Review

COVID-19 and Glucose Metabolism

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COVID-19 and Glucose Metabolism

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Abstract

The COVID-19 pandemic has disrupted the lives of the world's population, resulting in over 7 million deaths. It was immediately noted that obese and/or diabetic subjects and frail elderly individuals with multiple comorbidities were more likely to have a more severe disease course. The cause of the increased morbidity and mortality in obese and/or diabetic subjects was found to be related to the presence of insulin resistance in these individuals. Furthermore, it was also discovered that COVID-19, particularly in its more severe forms, was capable of causing de novo type 1 and type 2 diabetes as well as worsening the disease course, if already present. This review aims to highlight the most accredited possible mechanisms by which subjects with insulin resistance may have a more severe disease course and those by which SARS-CoV-2 infection may cause new onset of diabetes or worsening of existing diabetes. To write this manuscript, the authors independently reviewed and compared the results of peer-reviewed and impacted journal publications, written in English, selected from the most well-known search platforms such as PubMed, Scopus, Science Direct, Google Scholar, and ResearchGate, using the following keywords: SARS-CoV-2, COVID-19, Insulin resistance, Glucose metabolism, Obesity, Diabetes, Hospitalization, Mortality.

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1. Introduction

The COVID-19 pandemic, particularly during the first two waves, characterized by more virulent variants, has produced a very high number of hospitalizations and deaths [1,2]. This occurred mainly in elderly, frail subjects and those with multiple comorbidities. Among the latter, it was immediately noted that obesity and, particularly, type 2 diabetes mellitus played a significant role in worsening the progression of the disease, leading to more serious outcomes [3,4]. On the other hand, it was also noted that, conversely, COVID-19 could also lead to the onset of both type 1 and, particularly, type 2 diabetes [5,6]. Emerging data indicate that patients who have recovered from the acute phase of COVID-19 are also more susceptible to developing a broad spectrum of symptoms collectively referred to as "Long COVID syndrome", among which the worsening of previous cases and the development of new cases of diabetes mellitus are frequent [7]. A systematic review and meta-analysis including 40 million participants showed that the incidence of new-onset diabetes was 15.53 (7.91-25.64) per 1000 person-years, and that the relative risk of diabetes after SARS-CoV-2 infection was elevated (RR=1.62). The relative risk of type 1 diabetes was RR=1.48 while that of type 2 diabetes was RR=1.70. Furthermore, it was showed that patients with more severe COVID-19 were at higher risk of diabetes (RR=1.67) and that the risk of diabetes was higher in the first 3 months after infection (RR=1.95) [8].

Scientific literature demonstrates that SARS-CoV-2 not only affects more severely patients who already have diabetes more severely, but also can cause metabolic alterations in previously healthy

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people. Several biological mechanisms have been identified to explain how COVID-19 can disrupt glucose balance:

1. Insulin resistance and inflammation: The cytokine storm and systemic inflammation triggered by the virus lead to significant insulin resistance, making it difficult for sensitive cells to utilize glucose [9–13]. **2. Stress response**: The infection stimulates the release of stress hormones such as cortisol, catecholamines, and growth hormone (GH), which are highly diabetogenic hormones that increase glucose production in the liver (gluconeogenesis) and reduce its use in peripheral tissues [12,13]. **3**. **Direct pancreatic damage**: The virus can directly infect pancreatic cells that produce insulin, since these express the ACE2 receptor, used by the virus to enter into the cells [14]**. 4**. **Metabolic reprogramming**: SARS-CoV-2 hijacks cellular metabolism toward glycolysis (a rapid way to produce energy using glucose) to promote its own replication [15]. Also, COVID-19 vaccinations, particularly boosters, can also cause an increase in insulin resistance and alterations in glucose metabolism, generally transient and mainly in subjects with pre-existing or genetic predisposition to diabetes [16].

2. Method

This review aims to analyze and highlight the profound and often bidirectional impact that SARS-CoV-2 infection has on glucose metabolism, attempting to revise and identify which could be the most accredited and actual pathophysiological mechanisms in determining the alterations in glucose homeostasis. To write this manuscript, the authors independently reviewed and compared the results of peer-reviewed and impacted journal publications, written in English, selected from the most well-known search platforms such as PubMed, Scopus, Science Direct, Google Scholar, and ResearchGate, using the following keywords: SARS-CoV-2, COVID-19, Insulin resistance, Glucose metabolism, Obesity, Diabetes, Hospitalization, Mortality.

