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The Association of Dietary Glycemic Index with the Prevention and Treatment of COVID-19: A Narrative Review

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ABSTRACT

In 2019, a new coronavirus causing a flu-like syndrome was discovered in Chinese province of Hubei and there was a subsequent outbreak in Wuhan in December 2019. The severity and mortality of COVID-19 are affected by several preexisting comorbidities such as type 2 diabetes mellitus (T2DM). A more severe complication of COVID-19 in patients with diabetes could be due to the fact that hyperglycemia and insulin resistance, as important features of diabetes mellitus, are associated with a higher expression rate of angiotensin-converting enzyme-2 (ACE-2). ACE-2 can act as the entry site for SARS-CoV-2 to lung cells. Furthermore, in diabetes mellitus, increased inflammatory responses and impaired immune function are often present. Glycemic index (GI) and glycemic load (GL) are the characteristics of the diet that can affect glycemic control and insulin resistance. These two characteristics could possibly affect infections through their effect on gut microbiota composition, free radical synthesis, and mitochondrial loading. Therefore, it can be proposed that dietary GI and GL might be important factors in the development of COVID-19.

Keywords: *COVID-19; Glycemic index; Glycemic load; Insulin resistance; Hyperglycemia*

Introduction

In 2019, a new coronavirus causing a flu-like syndrome was discovered in Wuhan, China, in December 2019. Owing to its pulmonary symptoms, the virus was called "severe acute respiratory syndrome associated with coronavirus 2" (SARS-CoV-2) and which was the cause of COVID-19. The clinical symptoms of COVID-19 include fever, dry cough, muscle pain, and breath shortening, and in a few patients it could develop into acute respiratory distress syndrome (ARDS) and numerous organ failures (Liu *et al.*, 2020). Severity and mortality rate of COVID-19 is affected by several preexisting factors such as old age, obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia, and cardiovascular disease (CVD) (Rajpal *et al.*, 2020). Diabetes is reported as frequent comorbidity in patients infected with COVID-19 (Orioli *et al.*, 2020). Comparing patients with COVID-19 admitted to ICU and non-ICU wards, patients in the ICU are two times more likely to be diabetic than those in non-ICU wards (Shahwan *et al.*, 2020). The mortality rate in diabetic COVID-19 patients was also reported to be three times higher

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than that of non-diabetic patients (Shahwan *et al.*, 2020). Diabetes has been shown to be a risk factor for severe and critical types of influenza pneumonia (Zou *et al.*, 2020), and coronavirus pneumonia in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics (Hussain *et al.*, 2020). More intense presentation of the illness in diabetic COVID-19 patients might be associated with hyperglycemia and the condition of insulin resistance in these patients. Hyperglycemia and insulin resistance are accompanied by enhanced production of glycosylation end products (GEP), pro-inflammatory cytokines, and the synthesis of inflammatory adhesive molecules in tissues. This inflammatory condition and cytokine storm can lead to more severe complications of COVID-19 in diabetic patients (Hussain *et al.*, 2020). In COVID-19 patients, counter-regulatory hormones like cortisol, glucagon, and epinephrine are highly released and along with the cytokine storm, these could possibly lead to hyperglycemia in previously healthy or prediabetic patients (Orioli *et al.*, 2020).

The potential role of nutrition in hyperglycemia, controlling diabetes as well as reducing the complications of COVID-19 disease is evident (Fernández-Quintela *et al.*, 2020, Mirabelli *et al.*, 2020, Zabetakis *et al.*, 2020). Dietary glycemic index (GI) and glycemic load (GL), which are effective indicators in determining the quantitative and qualitative effect of dietary carbohydrates on postprandial blood sugar (Brouwer-Brolsma *et al.*, 2019), are considered as two dietary factors affecting insulin resistance and serum blood sugar levels (Shahrdami *et al.*, 2020). Studies have shown that high GI and GL diets can lead to reduced pulmonary function, poor consequences of chronic obstructive pulmonary disease, respiratory infection, as well as greater risk of mortality due to the respiratory diseases (Huang *et al.*, 2021).

