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Letter to the Editor

COVID-19 and diabetes: Is metformin a friend or foe?



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To The Editor

We read with great interest the letter by Pal and Bhadada [1] highlighting the potential effect of anti-diabetic drugs in novel coronavirus disease (COVID-19).

As already suggested by the authors, the epidemiological link between diabetes and COVID-19 may be explained - at least in part - by the frequent co-treatment with angiotensin converting enzyme (ACE) inhibitors (ACEi) or angiotensin II receptor blockers (ARBs). Indeed, to the current knowledge, human ACE2 represents the docking site used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for invading target cells.

Furthermore, they reviewed the potential impact of frequently used anti-diabetic medications on COVID-19 clinical outcome. Of interest, many of these hypothetical effects are supposed to be mediated by an upregulation of ACE2, as demonstrated mainly by preclinical studies.

In this report, metformin - used in up to 88% of patients with diabetes in Europe [2], where COVID-19 had spread more than any other part of the world - has been labelled as "no concern". However, we feel that some interest may rise also in this molecule.

The 5'-AMP-activated protein kinase (AMPK) is the molecular effector of most of the pharmacological actions of metformin. An elegant article by Zhang et al. [3] elucidated the potential role of AMPK in regulating ACE2 expression and stability. Authors demonstrated that metformin increases ACE2 expression and its phosphorylation at Ser680 residue in HUVEC cells. Moreover, AMPK-mediated phosphorylation of

ACE2 induced by metformin improves ACE2 stability by hampering its ubiquitination and proteasomal degradation.

In the light of this work, we speculate that metformin - synergistically with ACEi or ARBs and similarly to what suggested by the authors for pioglitazone, liraglutide - may theoretically increase ACE2 availability in respiratory tract thus promoting SARS-CoV2 infection.

On the other side, optimal management of glucose levels [4] and the immune-modulating properties of metformin [5] may result in a beneficial effect on patients' outcome. Hence, according to the current knowledge, we can't still ascertain if metformin is friend or foe of SARS-CoV-2 infected patients with diabetes. Retrospective analysis of COVID-19 diabetic cohorts may shed light on our hypothesis.

1. Contributors

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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