Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The Bidirectional Association Between Metabolic Syndrome and Long-COVID-19

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Background: The rapid global spread of a new coronavirus disease known as COVID-19 has led to a significant increase in mortality rates, resulting in an unprecedented worldwide pandemic.

Methods: The impact of COVID-19, particularly its long-term effects, has also had a profound effect on the health and well-being of individuals.Metabolic syndrome increases the risk of heart and brain diseases, presenting a significant danger to human well-being.

Purpose: The prognosis of long COVID and the progression of metabolic syndrome interact with each other, but there is currently a lack of systematic reports.In this paper, the pathogenesis, related treatment and prognosis of long COVID and metabolic syndrome are systematically reviewed.

Keywords: Long COVID, Metabolic syndrome, Cardiovascular disease, pathway, drugs

Introduction

COVID-19, a new disease caused by the novel coronavirus SARS-CoV-2, primarily impacts the respiratory system and has quickly spread worldwide since its first detection in December 2019,[1–3] posing a significant threat to global health. The global health crisis caused by the pandemic is one of the most significant challenges that humanity has encountered in the past century.[4,5] As of January 16, 2023, the World Health Organization (WHO) reported that over 662 million people had been infected, resulting in more than 6.7 million deaths globally.[6] New information suggests that symptoms that continue for at least 4 weeks after being diagnosed with or experiencing acute symptoms of COVID-19 can be classified as "long COVID", as defined by NICE as post-COVID conditions or ongoing symptomatic COVID-19.[7] The prolonged effects of COVID-19, encompassing various health issues that may persist for an extended period of time, have emerged as a significant worldwide concern.In this COVID-19 pandemic era, metabolic syndrome has received increased attention.In our 2020 report, we examined the connection between COVID-19 and metabolic syndrome.[8] Vascular diseases can be viewed as complications of COVID-19.[9,10]

Metabolic syndrome is a group of heart disease risk factors that consist of central obesity, dyslipidemia, impaired glucose metabolism, high blood pressure, and low levels of HDL cholesterol, all of which are consistently identified as major risk factors for severe COVID-19.[11] Additionally, metabolic syndrome is becoming a notable contributor to complications in individuals with COVID-19.[2,12] Metabolic syndrome is especially significant in relation to COVID-19, as it results in a three times higher risk of mortality and a four to five times higher risk of needing invasive mechanical ventilation, acute respiratory distress syndrome, and being admitted to an intensive care unit.In this paper, the latest finding on the relationship between long COVID and metabolic syndrome are summarized and its possible mechanisms are described.Additionally, we examined pathways associated with cardiovascular damage in long COVID-19, as these elements have been identified as potential contributors to the development of long COVID-19.Our earlier publication examined the elements of metabolic syndrome, including dyslipidemia, high blood pressure, type 2 diabetes, and obesity, which are prevalent and greatly elevate the likelihood of hospitalization and mortality in individuals with COVID-19.[12] Besides the high rates of severe illness and death within the initial weeks following infection, as many as 70% of

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individuals who recover from COVID-19 may face enduring issues.[13–15] These lingering symptoms can persist for weeks to months, significantly impacting the well-being of patients long after the virus has cleared.Symptoms that persist for at least 2 months after the onset of COVID-19, lasting for typically 3 months, are commonly referred to as "long COVID" and cannot be attributed to another diagnosis.[16] The aim of this review was to provide a concise overview of the latest information on health issues following COVID-19 and their connection to individuals with metabolic syndrome.

Defining Metabolic Syndrome and Long-Term COVID-19

Metabolic syndrome, also known as MetS, is a medical condition identified by the accumulation of metabolic risk factors.Gerald Reaven was the first to propose criteria for diagnosing MetS, renaming it "syndrome X", a term later adopted by the WHO in 1998,[17] with a focus on insulin resistance as a key risk factor.MetS is characterized by metabolic abnormalities such as high blood sugar, high blood pressure, abnormal lipid levels, low HDL-cholesterol levels, and obesity, all of which increase the risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs).[18] Defining MetS with a standard definition has been difficult due to specific constraints and limitations. Metabolic syndrome has become more common in advanced nations, affecting 20–25% of adults, with its frequency rising steadily.[19–22] The WHO, AACE, EGIR, and IDF have each established their own criteria for MetS, which have been updated[22,23].Various organizations have supported slightly different definitions of MetS.The definitions encompass central obesity, dyslipidemia, insulin resistance, and hypertension, each with varying thresholds for risk assessment.Heart disease, diabetes, stroke, and other health issues have been associated with all risk factors of metabolic syndrome.[24]

As per the guidelines from NCEP Adult Treatment Panel III (NCEP ATP III), the identification of the condition did not align with the earlier criteria of having identical components.[25] The American Heart Association and the National Heart, Lung, and Blood Institute (NHLBI) introduced changes to the ATP III criteria for MetS in 2005.[26] Diagnosing the syndrome required the presence of central obesity according to the International Diabetes Federation (IDF), unlike the Joint Interim Societies (JIS) which did not consider central obesity a crucial factor.According to data from the World Health Organization, new definitions and diagnostic criteria for MetS have been released, which now encompass individuals with diabetes or those with confirmed cardiovascular disease (CVD); this data can forecast the likelihood of developing the condition, reducing the importance of diabetes and CVD in routine medical care; they are now considered a precursor to illness rather than a formal diagnosis.[27]

The prevailing consensus is that the primary factor in metabolic syndrome, obesity, and other cardiometabolic risk factors often contribute to inflammation and endothelial dysfunction, ultimately leading to a delayed recovery from COVID-19, known as long-COVID-19.[28,29] Numerous health organizations at both national and global levels have put forth various definitions to characterize what is known as long-COVID-19.[30–33]

At present, there is no agreement on the exact definition of long COVID syndrome.Patients typically must wait a minimum of 4 weeks following diagnosis or the appearance of acute COVID-19 symptoms before categorizing symptoms as persistent.NICE has differentiated between persistent symptomatic COVID-19 and long COVID-19 syndrome for individuals experiencing symptoms for over 12 weeks after initial acute symptoms.[34] Over 50 common long-term effects of SARS-CoV-2 infection have been recognized, such as tiredness, migraines, difficulty breathing, cognitive issues, numbness, mood disorders, loss of smell and taste, reduced appetite, ongoing cough, chest discomfort, and rapid heartbeat.[35]

Long-COVID-19 and Metabolic Syndrome

Metabolic syndrome, encompassing obesity, insulin resistance, hypertension, and hyperlipidemia, influences the pathophysiological processes associated with long COVID-19 through multiple mechanisms, as illustrated in Figure 1. These mechanisms include viral interference with pancreatic hormones, activation of the renin-angiotensin-aldosterone system (RAAS), augmentation of endoplasmic reticulum and oxidative stress, and the maintenance of a chronic inflammatory state within the immune system. Such pathological alterations not only intensify the severity of the acute phase of COVID-19 but also contribute to the persistence of long-term symptoms, including fatigue, dyspnea, and other clinical manifestations.

