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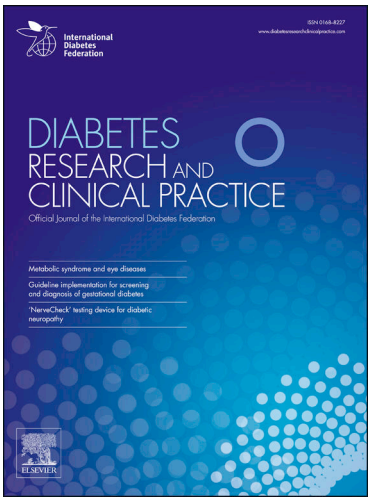

Commentary

Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?

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PII: S0168-8227(20)30396-X
DOI: https://doi.org/10.1016/j.diabres.2020.108146
Reference: DIAB 108146

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 3 April 2020
Accepted Date: 4 April 2020

Please cite this article as: R. Pal, S.K. Bhadada, Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?, *Diabetes Research and Clinical Practice* (2020), doi: https://doi.org/10.1016/j.diabres.2020.108146

Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?

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Conflicts of Interest: The authors declare that they have no conflicts of interest

Funding: None

Acknowledgement: None

Word count: 930

Keywords: COVID-19, T2DM; Diabetes Mellitus; Angiotensin-converting enzyme 2.

Ever since its outbreak in December 2019, novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to more than 200 nations, affecting over 509,000 individuals and inflicting over 23,000 fatalities globally (1). Although the overall mortality rate is low, ranging from 1.4%-7.2%, people with diabetes mellitus (DM) tend to have more severe disease, acute respiratory distress syndrome and increased fatality (2,3). Of the 1099 confirmed COVID-19 patients reported from China, 173 had severe disease; DM was more prevalent in those with severe disease (16.2%) as compared to those with non-severe disease (5.7%) (2). In addition, DM has been reported to be associated with poor prognosis in other viral infections, notably seasonal influenza, pandemic influenza A H1N1 (2009), Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Proposed mechanisms for this apparent association between COVID-19 and DM include impaired innate immune system in people with DM. In addition, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs), used so widely in people with DM have been implicated as a connecting link between COVID-19 and DM. ACEi/ARBs leads to upregulation of angiotensin-converting enzyme 2 (ACE2), a type 1 integral membrane glycoprotein that is constitutively expressed in the lungs, heart, intestine, kidney and vascular endothelium. SARS-CoV-2 utilizes ACE2 as a receptor for entry into host pneumocytes, hence, upregulation of ACE2 by ACEi/ARBs might explain the severe and fatal consequences of COVID-19 (3).

Considering the high-risk, persons with DM should take extra precautions amid COVID-19 pandemic. Strict social distancing and proper hang hygiene should be the norm. Good glycemic control should be of utmost importance as it has been shown to boost the innate immune system. Although it would be wise to stick to the ongoing

therapy or intensify the same, physicians may however consider reviewing the prescription.

Insulin is a safe choice under most circumstances and remains the sole therapy for people with type 1 diabetes mellitus and can be considered as a superior alternative in people with type 2 diabetes mellitus (T2DM) having poor glycemic control. Although no direct effect on ACE2 is reported, insulin treatment has been shown to attenuate renal ADAM-17 (a disintegrin and metalloproteinase-17) expression in diabetic Akita mice (4). In normal physiology, ADAM-17 cleaves ACE2, thereby inactivating the enzyme. Whether the same phenomenon is replicated in human pneumocytes is not known. Metformin and sulfonylureas exhibits no interaction with either ACE2 or ADAM-17 and can be safely continued. On the contrary, pioglitazone has been shown to upregulate ACE2 in insulin-sensitive tissues in rats and reduce ADAM-17 activity in human skeletal muscles (3,5). Similarly, liraglutide, a glucagon-like peptide 1 (GLP1) analogue, increases cardiac and pulmonary ACE2 expression in Type 1 diabetic rats (6). Data also supports promotion of ACE2 activity by sodium-glucose transporter 2 inhibitors (SGLT2i); this has been proposed as a plausible mechanism of renoprotection with this class of drugs (7).

