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Review

Recent advances in nutritional metabolism studies on SARS-CoV-2 infection

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ABSTRACT

In the context of the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), metabolic research has become crucial for in-depth exploration of viral infection mechanisms and in searching for therapeutic strategies. This paper summarizes the interrelationships between carbohydrate, lipid, and amino acid metabolism and COVID-19 infection, discussing their roles in infection progression. SARS-CoV-2 infection leads to insulin resistance and increased glycolysis, reducing glucose utilization and shifting metabolism to use fat as an energy source. Fat is crucial for viral replication, and imbalances in amino acid metabolism may interfere with immune regulation. Consequently, metabolic changes such as hyperglycemia, hypolipidemia, and deficiency of certain amino acids following SARS-CoV-2 infection can contribute to progression toward severe conditions. These metabolic pathways not only have potential value in prediction and diagnosis but also provide new perspectives for the development of therapeutic strategies. By monitoring metabolic changes, infection severity can be predicted early, and modulating these metabolic pathways may help reduce inflammatory responses, improve immune responses, and reduce the risk of thrombosis. Research on the relationship between metabolism and SARS-CoV-2 infection provides an important scientific basis for addressing the global challenge posed by COVID-19, however, further studies are needed to validate these findings and provide more effective strategies for disease control.

1. Introduction

The coronavirus family includes viruses that infect a range of animal species and that can cause mild to severe respiratory and intestinal infections in humans.[1] Severe acute respiratory syndrome coronavirus (SARS-CoV) was identified in 2002, and the highly pathogenic coronavirus Middle East respiratory syndrome coronavirus (MERS-CoV) was identified in 2013, which causes severe respiratory infection.[2] However, a novel coronavirus, SARS-CoV-2, emerged in 2019. Its high transmissibility resulted in a global pandemic, with an infection scale and geographic scope far exceeding those of SARS-CoV and MERS-CoV. This unprecedented challenge to global health systems has led to the loss of millions of lives. As SARS-CoV-2 continues to spread globally, vaccination remains a key measure in controlling the pandemic,[3] significantly reducing infection rates and mortality. However, ongoing viral mutations, particularly the emergence of the Omicron variant, have increased the risk of breakthrough infections.[4] While Omicron SARS-CoV-2 has lower virulence, its high transmissibility continues to challenge pandemic control efforts.

When a virus infects the human body, it interferes with metabolic processes to obtain necessary energy and materials, disrupting metabolic balance. Carbohydrate metabolism is the primary energy source for the human body, and viral infection can cause hyperglycemia.

Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019; ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; MPC, mitochondrial pyruvate carrier; LDH, lactate dehydrogenase; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DGAT-1, diacylglycerol o-acyltransferase 1; FASN, fatty acid synthase; Trp, tryptophan; DMVs, double-membrane vesicles; CRP, C-reactive protein; 2-DG, 2-deoxy-D-glucose; ICU, intensive care unit.

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Patients with type 2 diabetes (T2D) are more prone to severe symptoms from viral infection.[5] Additionally, SARS-CoV-2 infection interacts with the tricarboxylic acid (TCA) cycle, increasing pyruvate production, reducing oxidative phosphorylation, and promoting glycolysis, further altering metabolic pathways.[6-8] Viral infection also impedes glucose utilization and reduces the efficiency of carbohydrate metabolism.

Carbohydrate and lipid metabolism are closely related, with glucose metabolism directly affecting lipid synthesis.[9] A decrease in glucose utilization may result in fat becoming the primary functional energy source within the body. Lipids, as crucial components of cell structure, energy supply, and signal transduction, also play significant roles in viral infections, especially during viral entry and egress where the virus must cross the cell lipid membrane. Abnormal amino acid metabolism is also closely related to inflammation and immune regulation disorders.[10] This review comprehensively explored the relationships among carbohydrate, lipid, and amino acid metabolism with coronavirus infection, aiming to reveal their impacts on disease progression and their potential roles in disease severity. Characterizing how metabolic processes interact with infection will provide deeper insights into the prevention, diagnosis, and treatment of novel coronavirus infections.