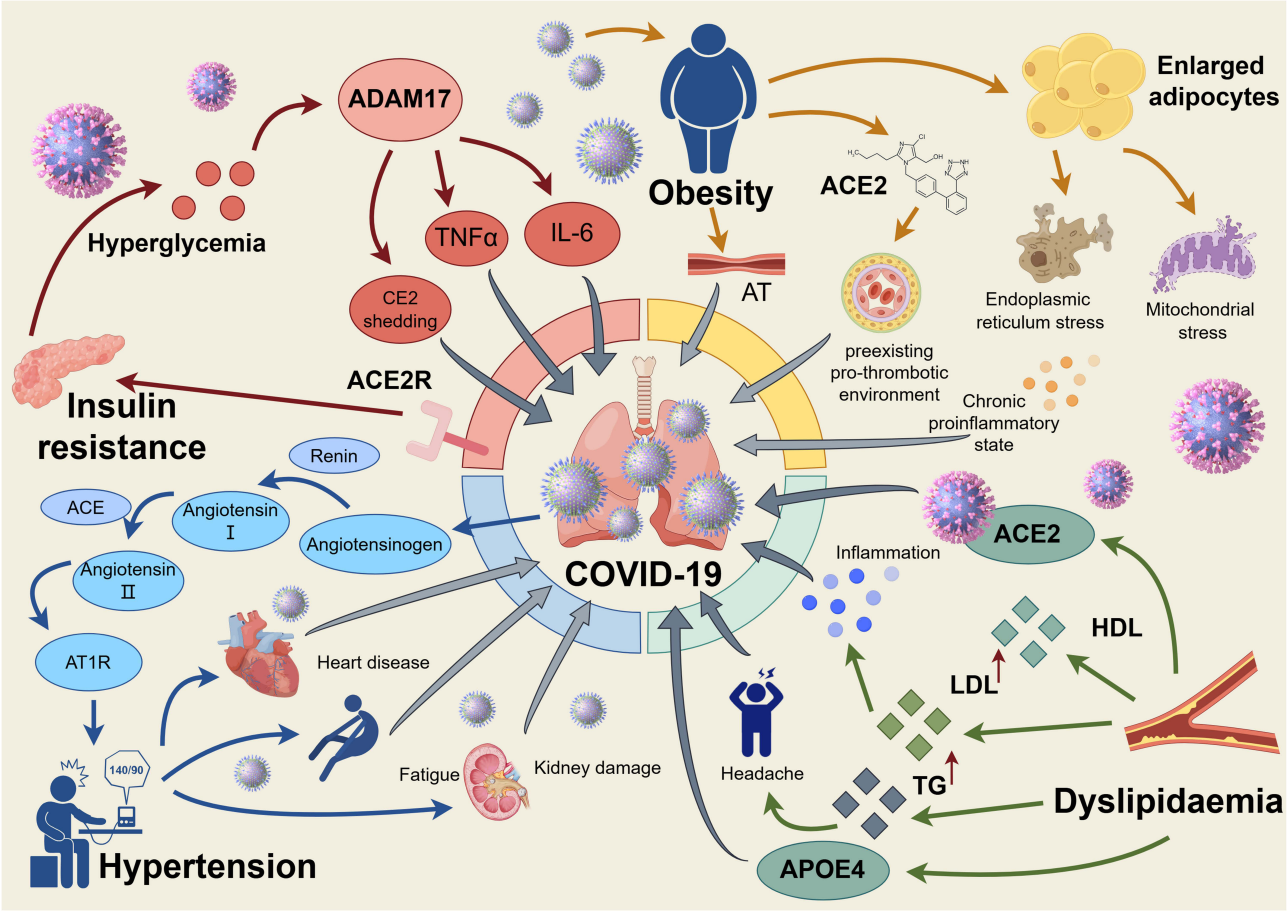

Figure 1 Metabolic syndrome, characterized by obesity, insulin resistance, hypertension, and hyperlipidemia, impacts the pathophysiology of long COVID-19 through multiple mechanisms. (By Figdraw, ID: PTWIS35373).

Insulin Resistance and Long COVID-19

Evidence suggests that the SARS-CoV-2 virus targets human pancreatic hormones and interferes with the formation of beta cells, leading to harm and a decrease in insulin production.[36] Imbalance of ACE/ACE2 caused by SARS-CoV-2 triggers RAAS activation, resulting in insulin resistance, ultimately leading to the development of COVID-19 symptoms and progression, as well as the emergence of long COVID-19, particularly in individuals with insulin resistance.[37] The relationship between COVID-19 and insulin resistance is two-way,[38] with diabetic patients experiencing more severe symptoms and worse clinical outcomes because of comorbid conditions and underlying endothelial inflammation. Research indicates that insulin resistance in COVID-19 is more serious and linked to worse clinical results, primarily because of existing health conditions and initial endothelial inflammation.[39–41]

Poorly managed diabetes is linked to a higher chance of sickness and death due to the fact that it worsens the severity of COVID-19.The COVID-19 outbreak leads to the development of insulin resistance, contributing to the poor management of diabetes and a rise in new cases of diabetes.[42,43] In theory, patients with long-term insulin resistance may be debilitated and susceptible to long-term COVID-19.Prolonged resistance to insulin can result in harm to organs, which may worsen in individuals with SARS-CoV-2 infection.The existing mild inflammation in insulin resistance could worsen and lead to persistent symptoms in patients following the onset of COVID-19,[44] which is a possibility worth considering.High doses of corticosteroids can result in insulin resistance and electrolyte imbalances, potentially leading to long-term COVID-19 complications. Therefore, steroids should be used judiciously and for the shortest duration possible, with careful monitoring of blood sugar levels to prevent worsening insulin resistance and the development of new diabetes.

Obesity and Long COVID-19

Obesity, which impacts 20%–25% of adults, is a major contributor to the onset of metabolic syndrome (MetS), posing a significant risk to worldwide health (16157765).Obesity may also decrease the efficacy of the COVID-19 vaccine.[45,46] Obese individuals have a constantly activated immune system that leads to inflammation and immunological disruptions, along with metabolic issues. This has been recognized as a separate risk factor for COVID-19 and is included in the high-risk criteria set by the Centers for Disease Control (CDC).[47] Mannose-binding lectin (MBL) is a serum protein produced by the liver that plays a role in the body's natural immune response.Obesity is linked to lower levels of circulating MBL, which can also attach to the SARS coronavirus, making individuals with obesity more vulnerable to SARS-CoV-2 infection.[48] Numerous reports from various countries, including those with diverse populations, have consistently indicated that individuals with obesity were disproportionately represented among patients needing hospitalization and admission to intensive care units (ICUs) because of COVID-19. The virus SARS-CoV-2 can enter cells through ACE2-dependent mechanisms, as well as through ectopic reservoirs in fat cells.[49] This increased susceptibility to COVID-19 may be linked to this factor, which could also have an affinity for angiotensin (AT), a vasoactive peptide that causes systemic vasoconstriction and aldosterone release, increasing the risk of acute respiratory failure, multiple organ failure, intrapulmonary and systemic inflammation.[50] Enlarged adipocytes are prone to triggering stress responses in the endoplasmic reticulum and mitochondria, leading to the development of a persistent condition of a chronic proinflammatory state in AT.[51,52]

In this instance, a substantial amount of evidence indicates a connection between obesity and weakened immune responses.Obesity-related lung changes, heightened virus entry points, reduced lung capacity,[53] and prolonged virus shedding all contribute to the complexity of SARS-CoV-2 infection.Research findings show that people who are overweight are more vulnerable to respiratory viruses, experience more severe illness and negative outcomes, which explains why individuals with obesity and associated metabolic issues are at a higher likelihood of being infected with SARS-CoV-2 during the ongoing COVID-19 crisis,[54] and facing worse outcomes when contracting the highly dangerous coronavirus SARS-CoV-2, such as increased chances of being hospitalized, admitted to the ICU, and dying, ultimately resulting in long-term effects of COVID-19.[55,56] This may be associated with upregulated angiotensin-converting enzyme 2 (ACE2) expression[57,58], chronic low-grade inflammation,[59] and a preexisting pro-thrombotic environment.[60]

A study unequivocally indicated a higher likelihood of blood clotting in COVID-19 patients who are obese.[61] The levels of antithrombin were significantly lower in patients with central obesity than in patients without obesity.[62] Therefore, we propose that persistent inflammation in both specific areas and throughout the body in individuals with obesity could result in immune system impairment, consequently heightening the likelihood of developing long-lasting COVID-19 complications.

