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Short Communication

Effects of Prebiotics on Glucose Homeostasis in COVID-19 Patients: A Cohort Study

Yan Yan[1#*]; Jiehui Huang[2#]; Feng Zhu[2]; Davgadorj Chantsalmaa[1]; Feng Zhang[3*]

[1]Laboratory for Infection and Immunity, The Fifth People's Hospital of Wuxi, Affiliated Hospital of Jiangnan University, Wuxi, China

[2]Department of Respiratory and Critical Care, The Fifth People's Hospital of Wuxi, Affiliated Hospital of Jiangnan University, Wuxi, China

[3]Department of Nutritional, Affiliated Hospital of Jiangnan University, Wuxi, China

***Corresponding author: Yan Yan**

Laboratory for Infection and Immunity, The Fifth People's Hospital of Wuxi, Affiliated Hospital of Jiangnan University, Wuxi, China.

Feng Zhang, Department of Nutritional, Affiliated Hospital of Jiangnan University, Wuxi, China.

Email: yanyan198134@hotmail.com; fengzhang@jiangnan.edu.cn

[#]These authors have contributed equally to this article.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections increase the risk of type 2 diabetes after recovery from mild coronavirus disease-2019 (COVID-19) [1]. It is well known that new-onset hyperglycemia, diabetic ketoacidosis and diabetes mellitus were observed in hospitalized patients with COVID-19, with worsening diabetes being most affected by reduced medical resources [1,2]. Thus, there remains an urgent need for therapeutic agents that prevent this complication and improve prognosis in patients with COVID-19.

During the treatment of COVID-19, prebiotics or probiotics have been recommended to improve gastrointestinal symptoms due to the mechanical link between gut dysbiosis and SARS-CoV-2 infection ("gut–lung axis") [3]. The potential effects of prebiotics to reduce the risk and severity of viral respiratory tract infections are supported by clinical studies on influenza, respiratory syncytial virus, and rhinovirus, in contrast, the effect on SARS-CoV-2 is modest [4]. Furthermore, published data on the specific efficacy of prebiotics in COVID-19-associated hyperglycemia is limited. To date, the specific efficacy of prebiotics in COVID-19-associated hyperglycemia, stressful-, infectious-, physiological-hyperglycemia, or diabetes remains elusive. Prebiotics may be an effective complement to treatment options for patients with hyperglycemia or diabetes.

This cohort study was conducted in the Department of Respiratory and Critical Care of a university-affiliated hospital (designated hospital for infectious diseases) from January 2021 to May 2022 (Ethics No. 2020-024-1). We enrolled COVID-19 hospitalized patients over 18 years and excluded patients with complicated infectious comorbidities and pregnancy (Figure 1A).

In this study, we sought to investigate the effect of prebiotics on blood glucose homeostasis during the COVID-19 epidemic and further evaluated the impact on viral re-positive. It will help

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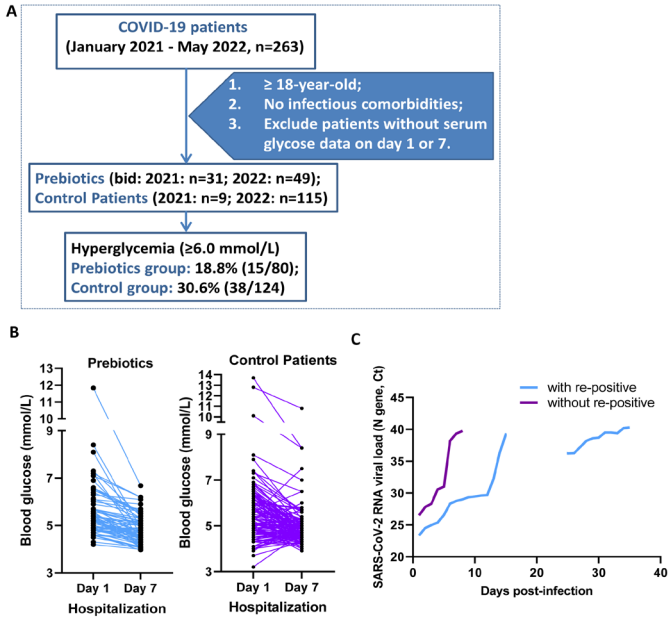

Figure 1: Comparison of blood glucose in COVID-19 hospitalized patients after administering prebiotics orally. Given the number of days to recover from acute symptoms, hospitalized COVID-19 patients were orally administered prebiotics twice a day (bid) (study group) for more than seven days half an hour before breakfast and dinner. Patients in the control group received only routine treatment.

to know more efficacies of prebiotics in regulating COVID-19 symptoms. Most of the patients in 2021 were unvaccinated with the COVID-19 vaccine, but all patients in 2022 were vaccinated. We compared serum glucose values on days 1 and 7 after admission between the study group (n=80, which administrated with prebiotics twice a day, 3 g/time, ≥7 days) and the control group (n=124, without prebiotics). Participants in both groups received routine clinical COVID-19 therapy every day, including blood tests and SARS-CoV-2 nucleic acid tests in nasopharyngeal and anal swab samples.