2. Carbohydrate metabolism and SARS-CoV-2 infection

The relationship between carbohydrate metabolism and SARS-CoV-2 infection involves multiple aspects, including the viral impact on glucose regulation and the influence of glucose metabolism on viral replication. Studies have revealed that patients infected with COVID-19 exhibit glucose metabolism disorders,[11] with most experiencing elevated blood glucose levels upon hospital admission.[12] Healthy individuals infected with SARS-CoV-2 can also develop new-onset hyperglycemia and insulin resistance.[11] Because of this, many consider diabetes to be a significant risk factor for COVID-19 infection and severe infection.[13,14]

2.1. The impact of COVID-19 infection on carbohydrate metabolism

2.1.1. Impact of SARS-CoV-2 on blood glucose levels and pancreatic function

In patients with mild to severe COVID-19, circulating blood sugar levels increase, including arabinose, ribose, sugar alcohols, maltose, and raffinose.[15] Compared with SARS-CoV-2-infected individuals without hyperglycemia, those with hyperglycemia tend to have longer hospital stays and higher mortality rates. New-onset hyperglycemia, insulin resistance, and excessive stimulation of pancreatic beta cells have also been observed in patients with COVID-19 without a prior history of diabetes.[16]

SARS-CoV-2 enters cells using angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) present on the surface of host cells, affecting multiple key tissues, including the lungs, liver, adipose tissue, and pancreatic cells. Pancreatic beta cells express ACE2 and TMPRSS2, making them primary targets for the virus. SARS-CoV-2 viral antigens, including SARS-CoV-2-E and SARS-CoV-2-N, as well as viral RNA, have been detected in pancreatic beta cells. Additionally, expansion and vacuolization of the endoplasmic reticulum (ER)-Golgi complex have been observed, indicating that ER stress and Golgi swelling lead to decreased cell functionality and reduced overall glucose responsiveness in pancreatic cells post-infection.[17-19]

In animal experiments, the interaction between fibroblast growth factor 7 and fibroblast growth factor receptor 2 upregulates the expression and activity of ACE2 in pancreatic beta cells, exacerbating SARS-CoV-2 infection.[20] The widespread impairment of the insulin and insulin-like growth factor signaling pathways in patients with COVID-19 may be influenced by interferon regulatory factor 1.[21] After viral infection of pancreatic cells, increased cell permeability leads to the infiltration of inflammatory cells and cytokines into the pancreas; this triggers stress responses in pancreatic cells and damages beta cells,[22] making it easier for the virus to enter the pancreas. Wu et al.[23] reported that neuropilin-1 (NRP1) expression in beta cells was significantly upregulated in patients with COVID-19 compared with uninfected patients. Treatment with NRP1 inhibitors could reduce SARS-CoV-2 infection and partially restore glucose-stimulated insulin secretion in the pancreas (Fig. 1). In summary, SARS-CoV-2 infection leads to impaired beta-cell function, reduced insulin secretion, hyperglycemia, and insulin resistance.

2.1.2. Mitochondrial dysfunction induced by SARS-CoV-2 infection and associated inflammation

Elevated blood glucose levels favor the replication of SARS-CoV-2. An *in vitro* study that altered glucose concentrations in monocytes revealed that elevated glucose levels could promote the replication of SARS-CoV-2 and the production of inflammatory factors in monocytes.[24] This suggested that SARS-CoV-2 infection induces the production of mitochondrial reactive oxygen species (mtROS), leading to the stable expression of hypoxia-inducible factor-1α, promoting glycolysis and cytokine storms. This finding aligns with those of another study that reported a widespread increase in the expression of genes encoding glycolytic enzymes and a decrease in lactate dehydrogenase B expression, along with an increase in lactate dehydrogenase A expression in the peripheral blood of patients with COVID-19.[25] These findings indicate that

