COMMENTARY

Reduced COVID-19 Mortality With Sitagliptin Treatment? Weighing the Dissemination of Potentially Lifesaving Findings Against the Assurance of High Scientific Standards

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In this issue of *Diabetes Care*, two reports from northern Italy provide preliminary evidence that treatment with dipeptidyl peptidase 4 (DPP-4) inhibitors in patients with type 2 diabetes hospitalized for coronavirus disease 2019 (COVID-19) reduce mortality. Solerte et al. (1) report on a retrospective case-control study describing a more than 50% reduction in mortality in 338 patients with type 2 diabetes hospitalized with pneumonia and impaired gas exchange during the initial wave of COVID-19 if they received sitagliptin treatment on top of insulin-based regimens as compared with insulin treatment alone. Mirani et al. (2) analyzed baseline conditions and outcomes in 385 patients hospitalized for COVID-19, 90 of whom had type 2 diabetes. In addition to predictors of mortality already described in previous studies (hypertension, coronary artery disease, chronic kidney disease, etc.), they found preexisting insulin treatment to be associated with worse outcomes (threefold higher mortality). Conversely, treatment with DPP-4 inhibitors was found to be associated with substantially and significantly lower mortality (hazard ratio 0.13 [95% CI 0.02–0.92] after adjustment for age and sex).

It is obvious that such a marked therapeutic effect will receive widespread attention given the paucity of therapeutic approaches associated with convincing success. Certainly, such a prominent reduction in mortality has not been described with antiviral, glucocorticoid, or any other treatments. Therefore, the question arises, are the conclusions drawn from the present reports sufficiently robust to justify immediate changes in the treatment of patients with severe COVID-19 infections? Therefore, it is crucial to carefully consider the limitations and shortcomings of the reports by Solerte et al. and by Mirani et al.

In the study of Solerte et al. (1), there was no random assignment to the treatment with sitagliptin, nor was there a placebo control or any attempt at blinded treatment. In fact, the use of sitagliptin in addition to insulin-based glucose-lowering regimens apparently was prompted by some previous publications that discussed a potential interaction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with DPP-4/CD26 as a virus binding site and anti-inflammatory actions of DPP-4 inhibitors (3–5). Such considerations appear to have been popular in the local environment of the participating hospitals, since some authors of the article by Solerte et al. had contributed to publishing these hypotheses (4). None of these publications (3–5) reported trials (not even case reports) in human patients. The question arises as to whether the prescription (or nonprescription) of sitagliptin by the treating physicians, outside any approved indication (other than for glucose-lowering in type 2 diabetes) was subject to confounding, e.g., by health insurance or educational or social status. Differences in such factors may, in turn, have been associated with more favorable outcomes in those receiving sitagliptin.

Second, data collection was not at all complete, even measured against the standards applied to studies of a retrospective nature: while the time to death or hospital discharge seemed to be available for the majority of patients, information on important secondary outcomes (need for intensive care, mechanical respiration, extracorporal membrane oxygenation) was lacking in 30% (sitagliptin treatment) and 40% (standard of care). Still, the influence of sitagliptin on these secondary outcomes qualitatively and quantitatively corresponded to the degree of mortality reduction.

Judging from the comparison of numbers and percentages, not all baseline characteristics were available for all patients, and information on missing data are also not reported for the follow-up