The use of dipeptidyl peptidase 4 inhibitors (DPP4i) in the present scenario merits detailed discussion. DPP4i target the enzymatic activity of DPP4, a type II transmembrane glycoprotein, expressed ubiquitously in many tissues, including immune cells. Apart from breaking down circulating GLP1, DPP4 activates T-cells, upregulates CD86 expression and NF-κβ pathway, thereby promoting inflammation. Hence, inhibition of DPP4 has given rise to concerns regarding a possible increase in the risk of infections. A few meta-analyses have identified an increased risk of nasopharyngitis and urinary tract infection while others have negated this finding. In

addition, human DPP4 acts as a functional receptor for MERS-CoV (MERS-Coronavirus). Transgenic diabetic mice expressing human DPP4 ($DPP4^{H/M}$ mice) developed a prolonged phase of severe disease and delayed recovery upon infection with MERS-CoV. Although SARS-CoV-2 does not require DPP4, the potential anti-inflammatory role of DPP4i raises questions as to whether DPP4 modulation might help offset the cytokine-mediated acute respiratory complications of COVID-19 (8). Nonetheless, DPP4i do not alter ACE2 expression as shown in diabetic mice.

Although rarely used, hydroxychloroquine can be good choice under present circumstances. Hydroxychloroquine, at a dose of 400 mg once a day, is approved by the Drug Controller General of India (DCGI) as a third-line add-on anti-diabetic drug after metformin and sulfonylurea in people with T2DM (9). The drug acts by raising intracellular pH that inhibits enzymatic degradation of insulin, resulting in recirculation of substantial proportion of insulin in active form. Consistent with its immunomodulator property, hydroxychloroquine also reduces pro-inflammatory cytokines, notably TNFα and IL6, thereby decreasing insulin resistance. Interestingly, hydroxychloroquine has also been found to be effective against SARS-CoV-2 *in-vitro* and in reducing viral load in COVID-19 patients. Mechanisms of action include impaired binding between host ACE2 and SARS-CoV-2 spike protein and increased intracellular/endosomal pH that inhibits antigen-presentation, T-cell activation, cytosolic Toll-like receptor (TLR)-signaling and transcription of pro-inflammatory cytokines, thereby, averting a cytokine storm (10). The drug has even been used as a prophylaxis against COVID-19 in many countries and the Indian Council of Medical Research (ICMR) has recently approved the prophylactic use of this drug in high-risk groups including healthcare workers at risk of infection.

Although there is no dearth of animal data, robust human studies in the field of COVID-19 and anti-diabetic medications are lacking. Hence, in the absence of strong evidence, it would be extremely unwise to consider one drug over the other. Good glycemic control should be the goal, no matter what drugs are being used. However, considering the low-cost, widespread availability, modest HbA1c reduction, once-daily dosing and relatively good tolerability, hydroxychloroquine may be a good add-on drug during this outbreak for patients with poor glucose control. Presence of diabetic retinopathy and cardiomyopathy should be investigated prior to recommending hydroxychloroquine.

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Anti-diabetic drug	Data from animal studies	Data from human studies	Concerns for use during COVID-19 pandemic
Insulin	Reduces renal ADAM-17 expression in diabetic mice thereby reducing urinary ACE2 shedding and increasing intrarenal ACE2 expression	-	No human data to support poor outcome
Metformin	-	-	No concern
Sulfonylureas	-	-	No concern
Pioglitazone	Upregulation of ACE2 in insulin-sensitive tissues of rats	Downregulation of ADAM-17 in human skeletal muscles	Theoretical risk of poor outcome, however, no data on human pulmonary ACE2 expression
Liraglutide	Upregulates ACE2 in cardiac and pulmonary tissues of diabetic rats	-	Theoretical risk of poor outcome, however, no data on human pulmonary ACE2 expression
SGLT2 inhibitors	-	Promotion of renal ACE2 activity	Theoretical risk of poor outcome, however, no data on human pulmonary ACE2 expression
DPP4 inhibitors	$DPP4^{H/M}$ mice develops severe disease with MERS-CoV DPP4i do not alter ACE2 activity in diabetic mice	DPP4i might exert overall anti-inflammatory role	Theoretically, DPP4 modulation might help offset the cytokine-mediated acute respiratory complications of COVID-19
Hydroxychloroquine	-	Reduction of viral load in COVID-19	Can be considered as a third-line add on drug in patients with poor glycemic control

Table 1. Table showing commonly prescribed anti-diabetic drugs and concerns regarding their use during COVID-19 pandemic. ACE2 (angiotensin-converting enzyme 2) acts as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Thus, any anti-diabetic drug that upregulates ACE2 directly or indirectly by inhibition of ADAM-17 (a disintegrin and metalloproteinase-17, an enzyme that cleaves and inactivates ACE2) is theoretically expected to promote SARS-CoV-2 infection.

COVID-19: Coronavirus disease 2019; ACE2: Angiotensin-converting enzyme 2; ADAM-17: a disintegrin and metalloproteinase-17; SGLT2: Sodium-glucose transporter 2; DPP4: Dipeptidyl peptidase 4; $DPP4^{H/M}$: Transgenic diabetic mice expressing human DPP4; MERS-CoV: Middle East Respiratory Syndrome – Coronavirus.