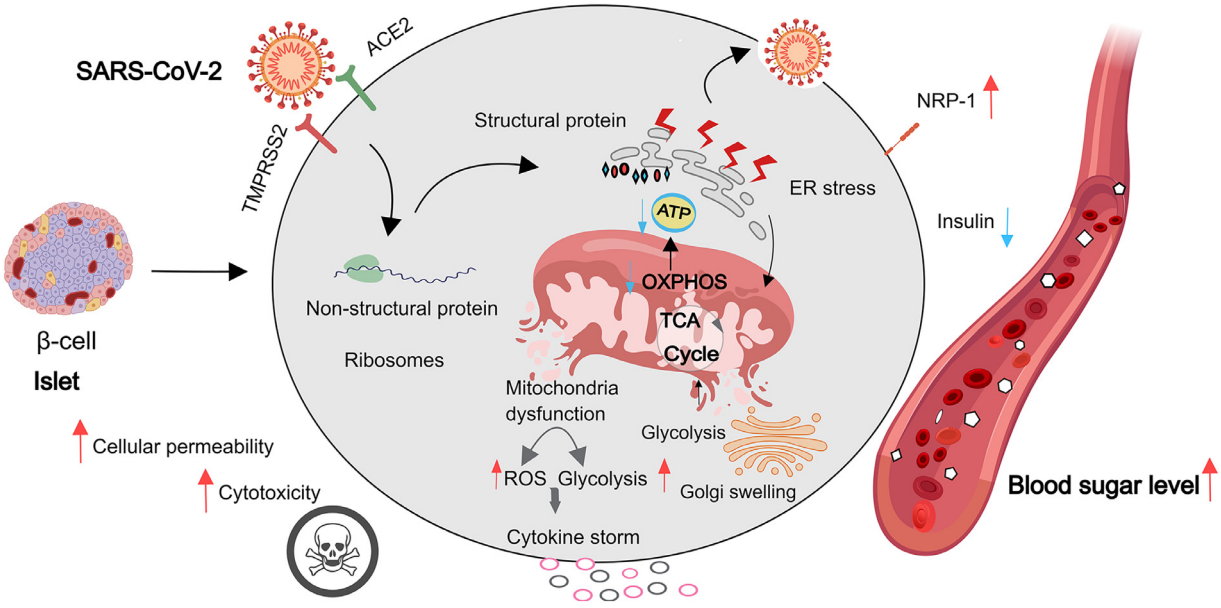

Fig. 1. SARS-CoV-2 enters cells through the host cell surface ACE2 and TMPRSS2, subsequently using ribosomes within β-cells to produce non-structural proteins and synthesize structural proteins in the ER. This process leads to ER stress and Golgi complex swelling, while also impairing OXPHOS and reducing ATP production, causing the TCA cycle to shift toward glycolysis; this results in mitochondrial dysfunction and increased reactive oxygen species (ROS). Ultimately, these changes trigger a cytokine storm, increased cytotoxicity, and enhanced cell permeability, damaging β-cells, reducing insulin secretion, and leading to elevated blood glucose levels.

Abbreviations: TMPRSS2, transmembrane protease serine 2; ACE2, angiotensin-converting enzyme 2; ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle; ROS, reactive oxygen species; NRP-1, neuropilin-1; ER stress, endoplasmic reticulum stress.

SARS-CoV-2 infection impairs oxidative phosphorylation, shifts energy metabolism toward glycolysis, and further induces cytokine storms. Zhu et al.[26] reported that inhibiting the mitochondrial pyruvate carrier (MPC) alleviated severe infection following SARS-CoV-2 pneumonia. The MPC inhibitor MSDC-0602 K suppressed pulmonary inflammation, and experiments on infected mice revealed that it lowered blood glucose levels and hyperlipidemia. Mechanistically, MPC enhances mitochondrial adaptability and disrupts hypoxia-inducible factor-1α, mitigating virus-induced inflammatory responses in mice and human lung macrophages.

2.1.3. Implications of carbohydrate metabolism in SARS-CoV-2 infection

In summary, SARS-CoV-2 infection has profound effects on carbohydrate metabolism, significantly impacting patient health. The infection impairs pancreatic beta-cell function, leading to reduced insulin secretion, hyperglycemia, and insulin resistance. These metabolic disturbances are exacerbated by mitochondrial dysfunction and increased glycolysis, driven by elevated mtROS. This interplay highlights the complex relationship between SARS-CoV-2 infection and carbohydrate metabolism, emphasizing the need to address these issues to improve patient outcomes. Understanding these mechanisms can inform management strategies, including lifestyle changes, blood glucose monitoring, and targeted therapies aimed at restoring carbohydrate metabolic balance.

2.2. The role of carbohydrate metabolism in COVID-19 prognosis and severity

Blood glucose levels after SARS-CoV-2 infection are closely related to patient prognosis; high levels (glucose > 170 mg/dL) may be associated with inflammatory responses, insulin resistance, and abnormal insulin secretion.[27] Maintaining blood glucose variability within 3.9–10.0 mmol/L can significantly reduce the risk of composite adverse outcomes and death associated with COVID-19.[28] Studies have revealed correlations between elevated blood glucose levels and prolonged hospital stays, disease progression, and increased mortality in patients with COVID-19. Monitoring blood glucose levels can help predict disease progression and prognosis, allowing for appropriate interventions. The inflammatory state in patients with COVID-19 leads to insulin resistance and abnormal insulin secretion, which further contribute to hyperglycemia in these patients.[27] Monitoring indicators of insulin resistance also provides some reference for preventing disease severity. Glycated hemoglobin (HbA1c) is an indicator of long-term blood glucose control, reflecting the average blood glucose level over the past 2–3 months. Some studies have shown a linear relationship between HbA1c levels in patients with COVID-19 and the risk of death or deterioration.[29] Higher HbA1c levels may indicate poorer long-term blood glucose control, which is associated with insulin resistance and inflammatory responses.[28] Because of this, monitoring HbA1c levels can

Table 1
Key warning indicators of nutrient metabolism following SARS-CoV-2 infection.

