



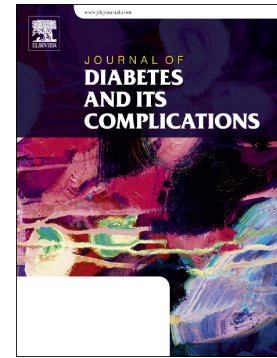
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COVID-19 and Diabetes: no time to drag our feet during an untimely pandemic

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Editorial/Commentary

The new severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV2) may cause pneumonia and severe disease (COVID-19) in high risk patients [1]. Since March 2020, COVID-19 has been declared a pandemic by the World Health Organization, with reported cases in most of the countries worldwide [2]. To date, compelling data strongly indicate that the severity and adverse progression of COVID-19 is related to older age and underlying conditions, primarily diabetes, obesity, and hypertension [3-5], *i.e.* conditions forming the spectrum of the metabolic syndrome [6]. SARS-CoV2, as other coronaviruses, has an enveloped single, positive-stranded RNA genome which encodes its proteins, including envelope, membrane, nucleocapsid and spike proteins [1, 7]. The latter facilitate entry into host cells by binding to the angiotensin-converting enzyme 2 (ACE-2) [7, 8]. Interestingly, type 2 diabetes (T2DM) appears to promote ACE expression in various organs, including the liver, heart and lungs [9], which may, at least in part, further contribute to higher susceptibility of these organs to SARS-CoV2 infection in patients with T2DM. Furthermore, animal model data in diabetic mice indicate that ACE-2 activity may be increased in the pancreas [9]. Thus, it is not surprising that ACE-2 overexpression is further explored as a risk factor for COVID-19 [10]. This potentially places patients with diabetes at additional risk of worsening hyperglycemia in case of a SARS-CoV2 infection, and further supports the clinical evidence that T2DM constitutes a crucial risk factor for rapid deterioration and worse prognosis of COVID-19 [11].

Due to the nature and rapid evolution of the COVID-19 pandemic, there is still limited standardization on what should constitute best routine care for diabetes in the context of this healthcare crisis. The UK National Diabetes Inpatient COVID Response Group has recently published guidelines for the management of both patients with diabetes and diabetes services during this pandemic, which are supported by NHS England, Diabetes UK, and the Association of British Clinical Diabetologists [12]. Along with other similar practical recommendations [13], these guidelines are expected to be revised as new evidence becomes available, and aim to inform clinical

practice about maintaining diabetes services during this crisis, whilst also offering safe and simple diabetes guidelines for treating inpatients with or suspected of COVID-19 [12].

Notably, as this pandemic has forced healthcare providers globally to re-organize and often postpone most outpatient and elective clinic services in order to focus on the response to COVID-19, it should be stressed that certain services treating serious complications of chronic diseases must be carefully maintained in order to manage high risk patients in an efficient and safe way. An important example of such crucial services in the context of diabetes, is the management of patients with acute and severe presentations of diabetes foot disease/ulcers. In the *Journal of Diabetes and Its Complications*, a relevant paper has been published on the surgical treatment of diabetic foot ulcers during the COVID-19 pandemic in China [14]. Based on the relevant local experiences and guidelines in China (*i.e.* the first epicenter of the COVID-19 pandemic), Tao et al. describe a "double triage, double buffer, and dual mode" model and the process for treatment of diabetic foot ulcers which was followed in the Renmin Hospital of Wuhan University during the COVID-19 pandemic [14]. This proposed strategy for diagnosis and treatment of diabetic foot ulcers under the emergency conditions posed by the COVID-19 outbreak aims not only to maintain the appropriate and timely care of patients with diabetic foot ulcers, but also mitigate the risks to the safety of involved healthcare professionals and other patients at the treating hospitals [14]. Indeed, practical ways of rigorous triage and various levels of buffer wards/zones are essential in order to achieve both these objectives.

Moreover, another fast track article on the role of podiatry during the COVID-19 pandemic has also been recently published [15]. In this paper, Rogers et al. propose a Pandemic Diabetic Foot Triage System, in-home visits, higher acuity office visits, and telemedicine/remote patient monitoring in order for podiatrists to effectively manage patients with diabetic foot disease during the COVID-19 outbreak and reduce the relevant burden on healthcare services by keeping these high risk patients functional, safe and, where possible, at home [15].

Overall, despite this disrupting pandemic, the appropriate use of both oral and injectable antidiabetic medications to control hyperglycemia should not be overlooked, since this has been and should remain at the heart of preventing and reducing risks related to diabetes, including diabetic foot disease [14-16]. This is also highlighted in another paper published in the Journal of Diabetes and Its Complications by Cushscieri & Greech which outlines how hyperglycemia may have a likely negative impact in the context of COVID-19, including suppression of the antiviral response, pulmonary structure changes and historic evidence of increased viral infection in hyperglycemia [17]. Therefore, the proper use of diabetes medications is also essential in managing the risk of COVID-19 to patients with diabetes. Interestingly, the most commonly prescribed medication in diabetes care, *i.e.* metformin, was in fact initially used as a drug for patients with influenza and malaria [18], and has been postulated to have the potential to not only prevent the entry of SARS-CoV-2 through the ACE-2 pathway, but also prevent detrimental sequelae by causing activation of ACE-2 through AMPK-signaling [19].

However, the contraindications and risks of various antidiabetic medications in patients with severe COVID-19 should also not be overlooked and the antidiabetic treatment of such patients should be promptly revised and/or optimized as clinically needed [12, 13]. Indeed, metformin itself can contribute to lactic acidosis as a consequence of severe dehydration in COVID-19 patients, so such patients should stop metformin and follow sick day rules [12, 13]. Similarly, there is a risk of both dehydration and diabetic ketoacidosis with the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors, which should be stopped in patients with COVID-19 and diabetes [12, 13]. On the other hand, dipeptidyl peptidase-4 inhibitors appear to be generally well-tolerated and can be continued, whilst insulin treatment should not be discontinued [12, 13]. Finally, it is noteworthy that other medications which are also commonly prescribed in patients with diabetes are currently under the spotlight regarding their potential impact on COVID-19 and its complications. Particularly for ACE inhibitors, an area of recent controversy and debate in relation to COVID-19, a recent meta-analysis suggests potentially that these drugs may be safe or even beneficial [20].

In conclusion, it is particularly important to note that faced with such a new disease and the rapid expansion of the research literature on COVID-19, dialectologists and all physicians treating patients with diabetes should keep abreast of the most recent published updates, guidelines and reviews in order to follow evidence based recommendations/guidelines and promptly revise management plans as needed. The challenge of doing so should, however, not be underestimated given the high demands required by clinical services and the acutely unwell patients needing care in both our hospitals and communities.

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