Hypertension and Long COVID-19

High blood pressure is a condition that affects various organs in the body, including the brain, heart, blood vessels, kidneys, and endocrine systems.It is a crucial factor in diagnosing Mets, being the most common feature of the syndrome and found in more than 80% of patients.Moreover, there is evidence indicating that hypertension is frequently seen in individuals with MetS,[63] and having MetS is linked to inadequate control of hypertension in patients with hypertension.[64] During the COVID-19 pandemic, there has been a rise in focus on hypertension.A single study found that having preexisting high blood pressure and a history of likely or confirmed SARS-CoV-2 infection was linked to long-term effects of COVID-19.[65] Hypertensive patients may have a higher mortality rate than healthy individuals when infected with COVID-19[66] due to the impact of the ACE2 receptor in the renin-angiotensin-aldosterone system associated with SARS-CoV-2 infection.[67,68] Additionally, it appears that medications targeting the renin-angiotensin system (RAS) could potentially worsen the advancement of COVID-19.However, there is no evidence to suggest discontinuing RAS inhibitors in patients with such hypertension.Prolonged COVID-19 impacts the progression of hypertension-associated conditions, including CVD, with CKD being one of the primary risk factors for severe COVID-19.[11,69] Individuals experiencing long-term effects of COVID-19 show elevated average blood pressure levels during a 24-hour period and notable fluctuations in blood pressure, leading to an increased likelihood of cardiovascular incidents later on.[70] A study

found that hypertensive patients revealed a larger number of long-term COVID symptoms and poor quality of sleep and migraine-like headaches than normotensive patients.[71,72] During the COVID-19 pandemic, the yearly regular check-up in the United States showed an increase in systolic blood pressure ranging from 1.1 to 2.5 mmHg and diastolic blood pressure ranging from 0.1 to 0.5 mmHg.[73] Out of 4182 patients primarily from the community in the UK, 13.3% reported having a persistent symptom lasting over four weeks after being infected, with half of them believed to be related to the heart.[74] According to surveys, the prevalence of cardiopulmonary symptoms in patients with long COVID-19 was two-thirds in one study.[75] In symptomatic prolonged COVID-19 (3 months after the acute phase), cardiac MRI revealed that 28% of patients had (postinflammatory) cardiac sequelae.[76] A meta-analysis of six retrospective studies conducted in 2020, involving 1558 individuals with COVID-19, identified hypertension, diabetes, and cardiovascular and cerebrovascular diseases as separate risk factors for worsening the condition.[77] The current data regarding the connection between hypertension and severe cases of COVID-19 is inconclusive. The management of blood pressure and the severity of hypertension could impact the onset and progression of cardiovascular issues related to COVID-19, as well as the duration of long-term COVID-19 symptoms.[78]

Most of the 222 Saudi Arabian patients who were hospitalized for COVID-19 in May and July 2020 experienced persistent symptoms lasting over 3 months, with the primary complaints being difficulty breathing (40.1%), coughing (27.5%), and fatigue (29.7%).[65] Another study in Norway, there are 312 patients diagnosed with COVID-19 between February and April 2020, found that symptoms containing fatigue, distractibility, smell disorders, memory deterioration and breathing difficulties persisted for more than six months.[79] Cohen et al Examined 87,337 individuals over the age of 65 in a retrospective analysis to track long-lasting medical consequences during the later stages of COVID-19 infection.Thirty-two percent of these patients needed medical intervention for sustaining clinical sequelae, mainly manifested as respiratory failure, fatigue, kidney damage, and arrhythmia.[80] Similar results were found in another study adjusted for age.[81]

In the initial phase of the COVID-19 outbreak, 1850 individuals diagnosed with COVID-19 were admitted to hospitals. Among them, 287 patients with high blood pressure were selected along with an equal number of healthy patients matched for age and gender.A greater proportion of patients with hypertension reported experiencing three or more long-lasting symptoms of COVID-19, including fatigue, trouble breathing while resting, and difficulty breathing during physical activity.[71] A retrospective analysis at multiple centers involved 515 COVID-19 patients who were hospitalized and categorized into groups based on hypertension status.The group with high blood pressure had preexisting conditions such as being overweight, having high blood sugar, heart problems, heart failure, a history of stroke, kidney issues, and lung disease.[82]

For people with hypertensive, evidence from this study suggests that the initial COVID-19 outbreak affected blood pressure control, affecting their long-term cardiovascular outcomes.A delayed identification of high blood pressure linked to heightened reluctance to start treatment due to the COVID-19 pandemic could result in poor blood pressure management, impacting the outcome of a SARS-CoV-2 infection and contributing to prolonged COVID-19 symptoms.

Dyslipidaemia and Long-COVID-19

Dyslipidaemia is one of the landmarks of metabolic syndrome and is characterized by abnormal cholesterol levels.[83] Cholesterol is crucial for the entry of SARS-CoV-2 into host cells.High levels of cholesterol in the body of individuals with dyslipidemia can result in a higher amount of ACE2 receptors located in lipid rafts of cells,[84] facilitating the entry of SARS-CoV-2 into cells and enhancing its binding to ACE2, ultimately boosting the infectivity of coronavirus.[85] Lower levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, and increased triglycerides were also found to be associated with the severity of the disease in studies.[86,87] An investigation on the lipid profiles of patients in the intensive care unit demonstrated reduced levels of LDL and HDL, providing additional evidence for the important role of lipoproteins in the development and outcome of COVID-19.[88] High-density lipoprotein (HDL) may have a beneficial effect in fighting COVID-19 by controlling inflammation and possessing antioxidant, cytoprotective, and anti-cell death properties.Alterations in the composition and functionality of HDL impact the development and result of COVID-19.[89,90] Certain research indicates that a lack of ApoE activity could result in the advancement of illness and issues in individuals with dyslipidemia caused by SARS-CoV-2.Additionally, the ApoE4 mutation was found to be a predictor of the severity of COVID-19.[91] The connection between the ApoE4/E4 genetic makeup and COVID-19 did not show any correlation

with existing conditions such as dementia, cardiovascular disease, or type 2 diabetes.[92] A study that looked at patients with COVID-19 found that they had lower lipid levels and higher levels of oxidative stress and inflammation compared to healthy individuals.This suggests that oxidative stress in COVID-19 is associated with derangements of the lipid profile and inflammation.[93] High levels of triglycerides are linked to increased risk of death in COVID-19 patients as well as long-lasting fatigue, headaches, and discomfort post-recovery.[94]

A retrospective analysis conducted at a single center found that levels of LDL-C, HDL, TC, and TG were notably reduced in COVID-19 patients compared to the control group.[95] Lower levels of total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were observed in individuals who did not survive compared to those who did, suggesting a connection between lipid levels and the seriousness and death rate in patients with COVID-19.[96] According to our study, a reduction in lipid parameters can predict the severity of COVID-19.[97]

Some research evidence suggests that high cholesterol is more likely to cause SARS-CoV-2 infection to turn into severe disease or sequelae of long-term COVID-19 because high cholesterol regulates protective immunity and promotes excessive lung and systemic inflammatory responses.Statins may offer potential benefits in SARS-CoV-2 infection by reducing lipids, boosting immune responses, and providing anti-inflammatory effects.

Metabolic Syndrome-Related Pathways and Metabolic Syndrome

Metabolic syndrome development is influenced by various pathways, with emerging research indicating that the cGAS/STING pathway, STAT2, and NF-kB play a role in its pathogenesis (Figure 2).