Nutrient metabolism	Warning indicators	References
Carbohydrate metabolism	Blood sugar level↑, HbA1c↑, LDH↑, LDHA↑, FGF21↑, MPC↑, LDHB↓	23-26,28-32
Lipid metabolism	HDL-C↓, TC↓, LDL-C↓, apoA-I↓, CRP/HDL-C↑, TG↑, RvD5↑	48,50,51,65-70
Amino acid metabolism	Trp↓, Arg↓, Val↓, Ala↓, Gly↓, Ser↓, His↓, Glu↓, Met↓, Kyn↑, Nam↑, Arg/Kyn, Cr/Arg	87-93

Abbreviations: HbA1c, glycosylated hemoglobin, type A1C; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A; FGF21, fibroblast growth factor 21; MPC, mitochondrial pyruvate carrier; LDHB, lactate dehydrogenase B; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA-I, apolipoprotein A-I; CRP/HDL-C, C-reactive protein/high-density lipoprotein cholesterol; TG, triglycerides; RvD5, resolvin D5; Trp, tryptophan; Arg, arginine; Val, valine; Ala, alanine; Gly, glycine; Ser, serine; His, histidine; Glu, glutamate; Met, methionine; Kyn, kynurenine; Nam, nicotinamide; Arg/Kyn, arginine/kynurenine ratio; Cr/Arg, creatinine/arginine ratio.

provide useful reference points for assessing the prognosis and severity of COVID-19.

In patients with COVID-19, mitochondrial dysfunction has been observed in peripheral blood mononuclear cells (PBMCs), leading to energy deficiency. The upregulation of fibroblast growth factor 21 (FGF21) can act as a compensatory mechanism to promote glycolysis and other metabolic pathways to meet cellular energy demands. FGF21 levels increase with the severity of COVID-19 and are highest in deceased patients[30] compared to the healthy group; FGF-21 levels in patients with COVID-19 can reach 2000–3000 pg/mL. Consistent with the findings of this study, lactate dehydrogenase (LDH) levels are elevated in patients with COVID-19, with those in severe cases (316.4 ± 86.4 U/L) being significantly higher than those in mild cases (222.4 ± 73.8 U/L). LDH is a strong predictor for the early detection of lung injury and progression to severe COVID-19[31-33]. Increased LDH levels are associated with approximately a six-fold increase in the likelihood of severe infection and a sixteen-fold increase in mortality in patients with COVID-19[34] (Table 1).

Regardless of whether COVID-19 patients have diabetes, studies have shown that blood glucose levels are closely related to COVID-19 susceptibility, infection severity, and outcomes (severity of illness, intensive care unit [ICU] admission rate, and mortality rate)[28,35-37], making monitoring blood glucose levels crucial. Indicators of glucose metabolism play a role in predicting the prognosis and severity of COVID-19. Blood glucose levels, insulin resistance indices, and HbA1c can provide some predictive value for condition progression and the risk of severe illness. However, it is necessary to consider multiple factors, including baseline metabolic status, nutritional condition, and treatment interventions, to accurately assess the relationships between glucose metabolism indicators and patient prognosis.

2.3. Carbohydrate metabolism as a potential therapeutic target for COVID-19

For hyperglycemic COVID-19 patients, glucose-lowering drugs, including 2-deoxy-D-glucose (2-DG), metformin, thiazolidinediones, insulin, and glucagon-like peptide-1 receptor agonists, can be used.[38-40] 2-DG targets glycolysis, preventing viral synthesis and inhibiting viral replication. The Indian Drug Administration has approved 2-DG for emergency use as an adjunctive therapy.[41] A retrospective medication analysis by Crouse et al.[42] revealed that the use of metformin before a COVID-19 diagnosis could reduce the mortality rate in diabetic patients by approximately threefold. Another cohort study of patients with COVID-19 with T2D who were taking metformin reported a significant association between metformin use and the incidence of metabolic acidosis.[43] Metformin also reduces heart failure and inflammation, though careful dose selection is crucial to avoid acidosis. Individuals with impaired renal function should use metformin with caution. Additionally, insulin injections in hospitalized hyperglycemic patients combined with sitagliptin reduced the relative risk of requiring mechanical ventilation by 74%[44] (Table 2).

In addition to pharmacotherapy for glucose-related diseases, a healthy lifestyle and a nutritious diet should also be emphasized. The number of COVID-19 cases and deaths in the United States and Japan differ by 12–17 times; a study revealed that this significant difference is partly due to the dietary habits of the two countries.[45] The U.S. diet, which is rich in high-sugar and high-fat junk food, has a high dietary inflammation index; this may increase the risk of COVID-19 infection, especially among minority groups. In contrast, the Japanese diet is more nutrient-dense, containing many beneficial substances that can prevent COVID-19. Japan, a coastal country, consumes more fish than noncoastal regions do, resulting in higher levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the body. DHA and EPA are converted into protectins, which inhibit excessive immune cell activity, support phagocytosis, and promote the differentiation of neutrophils, further preventing COVID-19 infection[46] (Table 2).

