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Can We Reduce Mortality of COVID-19 if We do Better in Glucose Control?



Coronaviruses (CoVs) are enveloped, single positive-stranded RNA viruses, which belong to the subfamily Coronavirinae, most of which are transmitted between animals and a few between humans. Two strains of coronaviruses, the severe acute respiratory syndrome CoV (SARS-CoV) and the Middle East respiratory syndrome CoV (MERS-CoV), have caused two out of four pandemics in 21 century [1]. A novel coronavirus, SARS-CoV-2, which causes a severe pulmonary respiratory syndrome, called COVID-19. Since the outbreak of COVID-19, it quickly spreads to more than 200 countries worldwide as an unprecedented global pandemic. As of May 3rd, the global number of confirmed patients has risen to more than 3,563,596, and the death rate has reached 248,135 (death rate ~ 6.96%) [2].

Unfortunately, so far, many vaccines are still under development, and we have no specific anti-SARS-CoV-2 drug, although FDA has approved the Remdesvir for treating COVID-19 for an emergency use [3]. The Remdesvir shows treatment benefits by reducing hospitalization time for 31%, but the reduction of the death rate has reduced has not reached statistical significance (8.0% vs. 11.6%, 0.059) [4]. On the other hand, some traditional Chinese medicines (TCM) have reported to likely have some effect, and probably can stabilize symptoms and avoid aggravation, such as *qingfei paidu decoction* (QPD) [5].

Understanding the clinical characteristics of mild and severe COVID-19 patients and the associated factors associated with the non-survivor will help us reduce the death rate. The clinical spectrum of COVID-19 ranges from mild, moderate, severe to critical conditions. Some patients show symptoms like a common cold, while others have severe lower airways symptoms and die. The most common COVID-19 symptoms were fever, fatigue, dry cough, and in a small number of patients, and very often, these symptoms were accompanied by nausea, vomiting, and diarrhea [6,7]. Male seems like more predominant in deceased patients than in recovered patients [8,9]. Most severe cases and non-survivor with COVID-19 have occurred in patients with comorbidities, particularly hypertension, cardiovascular disease (CVDs), diabetes mellitus, and obstructive pulmonary disease [6,8–10]. For patients with diabetes and other chronic primary diseases, the probability of suffering from COVID-19 is higher, the condition is more severe after infection, and the prognosis is poor [11,12]. Patients with diabetes or hypertension had a 2-fold increase in the risk of severe disease or requiring intensive care unit (ICU) admission [13]. More strikingly, the diabetes rate is much higher in the non-survivor than survivors (34% vs. 14%) [8]. Globally, approximately 20–50% of COVID-19 patients have diabetes, much higher than the diabetes incidence rate in the world [14]. A recent CNN reported that novel coronavirus pneumonia patients generally have one or more underlying diseases in the most extensive health care system in New York, including the highest mortality rate among

diabetics [15]. In their study, novel coronavirus pneumonia patients have a higher risk of fatal diabetes than 50% without diabetes.

Diabetes is also a risk factor for many other epidemic diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [16–20]. The odds ratio of developing severe or lethal disease following MERS-CoV infection with comorbid diabetes ranges from 2.47 to 7.24. Compared with others, diabetes patients, severe infection, the mortality rate, ICU care, and the need for mechanical ventilation were 3.0–3.3 times higher in people with diabetes than in nondiabetic patients with the severe acute respiratory syndrome (SARS) [21,22]. The number of complication patients with influenza A (H1N1) admitted to an intensive care unit is 4.29 times that of nondiabetic [23].

Diabetes is likely to cause a dysregulated immune response in MERS cases, resulting in more severe and prolonged lung pathology. The same mechanism seems to occur in COVID-19. The following factors may cause a high mortality risk of COVID-19 with diabetes. First, the level of blood glucose control directly affects the immune response and state of the body. Diabetic patients have low immunity and are prone to increase the risk of disease. Once infected, it is likely to aggravate the condition of diabetic patients further, increase the difficulty of blood glucose control, and more easily aggravate the infection, thus leading to cytokine storm and acute inflammatory response. Inflammation is closely related to the occurrence and development of diabetes [24,25]. A clinical study found that COVID-19 patients without other comorbidities but with diabetes had higher serum levels of inflammation-related biomarkers such as IL-6 and were susceptible to a cytokine storm, leading to rapid deterioration of COVID-19 [17]. Inflammatory cytokines can cause structural and functional abnormalities of endothelial cells, leading to insulin transport disorder in human tissues and cells, and thus lead to insulin resistance. At the same time, inflammatory cytokines may lead to structural changes and dysfunction of β cell, promote apoptosis of β cell, cause insufficiencies of insulin secretion, and eventually lead to the rise of blood glucose. In the later stage of life for COVID-19 with diabetes, “cytokine storm” will start rapidly and enter the state of multiple organ failure, including liver and kidney failure [12]. When the liver tissue of patients with COVID-19 is extensively damaged, the ability of liver cells to use glucose to synthesize glycogen is decreased, which leads to the aggravation of insulin resistance and the increase of blood glucose. Recently, a study found that the influenza virus can induce IFN regulatory factor 5 (IRF5) to bind to O-GlcNAc transfer (OGT), the key enzyme of the hexosamine biosynthesis pathway (HBP) [26]. This binding leads to O-GlcNAcylation of IRF5, which required for K63-linked ubiquitination of IRF5 and triggered cytokine storm. It also proved that patients with high blood sugar levels are more vulnerable to virus attacks. Because cytokine storms cause the final deaths of both

influenza and COVID-19, it is speculated that patients with diabetes have a higher mortality rate²⁶. Second, studies have shown that the affinity between the S protein of SARS-CoV-2 and the cell surface receptor, ACE2 is about 10–20 times higher than that of SARS virus [20].