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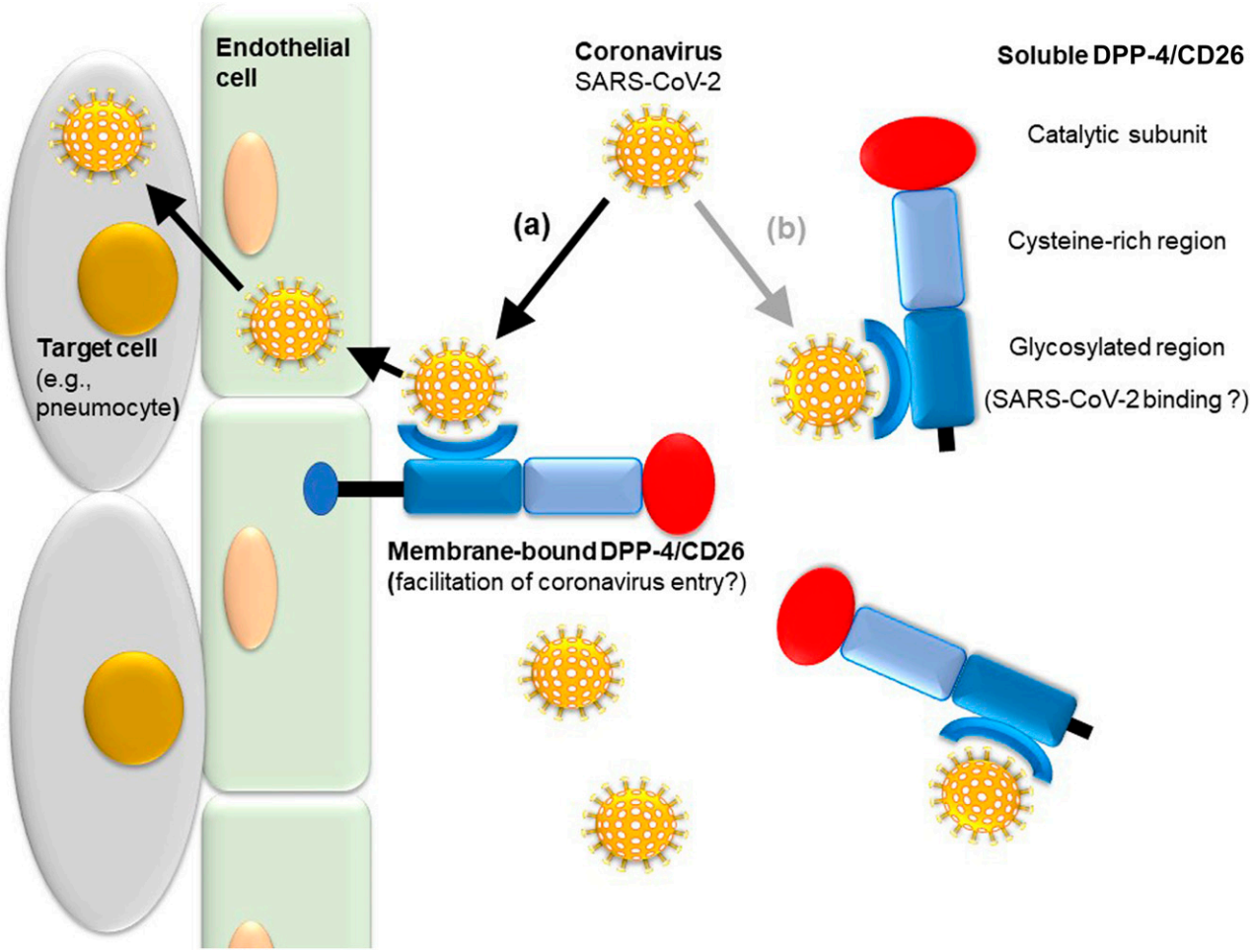

Figure 1—Illustration of a hypothetical mechanism for how DPP-4 inhibition by sitagliptin may influence COVID-19. DPP-4/CD26 exists as a membrane-bound form (e.g., attached to endothelial cells) and as a soluble form circulating in plasma. DPP-4 inhibition has been shown to increase soluble DPP-4/CD26 (13). While membrane-anchored DPP-4/CD26 may facilitate virus entry into tissues and cells relevant to SARS-CoV-2 infection (11) (a), increased amounts of soluble DPP-4/CD26 after DPP-4 inhibitor treatment might offer binding sites that keep coronavirus away from target cells and tissues involved in the disease process (b).

examinations. Of note, C-reactive protein at baseline was significantly lower by 26% in those treated with sitagliptin, and similar trends are reported for other inflammatory markers (although not significant). Questions remain whether the baseline conditions in the two subgroups were truly comparable. This consideration can be extended to confounders beyond data assessed as baseline characteristics, which are classically taken care of by randomization (6–8).