3. Lipid metabolism and SARS-CoV-2 infection

Lipids play a crucial role in the viral life cycle, influencing viral entry by affecting cell fusion or receptor conformation. After infection, viruses can reprogram cell metabolism to alter lipid membranes and promote the

Table 2
Potential therapeutic targets for major nutrient metabolism following SARS-CoV-2 infection.

Nutrient metabolism	Potential therapeutic targets	References
Carbohydrate metabolism	Metformin, thiazolidinediones, glucagon-like peptide-1, insulin, 2-deoxy-D-glucose, sitagliptin, and a nutrient-dense diet	36-39,42,44
Lipid metabolism	Lipid-lowering drugs, methyl-β-cyclodextrin, orlistat, increasing dietary omega-3 long-chain polyunsaturated fatty acids, and arachidonic acid	62,71,75-79
Amino acid metabolism	Supplementing arginine and L-arginine, indolmod	84,94,95

production of new viral particles. Lipids are essential for energy and signal transduction in the SARS-CoV-2 life cycle,[47] including key steps such as endocytosis, signal transduction, viral protein transport, and viral assembly. Exploring the role of lipid metabolism in viral infection and targeting lipid metabolism as a potential therapeutic target for COVID-19 is necessary.

3.1. The impact of COVID-19 infection on lipid metabolism

3.1.1. Changes in lipidomics and metabolomics in COVID-19

Lipidomic and metabolomic analyses of patients with COVID-19 have revealed changes in immune and metabolic components related to infection severity. Compared with those in healthy individuals, more than 100 lipids are downregulated in COVID-19, including sphingolipids, glycerophospholipids, and fatty acids such as phosphatidic acids, phosphatidylinositols, and phosphatidylcholines.[48,49] Additionally, more than 50 lipids upregulated by infection have been found, including triacylglycerols, diacylglycerols, and lysophosphatidylcholines.[50] The levels of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol in the serum of infected patients sharply decrease,[51,52] and HDL cholesterol concentration is negatively correlated with C-reactive protein (CRP) concentration[53-55] (Fig. 2).

3.1.2. The impact of lipid droplets and rafts on SARS-CoV-2 replication

Lipid droplets (LDs) are organelles that play crucial roles in lipid metabolism, energy homeostasis, and intracellular transport, in addition to performing various functions in infection and inflammation. Compared with healthy volunteers, the accumulation of LDs in the monocytes of patients with COVID-19 is increased; this is accompanied by the upregulation of pathways involved in lipid uptake (such as CD36), transcription factors primarily involved in lipogenesis (PPARγ and SREBP-1), and enzymes involved in triacylglycerol synthesis (DGAT-1). Using drugs to inhibit DGAT-1, a key enzyme in LD formation, can reduce viral replication and prevent cell death in SARS-CoV-2-infected monocytes.[56-58] Lipid rafts are microdomains within cell membranes rich in cholesterol and sphingolipids that are crucial for viral invasion and signal transduction. Studies have shown that sphingolipid levels are reduced in both non-severe and severe cases of COVID-19.[48] SARS-CoV-2 utilizes lipid rafts to facilitate entry into host cells as well as for viral assembly[59] (Fig. 2).

3.1.3. SARS-CoV-2 induced changes in endoplasmic reticulum structure and fatty acid metabolism

During SARS-CoV-2 infection, the structure of the ER membrane changes, resulting in the formation of organelles such as double-membrane vesicles (DMVs), which are used for viral replication.[60] These changes may be driven by altering the reticulon proteins RTN3 and RTN4 to promote DMV formation, facilitating viral replication.[61] Alternatively, they may depend on the production and distribution of phosphatidic acid (PA); the use of PA inhibitors such as chloroquine can impede the formation of autophagosome-like DMVs, inhibiting viral replication.[62,63] Fatty acid metabolism is a crucial metabolic pathway during SARS-CoV-2 infection. Fatty acid synthase (FASN) plays a key role in fatty acid synthesis.[64] Studies have shown that in cells lacking FASN, the viral titer of SARS-CoV-2 is significantly reduced[65,66] (Fig. 2).

SARS-CoV-2 affects host cell lipid metabolism through various mechanisms, including the generation and utilization of lipid droplets, the remodeling of lipid rafts, and the synthesis and transport of fatty acids. These mechanisms work together to support viral replication and dissemination, causing extensive impacts on host cells. Understanding these mechanisms can help in the development of therapeutic strategies that target lipid metabolism pathways to control the spread of COVID-19 and mitigate its damage to the host.