1.2.1. COVID-19, Insulin Resistance and Inflammation Interaction

SARS-CoV-2 infection can trigger new-onset hyperglycemia, worsen pre-existing diabetes and, in some cases, produce hyperglycemic emergencies. Some studies have associated the degree of hyperglycemia with the severity of viral infection, since high glucose levels may promote viral replication with stimulation of cytokine production and T-cell dysfunction [17,18]. SARS-CoV-2 infection can trigger a systemic immune response characterized by elevated production of pro-inflammatory cytokines (such as IL-6, TNF-α, and IL-1), which, in extreme cases, determines what is defined as cytokine storm [19]. These cytokines activate intracellular signaling pathways that directly interfere with insulin receptors, preventing cells from responding properly to the hormone (insulin resistance).

This leads to the onset of acute insulin resistance, which causes hyperglycemia even in patients who were not previously diabetic [20]. Insulin resistance is not only a consequence, but also an amplifier of the inflammatory state [11].

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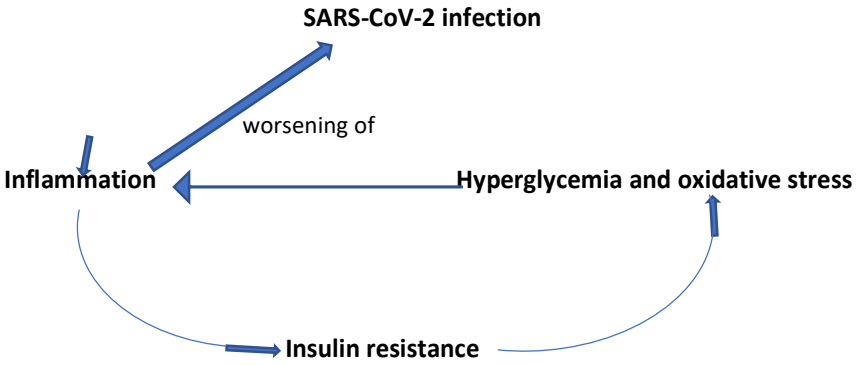

Figure 1. The vitious circle among SARS-CoV-2 infection, inflammation, insulin resistance, hyperglycemia and oxidative stress, further inflammation which, in turn can worsen the course of the disease.

Among other things, the virus can also directly infect fat cells, significantly reducing the production of adiponectin, an important hormone secreted by adipose tissue with multiple beneficial effects: insulin-sensitizing, anti-inflammatory and anti-atherosclerotic, and stimulating fatty acid oxidation [21,22] (Figure 2).

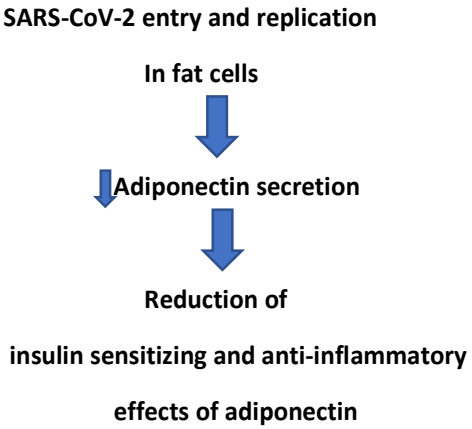

Figure 2. SARS-CoV-2 infection of far cells causes a reduction in adiponectin secretion by these cells, with a reduction in ita insulin-sensitizing and ant-inflammatory effects.

Adiponectin's insulin-sensitizing effects in the liver and skeletal muscle are important, as they reduce gluconeogenesis and increase glucose uptake and utilization. Furthermore, it reduces inflammation in macrophages, endothelial cells, and muscles by reducing reactive oxygen species (ROS). This hormone also stimulates fatty acid oxidation in the liver and muscles through activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR-α) [23].

2.2. COVID-19 and Stress Response

2.2.1. Cortisol

During the acute phase of the disease, cortisol levels serve as a key indicator of the severity of the infection. Patients with severe COVID-19 often have significantly higher blood cortisol levels than those with mild symptoms. This increase is a natural response to the extreme physical stress caused by the virus.