NF-kB Signalling Pathway

NF-κB, a crucial transcription factor, regulates various biological processes including immune differentiation, cell fate, and stress response.[98] Decreasing inflammatory cytokines and inhibiting the NF-κB signaling pathway can help decrease lipid accumulation and enhance obesity outcomes.[99] Obesity-induced elevated palmitic acid promotes inflammation and glucose metabolism disorders through the GPR/NF-κB/KLF7 signalling pathway.[100] Increased angiotensin II (Ang II) levels trigger the renin-angiotensin system (RAS) and negatively impact the heart.[101] Blocking essential proteins in the

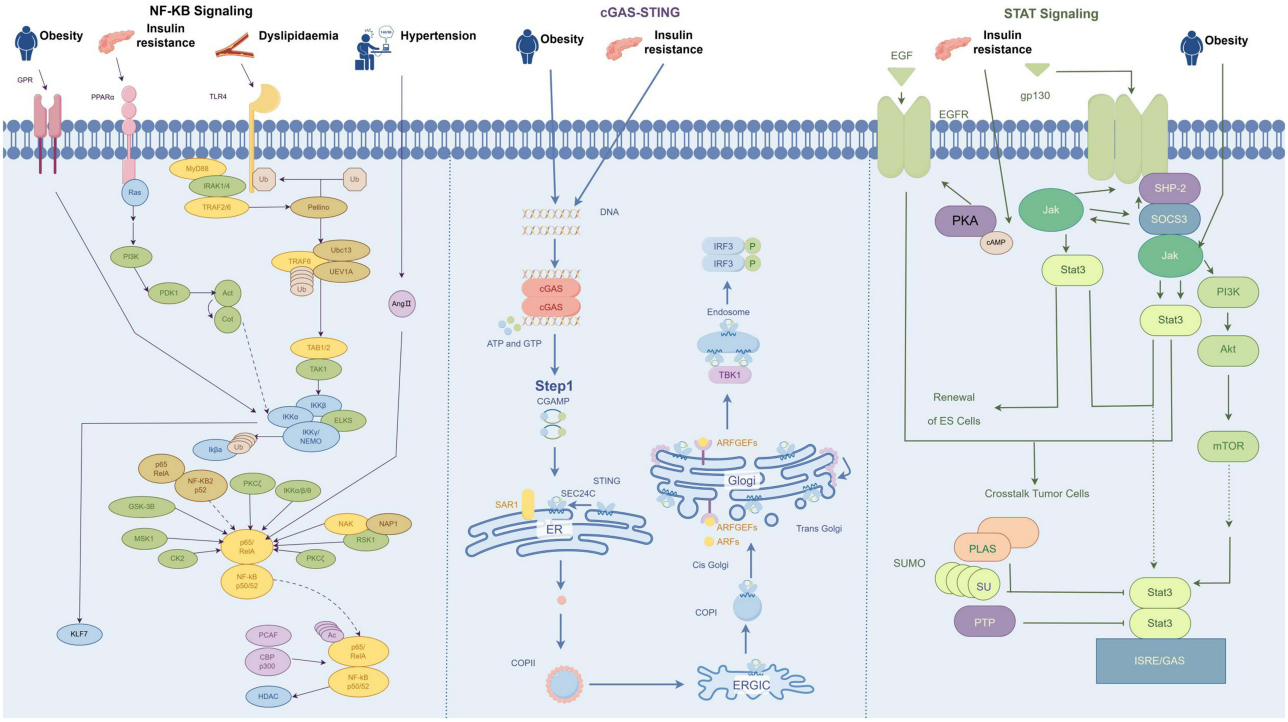

Figure 2 The key signaling pathways implicated in metabolic syndrome, including obesity, insulin resistance, hypertension, and hyperlipidemia. (By Figdraw. ID: UOWSS33293).

Ang II-triggered inflammatory pathway could potentially offer significant protection against heart failure in individuals with hypertension.[102] A study demonstrated that corynoline alleviates hypertensive heart failure induced by Ang II by enhancing the connection between PPARα and P65 to block the NF-κB pathway.[103] Prior studies indicate that individuals with type 2 diabetes exhibit lower levels of IκB in their muscles, suggesting an increased IκB/NFκB signaling pathway.[104] The NF-κB pathway is linked to T2DM and is involved in controlling inflammatory cytokines,[105] making it a promising target for new therapeutic approaches in managing or preventing diabetes.[106] Furthermore, certain medications like berberine have the ability to reduce streptozotocin (STZ)-induced kidney damage, the inflammatory reaction, and high glucose (HG)-induced podocyte apoptosis by deactivating the TLR4/NF-κB pathway, ultimately enhancing diabetic nephropathy.[107]

cGAS-STING Signalling Pathway

The signaling molecule GMP-AMP synthase/stimulator (cGAS) of interferon genes (STING), also referred to as transmembrane protein 173 (TMEM173), has the ability to trigger robust type I interferon (IFN) immunity.[108] New research on the cGAS-STING pathway indicates that it can be triggered by host DNA in the cytoplasm, resulting in higher insulin resistance and the onset of nonalcoholic fatty liver disease (NAFLD). This discovery implies that targeting this pathway could be beneficial in the prevention and treatment of metabolic disorders caused by obesity.[109] Being overweight increases the likelihood of developing various age-related illnesses like type 2 diabetes, heart disease, and cancer.

Obesity specifically causes vascular aging and long-term low blood pressure, resulting in inflammation throughout the cardiovascular system.Research has indicated that obesity triggers inflammation in endothelial cells via the cGAS-STING pathway, resulting in the development of cardiovascular diseases.[110] H, Q, Hu et al showed that activation of the cGAS- STING-IRF3 pathway triggers inflammation and apoptosis of pancreatic β cells, leading to β-cell damage and dysfunction.Therefore, blocking this communication pathway could be a new strategy for protecting β-cells in type 2 diabetes mellitus.[111] Skin samples from diabetic patients were analyzed using immunohistochemistry, revealing activation of the cGAS-STING pathway in HaCaT cells and a notable rise in the expression of cGAS-STING.Thus, we are of the opinion that blocking the cGAS-STING pathway activation could enhance the progression of psoriasis in individuals with diabetes.Obesity-induced metabolic stress triggers inflammation and activation of endothelial cells, with cGAS-STING playing a crucial role in immune response and inflammation.The cGAS-STING pathway, which is responsible for mitochondrial damage, plays a crucial role in inducing endothelial inflammation under metabolic stress conditions. Targeting this pathway could be a promising strategy for mitigating cardiovascular diseases and insulin resistance in obese individuals.[112] Research on animals revealed a reduction in cGAS-STING levels in the pancreatic islets of db/db mice and individuals with type 2 diabetes, indicating a potential involvement of cGAS-STING in the impairment of β-cells and the control of insulin release. This highlights the importance of carefully adjusting cGAS-STING in β-cells and insulin-responsive tissues to uphold glucose balance.These documents have all elucidated the crucial function of the cGAS-STING signaling pathway in metabolic syndrome and its potential connection to insulin resistance, inflammation, and various other elements.Thorough investigation into the cGAS-STING signaling pathway could aid in the management and therapy of metabolic syndrome.

STAT signalling pathway

The STAT pathway controls important cellular functions such as immune response, growth, specialization, movement, and cell death.[113] Obesity and metabolic syndrome (MetS) is currently common worldwide.[114,115] However, the biology and function of macrophages are substantially altered under obesity/MetS conditions.Systemic inflammation and immune dysfunction are induced by it, with the STAT pathway being crucial in this mechanism.[116] Epidemiological evidence suggests that patients with obesity and T2DM have a significantly higher risk of developing chronic low-intensity inflammatory, nonalcoholic fatty liver disease (NAFLD).Growing pathological data indicates that molecules involved in the STAT signaling pathways have the ability to start or facilitate signal transmission, control cell function and balance to heal injured tissues and organs, and play a role in the development, advancement, management, and avoidance of obesity and T2DM.[117] Regulating the activity of STAT3 and promoting the differentiation of brown adipose tissue (BAT) have

been demonstrated to slow down the advancement of obesity, which is influenced by signal transducer and activator of transcription (STAT) 3.[118]

A different research study demonstrated that blocking STAT3 with the diabetes medication exenatide provided protection against obesity and obesity-related liver cancer (HCC) by affecting the cAMP/PKA/EGFR/STAT3 pathway.[119] Activation of the STAT pathway by IL-6 is a crucial process that regulates inflammation in ECs and migration and proliferation in SMCs, potentially heightened in individuals with T2DM.[120] Elevated glucose levels hinder the process of autophagy by triggering the STAT pathway in mice and podocytes, which hinders the removal of damaged proteins and organelles in living organisms, leading to the prevention of cell death and worsening podocyte damage and the advancement of diabetic kidney disease.[121]

Drugs and Long-COVID-19 Risk

Long-COVID-19 and Antihyperlipaemia Drugs

The use of statins should not be discontinued during COVID-19, especially in those who have dyslipidaemia, where the benefit from statins will be more prominent.Elevating cellular cholesterol levels enhanced the attraction of lipid rafts by ACE2, facilitating the infiltration of SARS-CoV-2 pseudovirus.[122] Medications that modify cholesterol levels can exhibit antiviral properties by changing the cholesterol in target cell membranes through decreasing systemic absorption or through direct antiviral actions.