3.2. The role of lipid metabolism in COVID-19 prognosis and severity

Abnormal lipid metabolism in patients with COVID-19 affects prognosis and severity. In patients who gradually recover, lower levels of TC and LDL cholesterol slowly return to normal.[53] In contrast, non-survivors exhibit persistent hypolipidemia, including TC, HDL and LDL cholesterol, and apoA-I. A gradually decreasing HDL concentration from days 1 to 7 after admission may serve as an indicator of poor prognosis[67]; as the severity of COVID-19 infection increases, HDL levels decrease by approximately 36%.[68] Additionally, the CRP/HDL and CRP/apoA-I ratios are significantly greater in patients who survive COVID-19 than in non-survivors; in the study by Li et al.[52], the best cut-off point for the CRP/HDL-C ratio

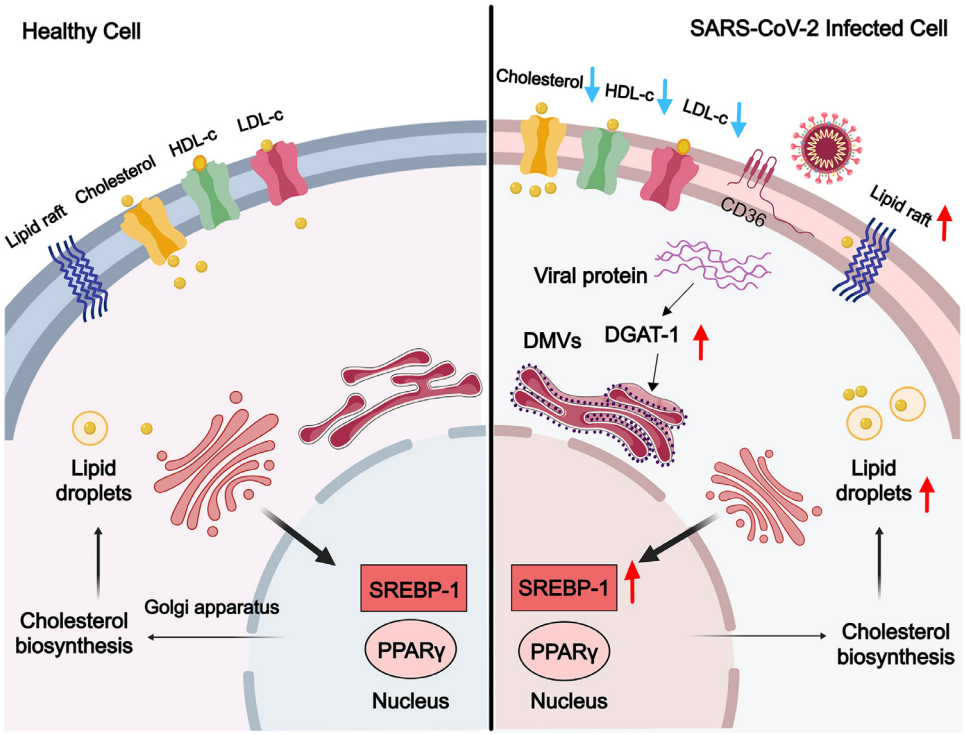

Fig. 2. The impact of SARS-CoV-2 infection on lipid-related metabolism in cells. SARS-CoV-2 infection reduces cholesterol levels in HDL and LDL receptors, increases lipid rafts, and causes LDL accumulation. The virus upregulates lipid uptake pathways (CD36) and diacylglycerol o-acyltransferase 1 (DGAT-1). It also modifies the ER membrane to form double-membrane vesicles (DMVs) and elevates PPARγ and SREBP-1 levels.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DGAT-1, diacylglycerol o-acyltransferase 1; DMVS, diacylglycerol-mediated vesicle secretion; SREBP-1, sterol regulatory element-binding protein 1; PPAR-γ, peroxisome proliferator-activated receptor gamma.

was 77.39, and that for the CRP/apoA-I ratio was 72.37. High CRP/HDL (> 77.39) and high CRP/apoA-I ratios (> 72.37) were defined as risk indicators. A high CRP/HDL ratio has also been shown to be an independent predictor of in-hospital mortality in patients with severe COVID-19. Several studies have reported increased triglyceride (TG) levels in patients with COVID-19.[50,69] Elevated TG levels are often associated with insulin resistance, as SARS-CoV-2 infection leads to impaired β-cell function, resulting in hyperglycemia and insulin resistance.[14,20] An increase in TG is positively correlated with disease severity and adverse clinical outcomes.[49,70,71] Additionally, some studies have reported increased concentrations of the bioactive lipid 17-hydroxy-docosahexaenoic acid downstream of RvD5 in patients with severe COVID-19 compared with those in control or mild groups[72,73] (Table 1).