Hyperglycemia and COVID-19

Previous studies have reported the effects of hyperglycemia on worsening the complications in other critical coronavirus infections such as SARS and MERS (Liu *et al.*, 2020). Similarly, in COVID-19, hyperglycemia is recognized as a significant risk factor for mortality in critically ill patients (Zabetakis *et al.*, 2020). Therefore, glycemic control could possibly affect severe symptoms and complications of the disease and is a usual concern in COVID-19 patients (Hussain *et al.*, 2020). Glycemic control might be also representative of reduced insulin resistance, which in turn has a key role in COVID-19 control (Rajpal *et al.*, 2020). Several mechanisms can be suggested for the role of hyperglycemia in increasing the risk and severity of COVID-19. This association might be in part related to the angiotensin-converting enzyme-2 (ACE-2), which is a cell surface protein expressed in pulmonary epithelial and lung alveolar cells and also many other cells in the body. The SARS-CoV-2 virus binds to ACE2 using spike-like protein on its surface and the complex is internalized leading to the intracellular reproduction of the virus. Therefore, ACE2 serves as SARS-CoV-2 receptor and is the main site to get the virus into the body (Rajpal *et al.*, 2020). The expression of ACE-2 was reported to be up-regulated in diabetic patients, and in response to hyperglycemia (Rajpal *et al.*, 2020). Prolonged uncontrolled hyperglycemia played a role in the pathogenesis through linking SARS-CoV-2 to ACE-2 (Brufsky, 2020). ACE2 is also expressed in insulin producing β-cells and it was reported that in COVID-19, as the virus enters the cells, β-cells are predisposed to cell impairment and apoptosis which could lead to relative insulin inadequacy and urgent hyperglycemic condition (Rajpal *et al.*, 2020). Moreover, the inflammatory responses are crucially involved in clinical manifestations of COVID-19 (Zabetakis *et al.*, 2020). Hyperglycemia enhances the expression of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) as well as monocyte chemoattractant protein-1 (MCP-1) in mononuclear cells. On the other hand, high blood glucose has pro-inflammatory effects, but insulin secretion is an anti-inflammatory condition (Sun *et al.*, 2014). Studies have also shown that insulin therapy in diabetic and even non-diabetic patients with COVID-19 hospitalized in the ICU, reduces the

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mortality rate (Orioli *et al.*, 2020). Immune responses are also highly related to glycemic control. Hyperglycemia could affect the cellular immune reaction, causing the susceptibility to infection and infection-associated mortality (Liu *et al.*, 2020). Activation of protein kinase C following hyperglycemia could restrain neutrophil migration, phagocytosis, superoxide formation, and microbial killing. In addition, it inhibits the function of neutrophils and apoptosis by inducing the expression of Toll receptors (Jafar *et al.*, 2016). High concentrations of glucose reduce the production of neutrophil extracellular traps and reduce vascular expansion and enhance permeability in the course of primary inflammatory responses, maybe by the activation of protein kinase C (Jafar *et al.*, 2016). Also, T2DM patients might have changes in their innate immune system which increase pro-inflammatory cytokines besides having an impaired host immune system in contact with viral infections through impeding IFN-1 formation and signaling (Rajpal *et al.*, 2020). Inadequately controlled diabetes is related to impaired lymphocyte, monocyte, macrophage, and neutrophil roles and causes unusual deferment type hypersensitivity response and complement activation impairment (Hussain *et al.*, 2020). Furthermore, hyperglycemia in COVID-19 patients can increase lung infection by reducing mucus clearance (Rajpal *et al.*, 2020).

Insulin resistance and COVID-19

In addition to hyperglycemia, insulin resistance can also be one of the causes of more serious complications in diabetic COVID-19 patients. In postprandial state, insulin is secreted into the bloodstream from pancreatic beta cells in response to the rise in blood glucose. Binding of insulin to cell surface receptors increases cellular glucose uptake and thus decrease blood sugar. In diabetes, lack of insulin action leads to hyperglycemia and long-term damage to various tissues and organs (Berbudi *et al.*, 2020). Insulin resistance is defined as an incomplete response of tissues to a certain amount of insulin. To compensate for this defect and for maintaining normal circulating glucose levels, insulin levels increase and hyperinsulinemia occurs (Bonakdaran and Barazandeh Ahmadabadi, 2014). Insulin resistance is common in T2DM and obese patients who are reported to be at greater risk for critical manifestations of COVID-19 (Bonakdaran and Barazandeh Ahmadabadi, 2014, Rajpal *et al.*, 2020). The association between insulin resistance and COVID-19 can be explained through several mechanisms. Increased expression of ACE-2 protein was reported in insulin resistance and thus the entry of the virus into the body is facilitated (Finucane and Davenport, 2020). Moreover, hyperinsulinemia drives the production of mitochondrial reactive oxygen species (mtROS) and diminishes cellular anti-oxidative countermeasures, which could be associated with the severity of infection (Cooper *et al.*, 2020). Insulin resistance also promotes the increased synthesis of pro-inflammatory cytokines including IL6, IL-8 and TNF-α. Furthermore, C-reactive protein (CRP), the inflammatory marker and a reactant of non-Exclusive acute phase, is usually increased in human insulin resistant state (De Luca and Olefsky, 2008). In general, insulin resistance and systemic inflammation cause oxidative stress and inflammatory reaction in the pulmonary system. It can also decrease respiratory muscle intensity leading to abnormal lung function (Rajpal *et al.*, 2020). It should be noted that insulin resistance in obese people can be one of the causes of chronic inflammation and more severe complications of COVID-19 disease in these people (Rajpal *et al.*, 2020).