A recent evaluation of the current regulations from the Food and Drug Administration (FDA) revealed that cepharanthine, a drug with potential anti-SARS-CoV-2 properties, effectively inhibits the attachment of the virus to cells.This compound from nature focuses on various elements of cellular metabolism, such as the transportation of cholesterol.[123] Statins reduce cholesterol levels inside and outside cells by inhibiting HMG-CoA reductase, which is the initial step in the cholesterol production pathway.

Studies have shown that statins can elevate cardiac ACE2 levels in rabbit models of atherosclerosis.[124].Evaluating the impact of statins on ACE2 levels in human lung cells is crucial, as it could influence the virus's ability to cause severe illness and lead to long-term symptoms like chronic cough and fatigue in COVID-19 patients.

Long-COVID-19 and Antihypertensive Drugs

Research indicates that high blood pressure may be linked to an increased chance of contracting SARS-CoV-2 and a more severe outcome of COVID-19, including Long-COVID-19.[125–127] There is uncertainty in hypertension about whether blockers of the renin-angiotensin system (RAS) may increase the risk of COVID-19 hospitalizations.The original suggestion to switch from RAS blockers to calcium channel blockers has caused the destabilization of numerous patients on these drugs, resulting in a temporary decrease in medication compliance.

Moreover, since ACE2 was implicated in the process and its levels were believed to be elevated by medications targeting the renin-angiotensin-aldosterone system, there was a theory that ACE inhibitors and ARBs might raise the likelihood of contracting the infection.Numerous studies have found a link between the lack of ACE inhibitors or ARB drugs and a higher risk of being hospitalized due to COVID-19.A meta-analysis indicates that ACE inhibitors may not elevate vulnerability to severe infection and severity of acute respiratory disease caused by coronavirus.[8,128–134] Among nearly 2 million individuals with hypertension monitored for 16 weeks, 2338 were admitted to the hospital, and 526 either passed away or required intubation due to COVID-19, indicating that ACE inhibitors and ARBs were linked to a reduced likelihood of COVID-19 hospitalization in comparison to CCBs.[135]

Mancia et al found that just 3.8% of patients were given MRAs, with no significant variations in disease outcome when compared to the control group.[136] Furthermore, patients who received β-blockers had a slightly decreased chance of testing positive for COVID-19 compared to those not taking these drugs. Additionally, individuals who had previously taken CCBs had a slightly increased risk of severe illness,[137] despite the strong evidence in favor of the safety and protective benefits of RAS blockers.Further investigation is necessary to understand the lasting effects of high blood pressure on individuals with SARS-CoV-2 infection, including conditions like post-COVID-19 syndrome and long covid.

Long-COVID-19 and Antihyperglycaemic Drugs

Given the pathophysiological mechanism related to hyperglycaemia of novel coronavirus, the therapeutic methods and dosages of hypoglycaemic drugs known to have anti-inflammatory effects, such as metformin, pioglitazone, glucose-sodium cotransport-2 inhibitors (SGLT2-I), DPP4 inhibitors and GLP-1RA, should be well understood.The presence of SARS-CoV-2 can disrupt the balance of glucose in both diabetic and non-diabetic individuals by causing a cytokine storm, reducing ACE2 levels, and damaging pancreatic beta cells.ACE2 receptors can be located throughout the human body, such as in adipose tissue, the liver, and the small intestine.These tissues are crucial in the development of insulin resistance and the progression of pathophysiology.

An examination of how disposition scores matched in 6,256 patients with T2DM and COVID-19 from 50 states revealed that individuals who took metformin had a 24% lower mortality rate than those who did not take metformin (HR 0.76, 95% CI 0.60–0.96, p = 0.02).[138] A national observational study of 2,851,465 patients with T2DM in England yielded comparable findings, confirming a decreased mortality risk (HR 0.77, 95% CI 0.73–0.81) in individuals using metformin compared to those who did not.[139] Yet, a different study using propensity score matching analysis (n = 1213) found no significant difference in mortality between individuals who used metformin and those who did not.[140] Certain studies indicate that DPP4 enzyme receptors could potentially serve as binding targets, potentially interacting with ACE2 receptors.However, other studies suggest that DPP4 inhibitors play a less prominent role in SARS-CoV-2 infection.[36,141].

Prospective CORONADO studies showed that patients previously using DPP-4i had a significantly higher discharge rate than nonusers (OR 1.22, 95% CI 1.02–1.47, p = 0.03) (615/2794).[142] Conversely, a substantial study conducted retrospectively with a sample size of 3351 individuals yielded contrasting findings, showing no disparities in outcomes between individuals who used DPP-4i and those who did not.[143] Interestingly, a different national observational study discovered that DPP-4i users had notably increased mortality rates compared to nonusers, with a hazard ratio of 1.07 and a 95% confidence interval of 1.01–1.13.[139] A substantial nationwide observational investigation conducted in the UK found a notable decrease in death rates among individuals using SGLT-2 inhibitors (266,505 out of 2,851,465) in comparison to those who did not use them (hazard ratio 0.82, 95% confidence interval 0.74–0.91).[139] Nevertheless, a different Phase III trial that was randomized, double-blind, and placebo-controlled yielded unfavorable outcomes.[144] Combined with previous studies, insulin therapy is actually more appropriate than other antidiabetic therapies for treating patients with COVID-19 and diabetes because of the lower risk of uncontrolled hyperglycaemia and diabetic ketoacidosis (DKA).

Discussion

Patients suffering from metabolic syndrome often experience a gradual recovery process that requires strict adherence to fundamental management principles and ongoing multidisciplinary collaboration.Timely treatment of infections is important.Proper nutrition of the patient should be ensured, especially by increasing protein intake and correcting vitamin and micronutrient deficiencies.Strict control of metabolic syndromes such as blood glucose and lipids and control of comorbidities during acute COVID-19 will reduce the development of long-term COVID-19 and help control it.On the upside, long COVID-19 has largely improved over time.In a single study, it was found that 13.3% of participants experienced persistent symptoms, with 189 individuals (4.5%) reporting symptoms lasting for at least 8 weeks and 95 individuals (2.3%) reporting symptoms lasting for at least 12 weeks.[74]

Conclusions

To sum up, our comprehension of long-lasting COVID-19 is getting better over time, yet further investigation is required. In particular, patients with metabolic syndrome need to pay attention to the control of cardiovascular risk factors such as blood sugar and blood lipids to prevent further development and increase the severity of long COVID-19.Data on the bidirectional adverse effects of metabolic syndrome and long COVID-19 are clearly needed and critical.

A large number of people impacted by metabolic syndrome experience the consequences of long-term COVID-19, leading to higher morbidity rates and an uncertain quality of life.This issue urgently requires a multipronged approach to optimal management strategies that address both individual patient care and public health challenges.

Data Sharing Statement

No new data was produced by this review.