3.3. Lipids and their metabolism as potential therapeutic targets for COVID-19

Certain lipid-lowering drugs can inhibit the replication of SARS-CoV-2. Methyl-β-cyclodextrin interacts with the lipid microenvironment through its hydrophobic core, competing with viral binding sites and preventing viral attachment.[74] Statins, which are commonly used as cholesterol-lowering medications, can inhibit the rate-limiting enzyme (HMGR) in cholesterol biosynthesis,[75] reducing available cholesterol levels, decreasing the expression of membrane ACE2 receptors, and blocking viral entry.[76] Statins also have other properties beyond cholesterol-lowering effects, including anti-inflammatory, antithrombotic, and immunomodulatory effects.[77] Several retrospective observational clinical studies have demonstrated the beneficial impact of prior and long-term use of statins as well as their introduction in hospitals after SARS-CoV-2 infection on patient prognosis.[78-80] These properties may enhance host defense against pathogens. Another study analyzed the binding capacity of the main protease Mpro (6UL7) of SARS-CoV-2 with seven statins and three common antiviral drugs, finding that the binding energies of the seven statins were similar to those of the three antiviral drugs, suggesting that statins may inhibit the main protease of SARS-CoV-2.[81] A recent *in vitro* study revealed that drug intervention targeting cellular lipid synthesis using the FAS inhibitor orlistat inhibited SARS-CoV-2 replication.[64] In addition to pharmacological treatments, a healthy diet may play a preventive role in future pandemics. Increasing dietary levels of omega-3 long-chain polyunsaturated fatty acids and arachidonic acid can also reduce the inflammatory effects caused by COVID-19[82,83] (Table 2).

4. Amino acid metabolism and SARS-CoV-2 infection

In addition to the studies mentioned above on glucose and lipid metabolism, research on amino acid metabolism

has gradually highlighted its critical role in SARS-CoV-2 infection. By studying changes in host amino acid metabolism following SARS-CoV-2 infection, researchers have revealed the impact of viruses on amino acid synthesis, degradation, and interactions within cells. These findings provide new insights into the progression of this disease and the development of therapeutic strategies.

4.1. Impact of COVID-19 on amino acid metabolism

Omics analysis of lipid metabolism in patients with COVID-19 compared with healthy individuals revealed significant changes in various amino acids and their metabolic pathways. The levels of key amino acids involved in the urea cycle, such as arginine, ornithine, and citrulline, were significantly decreased in COVID-19 patients.[84,85] Citrulline is an important intermediate in the urea cycle, which occurs in the liver; SARS-CoV-2 infection may disrupt the urea cycle and liver dysfunction. L-arginine affects T-cell function and expression[86]; its reduction in COVID-19 patients diminishes L-arginine levels, impacting T-cell proliferation. Another study revealed that reduced arginine levels and increased ornithine levels inhibit the ability of $CD8^+$ T-cells to produce cytokines such as IFN-γ and TNF-α, impairing the T-cell immune response.[85] In whole blood analyses, critically ill patients presented a sharp increase in phenylalanine and tryptophan (Trp) metabolism. Trp metabolism is considered an inflammatory biomarker, with Trp degradation products promoting T-cell exhaustion.[87] As the condition of COVID-19 patients worsens, serum alanine levels significantly decrease, negatively affecting muscle health and energy metabolism and increasing mortality risk.[88] Decreases in malic acid and aspartic acid, which are essential for purine and pyrimidine nucleotide biosynthesis, were also observed.[89] The authors suggested that the depletion of these substances may partially result from SARS-CoV-2 hijacking nucleic acids during host cell replication. Additionally, histidine, L-valine, L-proline, and Trp were downregulated in COVID-19 patients. L-valine is involved in pantothenic acid and coenzyme A biosynthesis, and its dysregulation can impair mitochondrial energy metabolism via coenzyme A.[49] In summary, COVID-19 infection causes significant changes in various amino acids and their metabolic pathways, impacting energy production, immune function, and liver metabolism, exacerbating COVID-19.

4.2. The role of amino acid metabolism in COVID-19 prognosis and severity

In COVID-19 patients, Trp metabolism increases with infection severity, and a deficiency in L-arginine significantly reduces resistance to infection. The rate of L-arginine depletion is positively correlated with disease severity and the length of ICU stay.[90] Another study revealed that the levels of Trp and its metabolites, 3-hydroxykynurenine and kynurenine, were negatively correlated with the SARS-CoV-2 viral load.[91,92] COVID-19 induces significant gluconeogenesis, leading to a reduction in most gluconeogenic amino acids, including valine, alanine, glycine, serine, histidine, glutamate, and methionine. A reduction in gluconeogenic amino acids is negatively correlated with disease severity.[93] Many studies have reported significant decreases in Trp, accompanied by increases in kynurenine and nicotinic acid,[91,94,95] which is positively correlated with disease severity and fatal clinical outcomes.[96] A small cohort study revealed that the arginine/kynurenine ratio had excellent predictive ability for distinguishing COVID-19 patients from healthy controls (threshold ≤ 15.7), with an area under the curve of 1.00 in receiver operating characteristic analysis. The creatinine/arginine ratio also accurately predicts mortality, with 100% accuracy for mortality prediction on ICU days 1 (threshold ≥ 3.4) and 3 (threshold ≥ 3.7).[90] Despite their promise as predictors, these results need to be replicated and validated in larger patient cohorts (Table 1).