Studies have shown that very high cortisol concentrations on hospital admission are associated with an increased risk of death [24].

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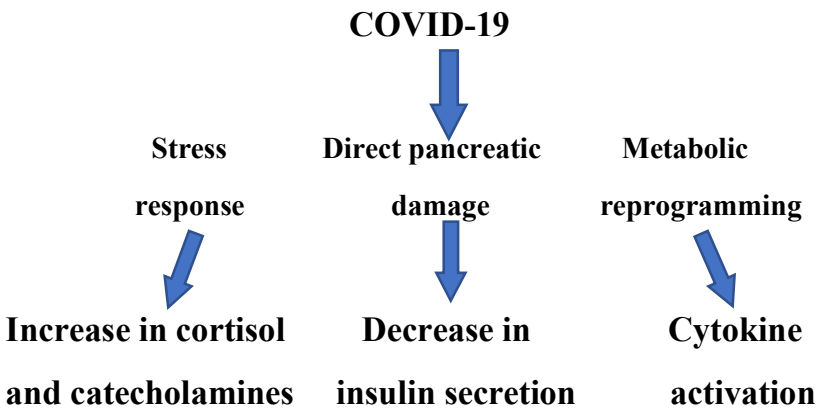

Figure 3. COVID-19 can cause stress response with consequent increase in diabetogenic hormones (cortisol and catecholamines), direct pancreatic damage with consequent decrease in insulin secretion and metabolic reprogramming with consequent cytokine.

Adrenal insufficiency in critical cases plays a pivotal role in some patients in intensive care. In some cases, the adrenal glands can become "exhausted," leading to unusually low cortisol levels, which worsens the prognosis. Cortisol excess (hypercortisolemia) is a well-known cause of insulin resistance and hyperglycemia [25]. Patients with more severe infection symptoms or increased anxiety as a result of isolation experience greater stress and respond with excessive cortisol secretion, which can undoubtedly promote insulin resistance and hyperglycemia. Furthermore, excessive secretion of cortisol by the adrenal gland, together with the adrenal localization of the virus, can ultimately lead to severe adrenal insufficiency with worsening of clinical conditions and prognosis [26].

2.2.2. Catecholamines

The interaction between COVID-19, stress, and catecholamines (such as adrenaline and noradrenaline) represents a key mechanism in the severity of the disease and its long-term complications [27]. Catecholamines (epinephrine, norepinephrine, and dopamine) are hormones and neurotransmitters that serve as primary mediators of the biological response to stress. When the brain perceives a stressor, such as the perception and/or development of a highly fatal disease like COVID-19, the sympathetic nervous system and the adrenal medulla secrete catecholamines into the bloodstream and central nervous system to induce immediate physiological changes in response to the stress [28,29].

In addition to their known effects on the cardiovascular and respiratory systems, and on cognitive function, catecholamines affect metabolism, particularly by stimulating the breakdown of glycogen into glucose and the mobilization of fats to provide rapid energy. However, in the presence of insulin resistance associated with viral disease, the glucose formed is not adequately utilized by the insulin-sensitive organs and therefore remains in circulation, causing blood sugar levels to rise [30,31]. Therefore, the increase in catecholamine secretion resulting from stress in association with the presence of insulin resistance, both caused by COVID-19, certainly becomes a diabetogenic condition.

2.2.3. Growth Hormone

Stress has a complex, dual relationship with GH, depending on both the type and duration of stress. In fact, while acute physical and emotional stress can stimulate an immediate rise in GH secretion to mobilize energy, long duration and chronic stresses often suppress the GH/IGF-1 axis via high cortisol levels. Chronic stress produces an increase of neuropeptide Y, which can inhibit the release of GH releasing hormone, reducing overall GH secretion [32]. Therefore, COVID-19,

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according to the duration of stress produced by the disease can produce high GH or GH deficiency depending on whether it is an acute episode of stress or a long-lasting stress. However, since the stress associated with the pandemic situation is predominantly chronic, GH deficiency is more likely to occur, particularly in patient groups prone to more severe infection such as the frail elderly, diabetics, and obese patients [33]. Research suggests a possible link between the severity of the infection and decrease in GH levels, particularly in hospitalized patients [33]. Therefore, a diabetogenic action of GH in most of the COVID-19 patients is highly improbable.