The approach taken by Mirani et al. (2) is quite different. Here, clinical information on a case series has been carefully examined for univariate and multivariate associations of baseline conditions and mortality. The message that stands out is that preexisting treatment with insulin (perhaps representing advanced stages of type 2 diabetes with complications) worsened mortality, but treatment with DPP-4 inhibitors seemed to improve outcomes dramatically (based on small patient numbers: 1 out of 11 patients treated with DPP-4 inhibitors died as compared with 37 out of 79 patients not receiving DPP-4 inhibitor treatment). However, there were at least trends for an association of DPP-4 inhibitor treatment with less severe laboratory inflammatory markers and fewer comorbidities (hypertension, obesity, stroke, or cancer). Furthermore, there was a reciprocal relationship with insulin treatment (none of the patients receiving DPP-4 inhibitors had been treated with insulin before hospital admission). Thus, DPP-4 inhibitor treatment was associated with a number of conditions that predicted favorable outcomes for the whole population studied and for the group of 90 patients with type 2 diabetes in particular. Therefore, the evidence for DPP-4 inhibitors reducing mortality can be described as suggestive at most.

Does a hypothesis that DPP-4 inhibitors reduce COVID-19 mortality in patients with type 2 diabetes deserve sufficient plausibility? There is little doubt that DPP-4/CD26 may play a role as a virus receptor for the coronavirus causing Middle East respiratory syndrome (9,10). There is some weaker evidence for a similar role in SARS-CoV-2 infections (11). But whatever role DPP-4/CD26 plays in the docking process of coronaviruses at membranes of relevant cells to be entered by the virus, there is very little information on whether inhibiting protease activity of DPP-4 with an enzyme inhibitor (DPP-4 inhibitor sitagliptin in the study of Solerte et al. [1]) would affect this role or not, e.g.,

by inducing a conformational change in the molecule. Perhaps an alternative explanation should be considered, one that takes into account the differentiation between cell membrane–bound and soluble (freely circulating) DPP-4/CD26 (12). A recent report from Daniel Drucker's laboratory has described a significant rise in soluble DPP-4 upon exposure of mice to various DPP-4 inhibitors (13)—by 50–100% over 3–7 days. Could a higher relative abundance of soluble DPP-4 bind SARS-CoV-2 and thus prevent attachment of coronaviruses to membrane-bound DPP-4/CD26 in, e.g., pneumocytes or other cells relevant for viral spread and replication in COVID-19? Such a hypothetical mechanism of action is shown in Fig. 1. Thus, there is some plausibility regarding potential mechanisms.

The dissemination of the findings by Solerte et al. (1) and by Mirani et al. (2) raises the overall question of whether it is justified to lower established scientific standards during times of a global pandemic in order to immediately inform the scientific community of any potential advances in the treatment of a novel disease, which, for the time being, remains incompletely understood. In favor of this suggestion, a rapid scientific exchange, even of preliminary findings, may speed up the development of powerful treatment strategies and their testing with definite study protocols and thus potentially save lives. On the other hand, early publication of medical observations prior to rigorous scientific assessment may prompt erroneous treatment decisions, thereby potentially risking adverse consequences and harm. Uncertainties regarding the quality of source data analyzed on benefits and harms related to the use of hydroxychloroquine as a therapeutic agent against COVID-19 have led to the retraction of publications in *The Lancet* (14–16). Likewise, an early report refuting the hypothesis (17) that ACE inhibitors/angiotensin receptor blockers might be harmful, published in the *New England Journal of Medicine* (18), was later retracted (19) for similar reasons. It is a reasonable assumption that authors and journals were striving for the rapid dissemination of novel findings, at the cost of scrutinizing data and analyses less stringently than they would do outside the special conditions of a pandemic. Along the same lines, the recently reported (20) exceptionally early approval of a vaccine against COVID-19 prior to the commencement of any phase 3 clinical trial needs to be questioned. While increasing our knowledge about SARS-CoV-2/COVID-19 rapidly is an undisputed priority, it seems crucial not to be misled by overexcitement regarding all-too-preliminary observations. This will pose an additional burden of responsibility on reviewers and editors of scientific journals inviting manuscripts that fall into this category.