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Disclosure

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References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): a Review. *JAMA*. 2020;324(8):782–793. doi:10.1001/jama.2020.12839
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062. doi:10.1016/S0140-6736(20)30566-3
3. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924. doi:10.1016/j.ijantimicag.2020.105924
4. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033–2040. doi:10.1182/blood.2020006000
5. Siso-Almirall A, Kostov B, Mas-Heredia M, et al. Prognostic factors in Spanish COVID-19 patients: a case series from Barcelona. *PLoS One*. 2020;15(8):e0237960. doi:10.1371/journal.pone.0237960
6. WHO. WHO COVID-19 Dashboard Available from: https://covid19.who.int/?mapFilter=cas. Acessed September 26, 2024.
7. COVID-19 rapid guideline: managing the long-term effects of COVID-19. National Institute for Health and Care Excellence: Clinical Guidelines; 2020.
8. Baral R, White M, Vassiliou VS. Effect of Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19: a Systematic Review and Meta-analysis of 28,872 Patients. *Curr Atheroscler Rep*. 2020;22(10):61. doi:10.1007/s11883-020-00880-6
9. Panagides V, Vincent F, Weizman O, et al. History of heart failure in patients with coronavirus disease 2019: insights from a French registry. *Arch Cardiovasc Dis*. 2021;114(5):415–425. doi:10.1016/j.acvd.2021.04.003
10. De Giorgi C, De Luca F, Di Vito M, Lamberti F. Modulation of expression at the level of splicing of cut-1 RNA in the infective second-stage juvenile of the plant parasitic nematode Meloidogyne artiellia. *Mol Gen Genet*. 1997;253(5):589–598. doi:10.1007/s004380050361
11. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881–895e820. doi:10.1016/j.cell.2022.01.014
12. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323(20):2052–2059. doi:10.1001/jama.2020.6775
13. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: a Meta-Analysis and Systematic Review. *J Infect Dis*. 2022;226(9):1593–1607. doi:10.1093/infdis/jiac136
14. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;(38):101019. doi:10.1016/j.eclinm.2021.101019
15. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232. doi:10.1016/S0140-6736(20)32656-8
16. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. Condition WHOCCDWGoP-C-. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022;22(4):e102–e107. doi:10.1016/S1473-3099(21)00703-9
17. Sarafidis PA, Nilsson PM. The metabolic syndrome: a glance at its history. *J Hypertens*. 2006;24(4):621–626. doi:10.1097/01.hjh.0000217840.26971.b6
18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539–553. doi:10.1002/(SICI)1096-9136(199807)15:7
19. Julibert A, Bibiloni MDM, Mateos D, Angullo E, Tur JA. Dietary Fat Intake and Metabolic Syndrome in Older Adults. *Nutrients*. 2019;11(8). doi:10.3390/nu11081901
20. Cano-Ibanez N, Gea A, Martinez-Gonzalez MA, et al. Dietary Diversity and Nutritional Adequacy among an Older Spanish Population with Metabolic Syndrome in the PREDIMED-Plus Study: a Cross-Sectional Analysis. *Nutrients*. 2019;11(5):958. doi:10.3390/nu11050958
21. Garralda-Del-Villar M, Carlos-Chilleron S, Diaz-Gutierrez J, et al. Healthy Lifestyle and Incidence of Metabolic Syndrome in the SUN Cohort. *Nutrients*. 2018;11(1). doi:10.3390/nu11010065
22. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018;20(2):12. doi:10.1007/s11906-018-0812-z
23. Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. *Am Heart J*. 2005;149(1):33–45. doi:10.1016/j.ahj.2004.07.013
24. Association AH What Is Metabolic Sydrome? Available from: https://www.heart.org/en/health-topics/metabolicsyndrome/about-metabolic-syndrome. Acessed September 26, 2024.

25. Expert Panel on Detection E. Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497. doi:10.1001/jama.285.19.2486
26. Grundy SM, Cleeman JI, Daniels SR, et al. Spertus JA, Costa F, American Heart A, National Heart L, Blood I. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112 (17):2735–2752. doi:10.1161/CIRCULATIONAHA.105.169404
27. Simmons RK, Alberti KG, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia*. 2010;53(4):600–605. doi:10.1007/s00125-009-1620-4
28. Fogarty H, Townsend L, Morrin H, et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. *J Thromb Haemost*. 2021;19 (10):2546–2553. doi:10.1111/jth.15490
29. Ritchie SA, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis*. 2007;17(4):319–326. doi:10.1016/j.numecd.2006.07.005
30. Centers for Disease Control and Prevention (2021) Post COVID conditions Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-efects/index.html. Acessed September 26, 2024.
31. Excellence NIfHa C COVID-19 rapid guideline: managing the long-term effects of COVID-19 Available from: https://www.nice.org.uk/guidance/ng188. Acessed September 26, 2024.
32. condition CdCpC. Coronavirus disease (COVID 19): post COVID 19 condition Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition. Acessed September 26, 2024.
33. Service NHNHS (2022) long term effect of coronavirus (long COVID Available from: https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-efects-of-coronavirus-long-covid/. Acessed September 26, 2024.
34. Guideline C-R Managing the Longterm Effects of COVID-19. National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners (RCGP) Available from: https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-. Acessed September 26, 2024.
35. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv*. 2021. doi:10.1101/2021.01.27.21250617
36. Al-Kuraishy HM, Al-Gareeb AI, Alblihed M, Guerreiro SG, Cruz-Martins N, Batiha GE. COVID-19 in Relation to Hyperglycemia and Diabetes Mellitus. *Front Cardiovasc Med*. 2021(8):644095. doi:10.3389/fcvm.2021.644095
37. Beyerstedt S, Casaro EB, Rangel EB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis*. 2021;40(5):905–919. doi:10.1007/s10096-020-04138-6
38. Lima-Martinez MM, Carrera Boada C, Madera-Silva MD, Marin W, Contreras M. COVID-19 and diabetes: a bidirectional relationship. *Clin Investig Arterioscler*. 2021;33(3):151–157. doi:10.1016/j.arteri.2020.10.001
39. Vasbinder A, Anderson E, Shadid H, et al. Inflammation, Hyperglycemia, and Adverse Outcomes in Individuals With Diabetes Mellitus Hospitalized for COVID-19. *Diabetes Care*. 2022;45(3):692–700. doi:10.2337/dc21-2102
40. Shao S, Yang Q, Pan R, Yu X, Chen Y. Interaction of Severe Acute Respiratory Syndrome Coronavirus 2 and Diabetes. *Front Endocrinol (Lausanne)*. 2021;(12):731974. doi:10.3389/fendo.2021.731974
41. Unnikrishnan R, Misra A. Diabetes and COVID19: a bidirectional relationship. *Nutr Diabetes*. 2021;11(1):21. doi:10.1038/s41387-021-00163-2
42. Misra A, Ghosh A, Gupta R. Heterogeneity in presentation of hyperglycaemia during COVID-19 pandemic: a proposed classification. *Diabetes Metab Syndr*. 2021;15(1):403–406. doi:10.1016/j.dsx.2021.01.018
43. Ghosh A, Anjana RM, Shanthi Rani CS, et al. Glycemic parameters in patients with new-onset diabetes during COVID-19 pandemic are more severe than in patients with new-onset diabetes before the pandemic: NOD COVID India Study. *Diabetes Metab Syndr*. 2021;15(1):215–220. doi:10.1016/j.dsx.2020.12.033
44. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr*. 2021;15(4):102146. doi:10.1016/j.dsx.2021.05.019
45. Wadman M. Why obesity worsens COVID-19. *Science*. 2020;369(6509):1280–1281. doi:10.1126/science.369.6509.1280
46. Ledford H. How obesity could create problems for a COVID vaccine. *Nature*. 2020;586(7830):488–489. doi:10.1038/d41586-020-02946-6
47. CD. Centers for Disease Control and Prevention Available from: https://www.cdc.gov/media/releases/2020/p0625-update-expands-covid-19.html. Acessed September 26, 2024.
48. Talbot HK, Coleman LA, Crimin K, et al. Association between obesity and vulnerability and serologic response to influenza vaccination in older adults. *Vaccine*. 2012;30(26):3937–3943. doi:10.1016/j.vaccine.2012.03.071
49. Bevilacqua MP, Pober JS, Majeau GR, Fiers W, Cotran RS, Gimbrone MA Jr. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci U S A*. 1986;83 (12):4533–4537. doi:10.1073/pnas.83.12.4533
50. Choi Y, Bowman JW, Jung JU. Autophagy during viral infection - a double-edged sword. *Nat Rev Microbiol*. 2018;16(6):341–354. doi:10.1038/s41579-018-0003-6
51. Wang C, Zhang H, Zhou M, et al. Prognosis of COVID-19 in patients with vein thrombosis: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2020;24(19):10279–10285. doi:10.26355/eurrev_202010_23252
52. Shimobayashi M, Albert V, Woelnerhanssen B, et al. Insulin resistance causes inflammation in adipose tissue. *J Clin Invest*. 2018;128 (4):1538–1550. doi:10.1172/JCI96139
53. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. *Int J Gen Med*. 2010;3:335–343. doi:10.2147/IJGM.S11926
54. Popkin BM, Du S, Green WD, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev*. 2020;21(11):e13128. doi:10.1111/obr.13128
55. Hu J, Wang Y. The Clinical Characteristics and Risk Factors of Severe COVID-19. *Gerontology*. 2021;67(3):255–266. doi:10.1159/000513400
56. Twig G, Geva N, Levine H, et al. Body mass index and infectious disease mortality in midlife in a cohort of 2.3 million adolescents. *Int J Obes (Lond)*. 2018;42(4):801–807. doi:10.1038/ijo.2017.263
57. Zheng YY, Ma YT, Zhang JY. Reply to: 'Interaction between RAAS inhibitors and ACE2 in the context of COVID-19'. *Nat Rev Cardiol*. 2020;17(5):313–314. doi:10.1038/s41569-020-0369-9

58. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259–260. doi:10.1038/s41569-020-0360-5
59. Aghili SMM, Ebrahimpur M, Arjmand B, et al. Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: a review and meta-analysis. *Int J Obes (Lond)*. 2021;45(5):998–1016. doi:10.1038/s41366-021-00776-8
60. McGonagle D, JS O, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol*. 2020;2(7):e437–e445. doi:10.1016/S2665-9913(20)30121-1
61. Verrijken A, Francque S, Mertens I, et al. Prothrombotic factors in histologically proven nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology*. 2014;59(1):121–129. doi:10.1002/hep.26510
62. Gazzaruso C, Paolozzi E, Valenti C, et al. Association between antithrombin and mortality in patients with COVID-19. A possible link with obesity. *Nutr Metab Cardiovasc Dis*. 2020;30(11):1914–1919. doi:10.1016/j.numecd.2020.07.040
63. Zisman A, Peroni OD, Abel ED, et al. Targeted disruption of the glucose transporter 4 selectively in muscle causes insulin resistance and glucose intolerance. *Nat Med*. 2000;6(8):924–928. doi:10.1038/78693
64. Anker SD, Coats AJ, Morley JE, et al. Muscle wasting disease: a proposal for a new disease classification. *J Cachexia Sarcopenia Muscle*. 2014;5(1):1–3. doi:10.1007/s13539-014-0135-0
65. Tleyjeh IM, Saddik B, AlSwaidan N, et al. Prevalence and predictors of Post-Acute COVID-19 Syndrome (PACS) after hospital discharge: a cohort study with 4 months median follow-up. *PLoS One*. 2021;16(12):e0260568. doi:10.1371/journal.pone.0260568
66. Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis. *J Infect*. 2020;81(1):e84–e86. doi:10.1016/j.jinf.2020.03.059
67. Bhalla V, Blish CA, South AM. A historical perspective on ACE2 in the COVID-19 era. *J Hum Hypertens*. 2021;35(10):935–939. doi:10.1038/s41371-020-00459-3
68. Azevedo RB, Botelho BG, Hollanda JVG, et al. Covid-19 and the cardiovascular system: a comprehensive review. *J Hum Hypertens*. 2021;35(1):4–11. doi:10.1038/s41371-020-0387-4
69. Shibata S, Kobayashi K, Tanaka M, et al. COVID-19 pandemic and hypertension: an updated report from the Japanese Society of Hypertension project team on COVID-19. *Hypertens Res*. 2023;46(3):589–600. doi:10.1038/s41440-022-01134-5
70. Ternushchak TM, Tovt-Korshynska MI, Varvarynets AV. Ambulatory Blood Pressure Variability in Young Adults with Long-Covid Syndrome. *Wiad Lek*. 2022;75(10):2481–2485. doi:10.36740/WLek202210131
71. Fernandez-de-Las-Penas C, Torres-Macho J, Velasco-Arribas M, et al. Preexisting hypertension is associated with a greater number of long-term post-COVID symptoms and poor sleep quality: a case-control study. *J Hum Hypertens*. 2022;36(6):582–584. doi:10.1038/s41371-022-00660-6
72. Wang YF, Wang SJ. Hypertension and Migraine: time to Revisit the Evidence. *Curr Pain Headache Rep*. 2021;25(9):58. doi:10.1007/s11916-021-00976-x
73. Laffin LJ, Kaufman HW, Chen Z, et al. Rise in Blood Pressure Observed Among US Adults During the COVID-19 Pandemic. *Circulation*. 2022;145(3):235–237. doi:10.1161/CIRCULATIONAHA.121.057075
74. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med*. 2021;27(4):626–631. doi:10.1038/s41591-021-01292-y
75. Ziauddeen N, Gurdasani D, ME O, et al. Characteristics and impact of Long Covid: findings from an online survey. *PLoS One*. 2022;17(3):e0264331. doi:10.1371/journal.pone.0264331
76. Kersten J, Baumhardt M, Hartveg P, et al. Long COVID: distinction between Organ Damage and Deconditioning. *J Clin Med*. 2021;10(17). doi:10.3390/jcm10173782
77. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging*. 2020;12(7):6049–6057. doi:10.18632/aging.103000
78. Yamazaki O, Shibata S. Severe COVID-19 and preexisting hypertension: a matter of age? *Hypertens Res*. 2022;45(9):1523–1525. doi:10.1038/s41440-022-00978-1
79. Blomberg B, Mohn KG, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med*. 2021;27(9):1607–1613. doi:10.1038/s41591-021-01433-3
80. Cohen K, Ren S, Heath K, et al. Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2022;376:e068414. doi:10.1136/bmj-2021-068414
81. Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2021(373):n1098. doi:10.1136/bmj.n1098
82. Mirza H, Noori MAM, Akbar H, et al. Hypertension as an Independent Risk Factor for In-Patient Mortality in Hospitalized COVID-19 Patients: a Multicenter Study. *Cureus*. 2022;14(7):e26741. doi:10.7759/cureus.26741
83. Syndrome AM About Metabolic Syndrome Available from: https://www.heart.org/en/healthtopics/metabolic-syndrome/about-metabolic-syndrome. Acessed September 26, 2024.
84. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL. Global epidemiology of dyslipidaemias. *Nat Rev Cardiol*. 2021;18(10):689–700. doi:10.1038/s41569-021-00541-4
85. Shoemark DK, Colenso CK, Toelzer C, et al. Molecular Simulations suggest Vitamins, Retinoids and Steroids as Ligands of the Free Fatty Acid Pocket of the SARS-CoV-2 Spike Protein*. *Angew Chem Int Ed Engl*. 2021;60(13):7098–7110. doi:10.1002/anie.202015639
86. Wang G, Zhang Q, Zhao X, et al. Low high-density lipoprotein level is correlated with the severity of COVID-19 patients: an observational study. *Lipids Health Dis*. 2020;19(1):204. doi:10.1186/s12944-020-01382-9
87. Hu X, Chen D, Wu L, He G, Ye W. Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. *Clin Chim Acta*. 2020;510:105–110. doi:10.1016/j.cca.2020.07.015
88. Tanaka S, De Tymowski C, Assadi M, et al. Lipoprotein concentrations over time in the intensive care unit COVID-19 patients: results from the ApoCOVID study. *PLoS One*. 2020;15(9):e0239573. doi:10.1371/journal.pone.0239573
89. Souza Junior DR, Silva ARM, Rosa-Fernandes L, et al. HDL proteome remodeling associates with COVID-19 severity. *J Clin Lipidol*. 2021;15(6):796–804. doi:10.1016/j.jacl.2021.10.005