2.3. Direct Pancreatic Damage

SARS-CoV-2 infection can directly affect the pancreas, potentially contributing to the development of new-onset diabetes or the worsening of a pre-existing condition [14,34]. SARS-CoV-2 mRNA has been found in pancreas islets of patients died for COVID-19 [35]. Evidence of microthrombi of the pancreatic venules, fibrosis and inflammation were found in autoptic pancreas examination of subjects died from COVID-19 [36]. COVID-19 vaccines are another possible cause of pancreatic damage. However, although rare acute pancreatic adverse events have been reported after vaccine injection, such as acute pancreatitis, it is not yet fully understood whether the damage causes temporary or permanent changes in the pancreas and glucose metabolism [37–40]. Rare cases of autoimmune pancreatitis have been reported in temporal association with COVID-19 vaccination, and the proposed mechanism for the development of this pathology is that of molecular mimicry, meaning antibodies generated against the SARS-CoV-2 spike protein can cross-react with the patient's own pancreatic cells, generating an immune response against them [41,42]. Regarding direct pancreatic damage during SARS-CoV-2 infection, the virus can enter pancreatic cells through specific receptors, causing structural and functional damage. Virus entry into cells occurs through the ACE2 and NRP1 receptors. The ACE2 receptor is expressed in both exocrine and endocrine cells (Langerhans cells) of the pancreas [43–46]. Some studies hypothesize that the NRP1 receptor also facilitates viral entry into β cells [47]. SARS-CoV-2 can infect and replicate in pancreatic β cells, resulting in a reduction in insulin secretion in response to glucose levels. Infection can directly lead to pancreatic cell death [14]. Furthermore, viral entry into cells reduces the expression of ACE2 on cell membranes through a receptor downregulation. This latter leads to a systemic RAAS imbalance resulting in excess angiotensin II, which can further impede insulin secretion [48–50].

The association between SARS-CoV-2 infection and autoimmune pancreatitis is a topic of growing interest, although cases reported in the literature are still quite limited [51,52].

It has been hypothesized that the infection may trigger an abnormal immune response in susceptible individuals, leading to the production of autoantibodies that attack pancreatic tissue. Cases of new-onset autoimmune diabetes or worsening of pre-existing conditions have been documented in conjunction with infection, suggesting significant functional damage to the organ.

2.4. Metabolic Reprogramming

SARS-CoV-2 infection induces significant metabolic reprogramming in host cells to increase viral replication and fuel the inflammatory response. By hijacking cellular pathways, the virus shifts host cellular energy production from efficient oxygen-based processes to rapid, but less efficient, methods that serve to construct essential "building blocks" for viral replication [53]. The virus can manipulate pancreatic cells and alter glycation processes, creating an environment favorable to its spread [54,55]. This interference is linked to the onset of diabetes or the worsening of pre-existing conditions. Under normal oxygenation, glucose is converted to pyruvate, producing large amounts of energy. However, under hypoxic conditions, pyruvate is converted directly to lactate, and hypoxia-inducible factor-1 shifts metabolism toward anaerobic glycolysis [56].

Infection induces significant changes in the management of cholesterol and fatty acids, essential for the formation of viral membranes, and of amino acids, essential for the synthesis of viral proteins.

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There is a close relationship between the immune response and metabolic alternation. Metabolic reprogramming plays a key role in activating the "cytokine storm" and regulating innate and adaptive defenses. These metabolic changes and systemic inflammation can damage blood vessels, the heart, liver, and kidneys, also contributing to Long COVID symptoms such as chronic fatigue and "brain fog" [57,58]. Pre-existing metabolic diseases such as obesity and diabetes cause immune dysfunction that significantly increases the severity of the infection [59].

3. Discussion

Obesity, insulin resistance, and type 2 diabetes form a vicious cycle that significantly compromises the body's ability to fight infections. This interaction, often referred to as meta-inflammation (metabolic inflammation), alters both innate and adaptive immune responses [60,61]. Excess adipose tissue is not just a fat deposit, but an active endocrine organ that, in obesity, becomes dysfunctional. Fat cells release pro-inflammatory cytokines and free fatty acids that activate macrophages, leading to a state of low-grade inflammation. This inflammatory state blocks insulin signals, preventing cells (especially in the liver and muscles) from properly absorbing glucose [62]. When the pancreas can no longer produce enough insulin to compensate for this resistance, blood sugar levels steadily rise, leading to type 2 diabetes [63,64].