4.3. Amino acids and their metabolism as potential therapeutic targets for COVID-19

Changes in arginine, Trp, and indoleamine 2,3-dioxygenase (IDO) can alter T-cell function, leading to severe COVID-19. Restoring exhausted T-cell function by supplementing or reducing specific amino acids to enhance the immune system shows promise as a potential therapeutic approach. Previous reports indicate that direct supplementation with arginine, the use of Indolmod to target Trp catabolism, or the use of Navomodu to target IDO1/TDO2 can promote T-cell metabolic recovery.[87] Additionally, the availability of L-arginine is associated with endothelial dysfunction and T-cell impairment. The inclusion of L-arginine in the standard treatment for patients with severe COVID-19 can significantly shorten hospital stays.[97] Another study demonstrated that supplementing α-ketoglutarate in SARS-CoV-2-infected hamsters reduced the accumulation of inflammation-induced cells in the alveolar cavity and the formation of clots in microvessels, as well as decreased apoptotic damage in infected lung tissue.[98] Dietary supplementation with α-ketoglutarate may be a good nutritional strategy to prevent thrombosis and inflammation in COVID-19 patients (Table 2).

5. Conclusion

Carbohydrate, lipid, and amino acid metabolism play crucial roles in SARS-CoV-2 infection, providing key insights into infection mechanisms and informing the de-

velopment of therapeutic strategies. SARS-CoV-2 infection leads to insulin resistance and increased glycolysis, reducing the utilization of glucose and shifting energy production to fat, which is critical for viral replication. Studies have found that SARS-CoV-2 infection induces insulin resistance and enhances glycolysis, leading to an imbalance in glucose metabolism, which affects immune responses and provides more energy for the virus. Lipid metabolism also shows abnormal changes, particularly in the generation and utilization of lipid droplets, the remodeling of lipid rafts, and the synthesis and transport of fatty acids, all of which are closely related to viral replication. Imbalances in amino acid metabolism may interfere with immune regulation, contributing to the progression of severe conditions in the presence of hyperglycemia, hypolipidemia, and deficiencies in certain amino acids. Amino acid metabolism, especially tryptophan metabolism, also exhibits significant changes at different stages of the disease. Studies have shown that the deficiency of L-arginine is closely associated with impaired immune function and disease progression. These metabolic changes are not only valuable for predicting and diagnosing the disease but also offer new perspectives for developing treatment strategies.

Monitoring changes in glucose, lipid, and amino acid metabolism can provide early warnings of disease progression, allowing for timely intervention. A clinical trial targeting patients with severe acute respiratory syndrome caused by SARS-CoV-2, who were also diagnosed with T2D and had elevated blood glucose levels, found that metformin glycinate (MG, 620 mg orally every 12 h) significantly and safely reduced the viral load in patients with COVID-19 while also lowering aspartate aminotransferase (AST) and lactate dehydrogenase (DHL) levels; at the end of the study, the glucose levels in the MG treatment group were close to normal values (110.3 mg/dL).[99] Another study also indicated that combined metabolic activators (CMAs), such as L-serine and N-acetyl-L-cysteine, can significantly improve these metabolic disorders and shorten the recovery time of patients with COVID-19. Phase 2 and 3 clinical trials have shown that CMA treatment significantly improves the levels of inflammation and antioxidant-related metabolic proteins and metabolites in plasma, suggesting that CMAs may accelerate patient recovery.[100] Additionally, lipid synthesis is crucial for SARS-CoV-2 replication. Inhibitors of FASN, such as orlistat, can significantly suppress viral RNA synthesis and the production of infectious viruses.[64] These findings suggest that modulating metabolic pathways can help reduce inflammatory responses, improve immune function, and decrease disease severity.

In-depth research into the relationships among carbohydrate, lipid, and amino acid metabolism with SARS-CoV-2 infection will enhance our understanding of the virus's pathogenic mechanisms and provide more effective treatment and intervention methods for this global health crisis. However, further studies are needed to validate the findings highlighted in this review to ensure that we accurately comprehend the roles of these metabolic pathways in disease progression and to provide a more solid scientific foundation for developing preventive and therapeutic measures.

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CRediT authorship contribution statement

Yufen Jiang: Writing – original draft. **Linle Xu:** Data curation. **Xuexing Zheng:** Supervision, Formal analysis. **Hongbo Shi:** Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

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