ACE2 is also expressed in islet cells. SARS-CoV-2 is likely to infect islet cells through the ACE2 receptor, affecting and destroying islet function and aggravating the imbalance of blood glucose metabolism [23]. Therefore, it is speculated that the pancreas may also be the target organ of SARS-CoV-2. The disease factor of blood glucose rise in patients with COVID-19 may be the high combination of SARS-CoV-2 and ACE2 receptor in islet cells, leading to islet cell damage. The virus infection symptoms and diabetes affect each other and aggravate each other, leading to further deterioration of the condition [20,23]. Third, medication also harms the control of blood glucose levels in COVID-19 with diabetic patients. If glucocorticoid is used, blood sugar will rise, hyperosmotic dehydration, ketoacidosis, and even death may occur [27]. The application of the protease inhibitor Lopinavir/Ritonavir can damage the insulin signal transduction system in the peripheral tissues, and damage the islet β cells by changing the glucose and lipid metabolism eventually leads to insulin resistance and diabetes [28,29]. Fluoroquinolones may affect blood glucose control in diabetic patients. Chloroquine phosphate, which was first used in the treatment of malaria, is gradually used in the treatment of multiple virus infections. Severe adverse reactions, such as hypoglycemia and loss of consciousness, can be seen in patients treated with diabetes drugs. Ribavirin is a synthetic nucleoside antiviral drug. Some studies have shown that ribavirin combined with interferon - α has new adverse reactions in patients with diabetes. Interferon α has a broad-spectrum antiviral effect and can improve the immune function of the body. However, interferon α can lead to hyperglycemia, body mass increase, hyperlipidemia and other endocrine disorders [15]. Therefore, the side effects of the drug can not be ignored in patients with diabetes.

In North America & Caribbean, 55 millions adults have prediabetes, at the risk of developing type 2 diabetes. Some studies have shown that about 5–10% of people with prediabetes develop diabetes every year. According to the national diabetes federation (IDF) diabetes map, the global prevalence of diabetes in 2019 is estimated to be 9.3% (463 million people), almost 1 in 5 people older than 65 years have diabetes. This is a large population at high risk of severe COVID-19 worldwide, so prevention of diabetes is also important for COVID and other health emergencies.

Long-term studies have shown that healthy dietary and exercise interventions can effectively reduce the incidence of diabetes. In the US, the Diabetes Prevention Program (DPP) trial provides the most reliable evidence of lifestyle intervention for diabetes prevention³⁰. The lifestyle intervention in the DDP trail was to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min per week. The DDP demonstrated that lifestyle intervention could reduce the risk of prediabetes to diabetes by 58% in 3 years and 27% in 15 years [30]. The 30-year Daqing study in China shows that lifestyle intervention can reduce the incidence of diabetes by 51% in patients with impaired glucose tolerance during the intervention period [31], and 39% in the cumulative risk of developing type 2 diabetes during 30 years after the cessation of lifestyle intervention [32]. The Finnish diabetes prevention study (DPS) found that after several years of a lifestyle intervention (median four years), the relative risk of diabetes in patients with impaired glucose tolerance was reduced by 38% during a median follow-up of 9 years [33].

Medical interventions may be considered for prediabetes patients at high risks, such as overweight or a history of gestational diabetes. or ineffective lifestyle intervention. Several studies have proved that medication such as metformin and acarbose can reduce the incidence of diabetes in prediabetic people by 27–31% [34]. However, these interventions are hard to adhere to in some people due to the expense and adverse side effects. In recent years, researches on the treatment of prediabetes with TCM have emerged. A recent meta-analysis has summarized 7 randomized, double-blind controlled clinical trials (RCTs) for prediabetes people, which

used TCM (including Tianqi capsule, JinQi Jiangtang tablets (JQJT), Tangzhiping granule, Shenzhu Tiaopi granule (SZTP) and Qiweitangping capsule). These studies showed that 12–36 months of TCM intervention significantly reduced the relative risk of prediabetes progression to T2D by 32.1–83.5% [35]. The excellent outcomes make TCM a possible preventive method for diabetes [34,36].

Up to now, there are several models using bigdata that predict the risk of diabetes. K Chien et al. constructed a simple point model using Cox regression coefficients, established a 10-year diabetes incidence model applicable to the Chinese population with an AUC of 0.702, which is better than traditional prediction models such as Framingham model [37]. Jianfeng Zhang et al. developed a diabetes diagnosis method based on a standardized tongue image using a support vector machine (SVM), which also has good predictive power [38]. However, neither of them can answer the most appropriate period of intervention for people who are at high risk. Previous research has shown that there is a critical transition period before the onset of diabetes [39], and this critical transition period may be the most appropriate time to prevent diabetes. We aim to establish models that can discriminate individuals in critical transition, and intervention can be applied to prevent diabetes and, therefore, contribute to reducing COVID-19 mortality.

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Author credits

DM wrote the general introduction and diabetes prevention sections; JL wrote the mechanisms of damage of hyperglycemia for COVID-19 patients; RY provided general comments of diabetes complications; JL had the original idea of diabetes prevention for COVID-19 patients, organized and revised the manuscript.

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