The link between these metabolic disorders and increased vulnerability to germs (bacteria, viruses, and fungi) is due to several biological mechanisms. Hyperglycemia (high blood sugar) and insulin resistance impair the function of white blood cells, particularly the ability of macrophages and neutrophils to migrate to the site of infection and destroy pathogens [65,66]. Pre-existing chronic inflammation "exhausts" the immune system, making it less effective in responding to new threats or, conversely, triggering excessive and harmful reactions (such as the "cytokine storm" observed in COVID-19) [67]. Insulin resistance and obesity, in particular visceral obesity, are strictly related, although it not yet well clear if obesity or insulin resistance appears first [68]. Unfortunately, both are increasing in developed and developing countries. In 2022, 43% of men and 44% of women aged 18 and over were overweight, and approximately 16% were frankly obese. Unfortunately, obesity is increasing, even in childhood [69]. The prevalence of insulin resistance is also steadily rising, and in the United States stands around 40%, depending on the regions examined [70]. Type 2 diabetes is the final stage of insulin resistance and, in fact, occurs when the pancreatic Langerhans cells are no longer able to secrete sufficient amounts of insulin to overcome insulin resistance and maintain blood glucose levels within a normal range. Insulin resistance precedes the development of diabetes by many years, even up to 15, simultaneously leading to a chronic increase in circulating insulin levels [63,69]. These chronically elevated insulin levels are the cause of many cardiovascular and other health problems [71]. Among other things, hyperinsulinemia and inflammation share a close, self-reinforcing bidirectional relationship that produces metabolic dysfunction. Chronically elevated insulin levels associated with insulin resistance trigger inflammation by increasing pro-inflammatory immune cells (macrophages) and oxidative stress. Inflammation, in turn, leads to a marked reduction in insulin sensitivity in sensitive organs and tissues, increasing insulin requirements [72]. Hyperinsulinemia associated with insulin resistance, with its chronic low-grade inflammation, is a significant risk factor that, when COVID-19 develops, creates a vicious cycle that, on the one hand, worsens insulin resistance and progresses toward worsening disease, resulting in a greater likelihood of death. SARS-CoV-2 infection can also cause new-onset insulin resistance, hyperglycemia, and even new-onset diabetes, even in individuals with no prior metabolic abnormalities [73]. The inflammation that develops following SARS-CoV-2 infection leads to a massive release of inflammatory mediators (including IL-6 and TNF-α), and the pre-existing chronic inflammation from hyperinsulinemia makes patients more susceptible to the development of a cytokine storm. Therefore, pre-existing insulin resistance, creating a state of chronic, low-grade inflammation, is a significant negative prognostic risk factor for severe COVID-19. SARS-CoV-2 infection worsens insulin resistance through direct

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pancreatic β-cell damage, stress induced hormonal changes (for example increased cortisol and catecholamine secretion) and overactive response [74,75].

For these reasons, it was hypothesized that metformin, an insulin-sensitizing antidiabetic drug, could be helpful in the treatment of COVID-19, particularly in obese subjects with insulin resistance. Unfortunately, however, a recent systematic review and meta-analysis of randomized controlled trials concluded that the current scientific evidence suggests there is no significant effect of metformin treatment on acute clinical outcomes in patients with non-severe COVID-19, while metformin may reduce the incidence of long COVID when used to treat this type of patient [76,77].

4. Conclusions

This review examines the most certain mechanisms that determine the vicious circle that is established between SARS-CoV-2 infection and alteration of glucose metabolism and, vice versa, the mechanisms that in obese or diabetic patients can determine worsening of the disease with worse outcomes. Insulin resistance associated with obesity and diabetes is a risk factor predisposing to worsening COVID-19. This is primarily due to the presence of chronic low-grade inflammation, which is aggravated and exacerbated to the point of producing a cytokine storm during infection. SARS-CoV-2 infection, on the other hand, can itself lead to the development of insulin resistance and diabetes even in individuals without predisposing metabolic disorders.

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