After all, the question is whether the information published by Solerte et al. (1) and Mirani et al. (2) is sufficient to recommend sitagliptin treatment in patients with type 2 diabetes with COVID-19. A convincing answer should depend on the perceived balance between potential benefits and harms. A substantial reduction in mortality is a strong message, and DPP-4 inhibitors have proven to be well tolerated and relatively free from serious adverse events (21). Whether this—as of now—is considered proof of a favorable benefit-harm relationship in COVID-19 patients with diabetes has to be judged by individual physicians and patients but cannot be taken for granted in view of the major limitations of these studies (1,2). Certainly, it is mandatory to take both publications as strong hypothesis-generating hints, pointing to potentially substantial benefits of sitagliptin treatment in patients with type 2 diabetes. Depending on the mechanism (to be elucidated), this may even apply to subjects without diabetes. We expect to see well-designed, randomized, prospective, high-quality clinical trials to address this point (see ClinicalTrials.gov; however, none is reported to be recruiting yet). The articles by Solerte et al. (1) and Mirani et al. (2) would be in a position to claim enormous credit if only these future studies confirmed a beneficial effect of sitagliptin (or DPP-4 inhibitors in general) on COVID-19 outcomes. This would also underscore the justification of publishing data from a retrospective case-control study and a case series analyzed for associations in spite of some obvious shortcomings and limitations. A confirmation of the potentially lifesaving consequences of using DPP-4 inhibitors in COVID-19 patients suggested by Solerte et al. and Mirani et al. is urgently needed.

Duality of Interest. M.A.N. has been a member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Menarini/Berlin-Chemie, Merck Sharp & Dohme, and Novo Nordisk; has received grant support from AstraZeneca, Eli Lilly and Company, Menarini/Berlin-Chemie, Merck Sharp & Dohme, and Novo Nordisk; and has served on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Menarini/Berlin-Chemie, Merck Sharp & Dohme, and Novo Nordisk. J.J.M. has received consulting and speaker honoraria from AstraZeneca, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Sevier and has received research support from Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

References

1. Solerte SB, D'Addio F, Trevisan R, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. Diabetes Care 2020;43:2999–3006
2. Mirani M, Favacchio G, Carrone F, et al. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: a case series from an academic hospital in Lombardy, Italy. Diabetes Care 2020;43:3042–3049
3. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract 2020;162:108125
4. Solerte SB, Di Sabatino A, Galli M, Fiorina P. Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. Acta Diabetol 2020;57:779–783
5. Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes Metab Res Rev. 26 April 2020 [Epub ahead of print]. DOI: 10.1002/dmrr.3330
6. de Graaf MA, Jager KJ, Zoccali C, Dekker FW. Matching, an appealing method to avoid confounding? Nephron Clin Pract 2011;118:c315–c318
7. Greenland S. Randomization, statistics, and causal inference. Epidemiology 1990;1:421–429
8. Jager KJ, Zoccali C, Macleod A, Dekker FW. Confounding: what it is and how to deal with it. Kidney Int 2008;73:256–260
9. Lu G, Hu Y, Wang Q, et al. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature 2013;500:227–231
10. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251–254
11. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect 2020;9:601–604
12. Hasan AA, Hocher B. Role of soluble and membrane-bound dipeptidyl peptidase-4 in diabetic nephropathy. J Mol Endocrinol 2017;59:R1–R10
13. Varin EM, Mulvihill EE, Beaudry JL, et al.: Circulating levels of soluble dipeptidyl peptidase-4 are dissociated from inflammation and induced

by enzymatic DPP4 inhibition. Cell Metab 2019; 29:320–334.e5
14. Funck-Brentano C, Nguyen LS, Salem JE. Retraction and republication: cardiac toxicity of hydroxychloroquine in COVID-19. Lancet 2020; 396:e2–e3
15. Mehra MR, Ruschitzka F, Patel AN. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020;395:1820
16. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 22 May 2020. DOI: 10.1016/S0140-6736(20)31180-6
17. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21
18. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19 [retracted]. N Engl J Med 2020;382:e102
19. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. N Engl J Med 2020;382:2582
20. Mahase E. Covid-19: Russia approves vaccine without large scale testing or published results. BMJ 2020;370:m3205
21. Farah D, Leme GM, Eliaschewitz FG, Fonseca MCM. A safety and tolerability profile comparison between dipeptidyl peptidase-4 inhibitors and sulfonylureas in diabetic patients: a systematic review and meta-analysis. Diabetes Res Clin Pract 2019;149:47–63