19 severity in patients with diabetes even in the absence of classical worrisome signs and symptoms and it may be useful to develop different clinical severity scores for patients with diabetes. The article by Guo et al[3] leaves, however, several relevant questions still opened. Does the association between Covid-19 and diabetes differ by different types of diabetes? Do anti-diabetes drugs impact on disease progression? Is the impact of ageing the same in diabetes as in peers without diabetes?

Nevertheless, the complete biochemical panel provided in this study in both people with and without diabetes starts to delineate an important mechanism possibly predisposing patients with diabetes to the more severe clinical presentation of Covid-19. People with diabetes are affected by a low-grade chronic inflammation which might facilitate the cytokine storm, which in turn appear to be the cause of the severe cases of Covid-19 pneumonias and of the eventual death of many patients.[6] Interleukin-6 (IL-6), among the different markers of inflammation (fibrinogen, C-reactive protein, D-dimer) that were found to be more elevated in Covid-19 cases with diabetes than in those without, deserves particular attention. IL-6 is a pleiotropic cytokine that mainly participates to acute phase inflammatory responses, but which is also significantly increased in conditions of chronic inflammation such as metabolic disorders and cardiovascular disease. The deleterious effects of overexpressed IL-6 signalling are tackled by tocilizumab, a monoclonal antibody against the IL-6 receptor approved for the treatment of some autoimmune disorders, such as giant cell arteritis or severe rheumatoid arthritis, and also successfully tested for other autoimmune disorders such as Graves orbitopathy.[7] Interestingly, preliminary observations suggest tocilizumab may significantly help the treatment of Covid-19 pneumonia, it is actually being used *off-label* in some Italian centres in patients with Covid-19 and it is currently being tested in an ad hoc randomized controlled trial.[8] If these observations will be confirmed, based on the data presented by Guo et al,[3] this drug may be particularly helpful in people with diabetes. As well, other drugs tackling the same pathway, such as drugs against IL6 itself (siltuximab) or Janus Kinase inhibitors (such as baricitinib, tofacitinib, upadacitinib), might be novel approaches to fight Covid-19,[9] especially in people with diabetes. However, fast and efficient trials are urged to give evidence based answers to all these unanswered questions. Noteworthy, the interaction between Covid-19 and diabetes could also be bi-directional, with SARS-CoV-2 potentially worsening preexisting diabetes or even predisposing to diabetes in non-diabetic subjects. Angiotensin Converting Enzyme 2 (ACE2) is the access door for SARS-CoV-2 to enter human cells[10] and ACE2 is widely expressed in the liver and in the endocrine pancreas, with a potential role in the development of insulin resistance and impaired insulin secretion.[11] Therefore, both hepatocytes and pancreatic beta-cells could be infected by SARS-CoV-2, worsening hyperglycaemia at least during the acute infection. In the long term, however, the infection of pancreatic beta cells could also trigger beta-cell autoimmunity in predisposed subjects. Should we also expect an increase in the incidence of autoimmune diabetes when Covid-19 pandemic will be solved? While the immediate consequences of Covid-19 pandemic represent the urgent problem we are called to solve as soon as possible, the long-term consequences of this infection should also be monitored in the immediate future.

In definitive, Covid-19 and diabetes represent two devastating pandemics with very different characteristics in terms of healthcare burden mainly because of different presentation (acute vs chronic) and transmission (communicable vs noncommunicable), but which may be much closer than previously thought.

CONFLICT OF INTERESTS

The authors declare no conflicts of interests related to this manuscript.

ORCID

Ernesto Maddaloni https://orcid.org/0000-0003-3844-9463
Raffaella Buzzetti https://orcid.org/0000-0003-1490-6041

REFERENCES

1. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Eng J Med*. 2020. (Epub ahead of print) https://doi.org/10.1056/NEJMoa2002032.
2. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)30627-9.
3. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020; e3319. https://doi.org/10.1002/dmrr.3319.
4. Booth CM. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA*. 2003;289:2801-2809. https://doi.org/10.1001/jama.289.21.JOC30885.
5. Allard R, Leclerc P, Tremblay C, Tannenbaum T-N. Diabetes and the severity of pandemic influenza a (H1N1) infection. *Diabetes Care*. 2010;33:1491-1493. https://doi.org/10.2337/dc09-2215.
6. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*. 2020.
7. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: a randomized clinical trial. *Am J Ophthalmol*. 2018;195:181-190. https://doi.org/10.1016/j.ajo.2018.07.038.
8. Chinese Clinical Trial Registry, A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19); 2020. http://www.chictr.org.cn/%0Dshowprojen.aspx?proj=49409. Accessed March 6, 2020.
9. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet (London, England)*. 2020;395:e30-e31. https://doi.org/10.1016/S0140-6736(20)30304-4.
10. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. *J Virol*. 2020;94:e00127-20. https://doi.org/10.1128/JVI.00127-20.
11. Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol*. 2009;302:193-202. https://doi.org/10.1016/j.mce.2008.09.020.