When COVID-19 participants were admitted to the hospital, the actual incidences of spontaneous hyperglycemia (≥6.0mmol/L) in the study and control groups were 18.8% and 30.6%, respectively, with no significant difference (p=0.0586). The two groups had no statistical difference in ages (42.5±11.1 *vs.* 42.1±11.4, p=0.5848) and length of hospitalization (16.1±2.3 *vs.* 16.7±1.4, p=0.5421). The serum glucose surveyed results showed that there was a significant difference in overall blood glucose levels of the two groups between days 1 and 7 post-hospitalization (study group: 5.8±0.2 *vs.* 4.9±0.1, p<0.0001, control group: 5.6±0.2 *vs.* 5.0±0.1, p=0.0003). In patients who have developed hyperglycemia on admission to the hospital, prebiotics does not play a significant role in decreasing the levels of blood glucose [20.0% (3/15) *vs.* 13.2% (5/38), p=0.5308]. For some COVID-19 patients who developed increased blood glucose (including within the normal range) on day 7 post-hospitalization, the proportion of elevated blood glucose cases in patients administrated with prebiotics was significantly lower than in patients administrated without prebiotics (3.8% *vs.* 18.5%, p=0.0015). In addition, two patients who did not take prebiotics developed hyperglycemia on day 7 post-hospitalization, which did not occur in the prebiotics group (Figure 1B). Therefore, the above results suggest that prebiotics help maintain blood glucose homeostasis during the SARS-CoV-2 infection.

Given that the viral re-positivity usually occurs in patients with mild symptoms [5], our results showed that there was no significant difference in overall viral re-positive rates between the study [6.3% (5/80)] and control [5.6% (7/124)] groups (p=0.8577). However, the re-positive rates in 2021 were significantly higher than in 2022 in two groups [study group: 16.1% (5/31) *vs.* 0% (0/49), p=0.0037; control group: 22.2% (2/9) *vs.* 4.3% (5/115), p=0.0253]. In addition, there was no statistically significant difference in the re-positive rates between the study group and the control group for two years [2021: 16.1% (5/31) *vs.* 22.2% (2/9), p=0.6719; 2022: 22.2% (0/49) *vs.* 4.3% (5/115), p=0.1469]. The prevalent strains in 2021 were the Beta, Delta, and Omicron SARS-CoV-2 variants, while in 2022, the Omicron variants. In conclusion, the above results have not shown a significant effect of prebiotics on viral re-positivity, and the two-year difference may be related to immunization against different virus strains or herd vaccination. In contrast, the original viral loads (Ct value) of the nasopharyngeal swabs in patients without re-positive were significantly lower (Ct ≥26.5) than in re-positive patients (Ct ≥23.7) (p=0.0061). The days of hospitalization were significantly less (9.4 days) than that of re-positive patients (36.7 days) (p<0.0001); viral nucleic acids in anus swabs were persistently positive until re-positivity occurred (Figure 1C).

Our study has several limitations. First, only two severely ill COVID-19 patients were enrolled in this cohort study. Most hospitalized COVID-19 patients developed mild symptoms, making it difficult to assess the effect of prebiotics on patients with severe symptoms, i.e., multi-organ dysfunction. Despite this limitation, our study is the first cohort study to explore the effect of probiotics on regulating glucose homeostasis in hospitalized patients with COVID-19. Second, the effects of prebiotics on gut microbiota composition in patients with COVID-19 need to be further studied ("gut–blood glucose metabolism axis") [3]. Overall, our study demonstrated that prebiotics significantly improved blood glucose homeostasis in hospitalized patients with mild COVID-19. However, these results need to be confirmed in a more extensive randomized cohort study.

Author Statements

Declaration of Competing Interest

The authors declare that the study was conducted without any commercial or financial relationships construed as a potential conflict of interest.

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