Diabetes Ther (2020) 11:1195–1197
https://doi.org/10.1007/s13300-020-00830-0

LETTER

COVID-19 and Diabetes Mellitus: May Old Anti-diabetic Agents Become the New Philosopher's Stone?

Theano Penlioglou · Stella Papachristou · Nikolaos Papanas

Received: April 24, 2020 / Published online: May 7, 2020

ABSTRACT

Corona virus infectious disease (COVID-19) is a new pandemic. In subjects with diabetes mellitus, infection may be more frequent and severe. We discuss the potential contribution of two traditional oral antidiabetic agents, metformin and pioglitazone, to the improvement of liver injury in COVID-19. Clearly, further experience is needed to shed light on these hypotheses.

Keywords: Antidiabetic agents; Corona virus infectious disease; Diabetes mellitus; Metformin; Pioglitazone; Treatment

Corona virus infectious disease (COVID-19) has now been recognised as a new pandemic with high mortality [1]. The risk and severity of infection are particularly high in subjects with comorbidities, such as old age, diabetes mellitus (DM), hypertension, respiratory tract diseases, cancer or coronary heart disease [2, 3]. DM is of paramount importance, given that subjects with COVID-19 and DM have increased mortality [3, 4]. Recent information from Italy has confirmed that approximately two thirds of subjects who died by COVID-19 had DM [5]. It now remains to be determined whether chronic diabetic complications play a role in this association. For instance, some thoughts have already arisen in relation to the diabetic foot [6], partly mediated by diabetic neuropathy [7].

In this context, it is useful to examine the role of anti-diabetic treatment and whether this has any effect on COVID-19 infection. Recently, it has been proposed that dipeptidyl peptidase 4 (DPP-4) inhibitors could play a crucial role in decreasing the risk of complications in subjects with DM and COVID-19 [8]. We would like to offer some thoughts on the potential role of two traditional oral antidiabetic agents, metformin and pioglitazone. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Metformin is a classical antidiabetic agent, which seems to have additional beneficial actions, even on viral infections, notably on hepatitis C virus (HCV) [9–11]. HCV, like severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2), is a ribonucleic acid (RNA) virus, which leads to liver injury [1]. Overall, it seems that metformin could be helpful in reducing insulin resistance in subjects infected by those viruses, thus affecting the cellular response to the infections [9–11]. For this positive result, it seems that the activation of adenosine monophosphate-activated protein kinase

T. Penlioglou · S. Papachristou · N. Papanas (✉)
Second Department of Internal Medicine, Diabetes Centre, Democritus University of Thrace, Alexandroupolis, Greece
e-mail: papanasnikos@yahoo.gr

(AMPK) is responsible, which could become beneficial for the infected subject [9–11]. Moreover, according to a randomised controlled trial, metformin therapy reduces liver fibrosis in patients with HCV and human immunodeficiency virus (HIV)-HCV [11]. Additionally, some studies have shown that it could also have a protective role on the liver [10, 12]. Of relevance, SARS-Cov 2 may lead to liver dysfunction [13, 14], allowing the speculation that metformin could be shown to offer some liver protection in DM subjects with COVID 19. Obviously, this speculation needs to be examined.

Pioglitazone is another classical antidiabetic agent with pleiotropic anti-inflammatory properties [15]. Interestingly, this agent has proven to be helpful in the management of viral diseases [16, 17]. In a randomised controlled trial, pioglitazone reduced HCV viral load, even in subjects who did not receive specific antiviral treatment [17]. Furthermore, pioglitazone is a drug of choice for non-alcoholic fatty liver [18, 19]. Taken together, this evidence appears to encourage, at least in theory, new therapeutic vistas for pioglitazone in COVID 19 treatment, indicating an option to improve liver injury caused by SARS-CoV-2 infection. Nonetheless, there is a considerably long way to go before this assumption is substantiated.

In conclusion, it is essential to find an effective therapy for the new pandemic. In this endeavour, it is worth reconsidering the therapeutic potential of older drugs, including metformin and pioglitazone.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Nikolaos Papanas has been an advisory board member of Astra-Zeneca, Boehringer Ingelheim, MSD, Novo Nordisk, Pfizer, Takeda and TrigoCare International; has participated in sponsored studies by Astra-Zeneca, Eli-Lilly, GSK, MSD, Novo Nordisk, Novartis and Sanofi-Aventis; has received honoraria as a speaker for Astra-Zeneca, Boehringer Ingelheim, Eli-Lilly, Elpen, MSD, Mylan, Novo Nordisk, Pfizer, Sanofi-Aventis and Vianex; and attended conferences sponsored by TrigoCare International, Eli-Lilly, Galenica, Novo Nordisk, Pfizer and Sanofi-Aventis. Theano Penlioglou and Stella Papachristou have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019)—recent trends. Eur Rev Med Pharmacol Sci. 2020;24:2006–11.

2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020. https://doi.org/10.1001/jama.2020.1585.

3. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY). 2020;8:12.

4. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. Lancet. 2020;395:1063–77.

5. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet. 2020;395:1225–8.

6. Papanas N, Papachristou S. COVID-19 and diabetic foot: Will the lamp burn bright? Int J Low Extrem Wounds. 2020. https://doi.org/10.1177/1534734620921382.

7. Papanas N. Diabetic neuropathy collection: progress in diagnosis and screening. Diabetes Ther. 2020;11:761–4.

8. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020;162:108125.

9. Joven J, Menéndez JA, Fernandez-Sender L, et al. Metformin: a cheap and well-tolerated drug that provides benefits for viral infections. HIV Med. 2013;14:233–40.

10. Tsai WL, Chang TH, Sun WC, et al. Metformin activates type I interferon signaling against HCV via activation of adenosine monophosphate-activated protein kinase. Oncotarget. 2017;8:91928–37.

11. Doyle MA, Singer J, Lee T, Muir M, Cooper C. Improving treatment and liver fibrosis outcomes with metformin in HCV-HIV co-Infected and HCV mono-infected patients with insulin resistance: study protocol for a randomized controlled trial. Trials. 2016;17:331.

12. Iranshahy M, Rezaee R, Karimi G. Hepatoprotective activity of metformin: a new mission for an old drug. Eur J Pharmacol. 2019;850:1–7.

13. Feng G, Zheng KI, Yan QQ, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol. 2020;8:18–24.

14. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420–2.

15. Radwan RR, Hasan HF. Pioglitazone ameliorates hepatic damage in irradiated rats via regulating anti-inflammatory and antifibrogenic signalling pathways. Free Radic Res. 2019;53:748–57.

16. Matthews L, Kleiner DE, Chairez C, et al. Pioglitazone for hepatic steatosis in HIV/Hepatitis C virus coinfection. AIDS Res Hum Retroviruses. 2015;31:961–6.

17. Chojkier M, Elkhayat H, Sabry D, Donohue M, Buck M. Pioglitazone decreases hepatitis C viral load in overweight, treatment naïve, genotype 4 infected-patients: a pilot study. PLoS One. 2012;7:e31516.

18. Oseini AM, Sanyal AJ. Therapies in non-alcoholic steatohepatitis (NASH). Liver Int. 2017;37(Suppl 1):97–103.

19. Hsiao PJ, Chiou HC, Jiang HJ, Lee MY, Hsieh TJ, Kuo KK. Pioglitazone enhances cytosolic lipolysis, β-oxidation and autophagy to ameliorate hepatic steatosis. Sci Rep. 2017;7:9030.