GI and GL of the foods and COVID-19

Hyperinsulinemia and insulin resistance are highly associated with dietary composition (Mirabelli *et al.*, 2020). Among the characteristics of diet that can affect the control of insulin resistance are GI and GL of the diet (Shahrdami *et al.*, 2020). GI and GL of the food/diet are indicators that are used to determine the quantitative and qualitative effect of dietary carbohydrates on postprandial blood sugar (Brouwer-Brolsma *et al.*, 2019). GI is used to classify foods based on their effect on postprandial

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blood glucose. Besides, GL considers the number of carbohydrates ingested and is obtained by multiplying the amount of carbohydrates available in food and the GI (Shahrdami *et al.*, 2020). Dietary fiber and carbohydrates are associated with immune system function (Fernández-Quintela *et al.*, 2020). In a study on adolescent football athletes, low GI diets were associated with higher increase in total leukocytes, compared to high GL diets (Setyarsih *et al.*, 2021). No previous study discussed the association between GI/GL of the diets and COVID-19 infection, but in the dietary recommendations released for the nutritional treatment of COVID-19, it was suggested to consider low GI carbohydrates in the patients' diets. This recommendation might be pertinent to the association between dietary GI and GL with insulin function and glycemic control (Brugliera *et al.*, 2020, Fernández-Quintela *et al.*, 2020). Besides, high GI foods have been proved to increase the mitochondrial load and free radical synthesis (Fernández-Quintela *et al.*, 2020). In addition, the consumption of these foods has been associated with inflammatory responses via increasing circulating amounts of pro-inflammatory cytokines like CRP, TNF-alpha, and IL-6 (Fernández-Quintela *et al.*, 2020). In COVID-19 infection, inflammation is a factor that complicates the patient's status. Dietary GI and GL are related to serum concentrations of inflammatory biomarkers (Milajerdi *et al.*, 2018, Rajpal *et al.*, 2020) such as CRP, TNF-α, and IL-6 (Fernández-Quintela *et al.*, 2020). According to a meta-analysis, Milajerdi et al. demonstrated that serum high-sensitivity C-reactive protein (hs-CRP) consistency reduced after consuming low GI and GL diets compared to high GI and GL diets (Milajerdi *et al.*, 2018). Another mechanism that could be explained for the effect of high GI/GL carbohydrate on COVID-19 infection is related to gut microbiota. Based on recent studies, diet is so effective in forming the community of the gut microbiota, thereby influencing the host health status (Durganaudu *et al.*, 2020). Consumption of whole grains, as a low GI food (Nagaraju *et al.*, 2020), and complex non-digestible carbohydrates existing in whole grains can considerably alter the large bowel microbial community and is considered to have valuable impacts on the host. Some whole grains can elevate the Firmicutes: Bacteroidetes ratio. In addition, consuming whole-grain barley increases genera Roseburia, Bifidobacterium, and Dialister, and the species of Eubacterium rectale, Roseburia faecis, and Roseburia intestinalis (Keim and Martin, 2014).

Specific carbohydrates found in cereals could enhance colonic butyrate generation. Butyrate is a short-chain fatty acid with positive effects on maintaining the integrity of colonocytes and increasing the generation and release of glucagon-like peptide 1, which can improve insulin sensitivity and glucose homeostasis and decrease food intake by releasing satiety-related intestinal peptides (Keim and Martin, 2014). Resistant starch, as a part of low GI food (Afandi *et al.*, 2021), alters the microbial ecology and enhances Lactobacillus, Bifidobacterium, and Akkermansia. This rearrangement in microbiota could reduce the release of inflammatory productions from the intestine to the bloodstream. The grain mixture produced in a study (containing whole-grain barley, brown rice, and the combination of these grains) could reduce peak postprandial glucose and plasma IL-6. These changes were related to the conversion in the markers of immunologic operation and improvements in blood glucose control (Keim and Martin, 2014). Exploration of a potential association between dietary GI and changes in the proportion of certain gut microbiota is relatively a new research area (Durganaudu *et al.*, 2020). On the other hand, changes in the gastrointestinal microbiome are associated with lung health and respiratory infections (Dhar and Mohanty, 2020). Finally, low GI/GL carbohydrates also decrease the hazard of COVID-19 infection and severity indirectly by decreasing the risk of certain diseases such as CVD and diabetes, which enhance the risk and complications of COVID-19 disease (Augustin *et al.*, 2002, Rajpal *et al.*, 2020). The mechanisms of the association between high GI diet and COVID-19 are summarized in **Figure 1**.

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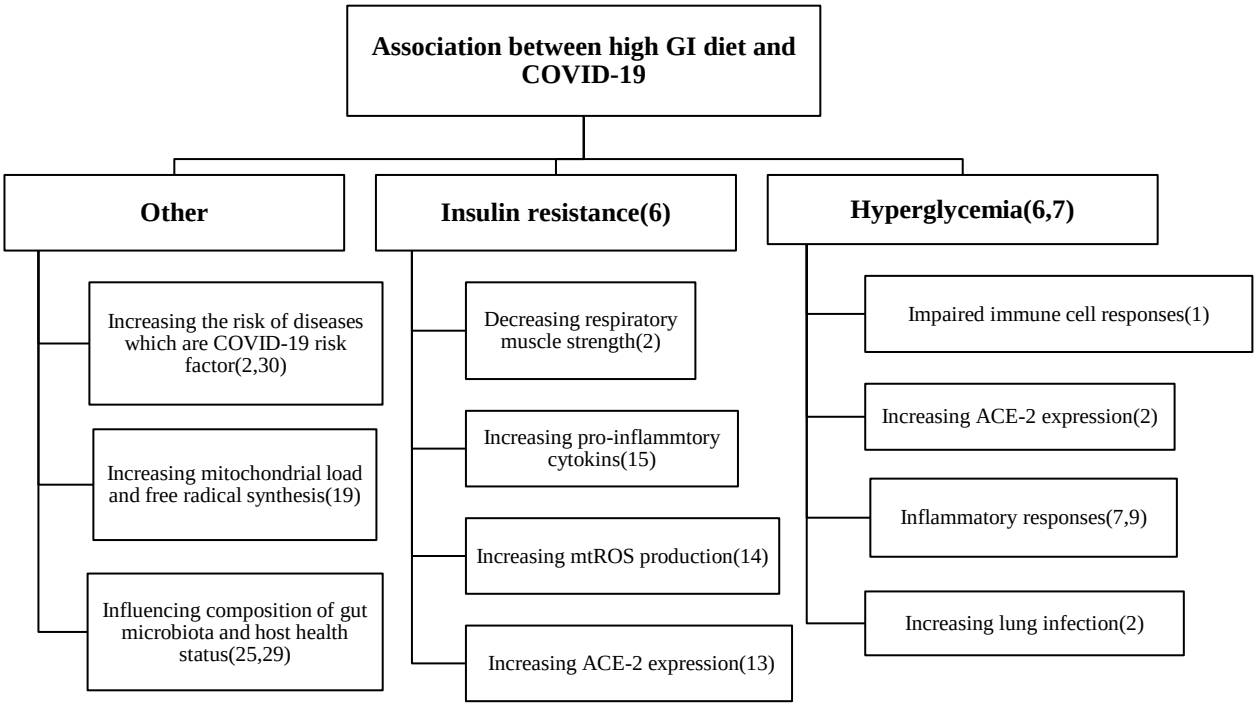

Figure 1. Mechanisms of association between high GI diet and prevention and treatment of COVID-19.

Conclusion

Hyperglycemia and insulin resistance are important factors affecting immune system, inflammation, and infections. It is asserted that most critical dietary determinants of insulin function are dietary GI and GL. Dietary GI and GL might affect infections through their impacts on the composition of gut microbiota, free radical synthesis, and mitochondrial loading. Therefore, it is proposed that dietary GI and GL could be possibly important factors in the prevention and control of COVID-19 patients, especially in people with diabetes.

Authors' contributions

Shamshirgardi E, Kazemi A and Akbarzadeh M conceptualized the study. Shamshirgardi E, Kazemi A, Sohrabi Z, Akbarzadeh M prepared the manuscript draft. Feren GA critically revised the manuscript. Shamshirgardi E and Akbarzadeh M have primary responsibility for content; and all authors read and approved the final manuscript.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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