90. Cho KH, Kim JR, Lee IC, Kwon HJ. Native High-Density Lipoproteins (HDL) with Higher Paraoxonase Exerts a Potent Antiviral Effect against SARS-CoV-2 (COVID-19), While Glycated HDL Lost the Antiviral Activity. *Antioxidants (Basel)*. 2021;10(2). doi:10.3390/antiox10020209
91. Kulminski AM, Barochia AV, Loika Y, et al. The APOE epsilon4 allele is associated with a reduction in FEV1/FVC in women: a cross-sectional analysis of the Long Life Family Study. *PLoS One*. 2018;13(11):e0206873. doi:10.1371/journal.pone.0206873
92. Goldstein MR, Poland GA, Graeber CW. Are certain drugs associated with enhanced mortality in COVID-19? *QJM*. 2020;113(7):509–510. doi:10.1093/qjmed/hcaa103
93. Aparisi A, Martin-Fernandez M, Ybarra-Falcon C, et al. Dyslipidemia and Inflammation as Hallmarks of Oxidative Stress in COVID-19: a Follow-Up Study. *Int J Mol Sci*. 2022;23(23):15350. doi:10.3390/ijms232315350
94. Dai W, Lund H, Chen Y, et al. Hypertriglyceridemia during hospitalization independently associates with mortality in patients with COVID-19. *J Clin Lipidol*. 2021;15(5):724–731. doi:10.1016/j.jacl.2021.08.002
95. Almas T, Malik J, Alsubai AK, et al. Effect of COVID-19 on lipid profile parameters and its correlation with acute phase reactants: a single-center retrospective analysis. *Ann Med Surg (Lond)*. 2022;78:103856. doi:10.1016/j.amsu.2022.103856
96. Mahat RK, Rathore V, Singh N, et al. Lipid profile as an indicator of COVID-19 severity: a systematic review and meta-analysis. *Clin Nutr ESPEN*. 2021;45:91–101. doi:10.1016/j.clnesp.2021.07.023
97. Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of COVID-19. *J Clin Lipidol*. 2020;14(3):297–304. doi:10.1016/j.jacl.2020.04.008
98. Zhang Q, Lenardo MJ, Baltimore D. 30 Years of NF-kappaB: a Blossoming of Relevance to Human Pathobiology. *Cell*. 2017;168(1–2):37–57. doi:10.1016/j.cell.2016.12.012
99. Al-Saiagh W, Tiun S, Al-Saffar A, Awang S, Al-Khaleefa AS, Pappalardo F. Word sense disambiguation using hybrid swarm intelligence approach. *PLoS One*. 2018;13(12):e0208695. doi:10.1371/journal.pone.0208695
100. Qiu T, Yang X, Wang J, et al. Obesity-induced elevated palmitic acid promotes inflammation and glucose metabolism disorders through GPRs/NF-kappaB/KLF7 pathway. *Nutr Diabetes*. 2022;12(1):23. doi:10.1038/s41387-022-00202-6
101. Mori J, Zhang L, Oudit GY, Lopaschuk GD. Impact of the renin-angiotensin system on cardiac energy metabolism in heart failure. *J Mol Cell Cardiol*. 2013;63:98–106. doi:10.1016/j.yjmcc.2013.07.010
102. Butts B, Gary RA, Dunbar SB, Butler J. Methylation of Apoptosis-Associated Speck-Like Protein With a Caspase Recruitment Domain and Outcomes in Heart Failure. *J Card Fail*. 2016;22(5):340–346. doi:10.1016/j.cardfail.2015.12.004
103. Wang M, Luo W, Yu T, et al. Coryneline protects ang II-induced hypertensive heart failure by increasing PPARalpha and Inhibiting NF-kappaB pathway. *Biomed Pharmacother*. 2022;150:113075. doi:10.1016/j.biopha.2022.113075
104. Sriwijitkamol A, Christ-Roberts C, Berria R, et al. Reduced skeletal muscle inhibitor of kappaB beta content is associated with insulin resistance in subjects with type 2 diabetes: reversal by exercise training. *Diabetes*. 2006;55(3):760–767. doi:10.2337/diabetes.55.03.06.db05-0677
105. Liu F, Fu Y, Wei C, Chen Y, Ma S, Xu W. The expression of GPR109A, NF-kB and IL-1beta in peripheral blood leukocytes from patients with type 2 diabetes. *Ann Clin Lab Sci*. 2014;44(4):443–448.
106. Meyerovich K, Ortis F, Cardozo AK. The non-canonical NF-kappaB pathway and its contribution to beta-cell failure in diabetes. *J Mol Endocrinol*. 2018;61(2):F1–F6. doi:10.1530/JME-16-0183
107. Zhu L, Han J, Yuan R, Xue L, Pang W. Berberine ameliorates diabetic nephropathy by inhibiting TLR4/NF-kappaB pathway. *Biol Res*. 2018;51(1):9. doi:10.1186/s40659-018-0157-8
108. Gaidt MM, Ebert TS, Chauhan D, et al. The DNA Inflammasome in Human Myeloid Cells Is Initiated by a STING-Cell Death Program Upstream of NLRP3. *Cell*. 2017;171(5):1110–1124e1118. doi:10.1016/j.cell.2017.09.039
109. Bai J, Liu F. The cGAS-cGAMP-STING Pathway: a Molecular Link Between Immunity and Metabolism. *Diabetes*. 2019;68(6):1099–1108. doi:10.2337/dbi18-0052
110. Hamann L, Szwed M, Mossakowska M, Chudek J, Puzianowska-Kuznicka M. First evidence for STING SNP R293Q being protective regarding obesity-associated cardiovascular disease in age-advanced subjects - a cohort study. *Immun Ageing*. 2020;17:7. doi:10.1186/s12979-020-00176-y
111. Hu HQ, Qiao JT, Liu FQ, et al. The STING-IRF3 pathway is involved in lipotoxic injury of pancreatic beta cells in type 2 diabetes. *Mol Cell Endocrinol*. 2020;518:110890. doi:10.1016/j.mce.2020.110890
112. Mao Y, Luo W, Zhang L, et al. STING-IRF3 Triggers Endothelial Inflammation in Response to Free Fatty Acid-Induced Mitochondrial Damage in Diet-Induced Obesity. *Arterioscler Thromb Vasc Biol*. 2017;37(5):920–929. doi:10.1161/ATVBAHA.117.309017
113. Lee M, Rhee I. Cytokine Signaling in Tumor Progression. *Immune Netw*. 2017;17(4):214–227. doi:10.4110/in.2017.17.4.214
114. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. *Nat Rev Endocrinol*. 2013;9(1):13–27. doi:10.1038/nrendo.2012.199
115. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab*. 2008;93(11):S9–30. doi:10.1210/jc.2008-1595
116. Wang Y, Zhang X, Xie X, et al. Obesity and metabolic syndrome related macrophage promotes PD-L1 expression in TNBC through IL6/JAK/STAT pathway and can be reversed by telmisartan. *Cancer Biol Ther*. 2020;21(12):1179–1190. doi:10.1080/15384047.2020.1838032
117. Tian S, Zhao H, Song H Shared signaling pathways and targeted therapy by natural bioactive compounds for obesity and type 2 diabetes. *Crit Rev Food Sci Nutr*. 2022: 1–18.doi:10.1080/10408398.2022.2148090.
118. Jhun J, Woo JS, Lee SH, et al. GRIM19 Impedes Obesity by Regulating Inflammatory White Fat Browning and Promoting Th17/Treg Balance. *Cells*. 2021;10(1):162. doi:10.3390/cells10010162
119. Zhou M, Mok MT, Sun H, et al. The anti-diabetic drug exenatide, a glucagon-like peptide-1 receptor agonist, counteracts hepatocarcinogenesis through cAMP-PKA-EGFR-STAT3 axis. *Oncogene*. 2017;36(29):4135–4149. doi:10.1038/onc.2017.38
120. Moshapa FT, Riches-Suman K, Palmer TM. Therapeutic Targeting of the Proinflammatory IL-6-JAK/STAT Signalling Pathways Responsible for Vascular Restenosis in Type 2 Diabetes Mellitus. *Cardiology Research and Practice*. 2019;2019:9846312. doi:10.1155/2019/9846312
121. Chen D, Liu Y, Chen J, et al. JAK/STAT pathway promotes the progression of diabetic kidney disease via autophagy in podocytes. *Eur J Pharmacol*. 2021;902:174121. doi:10.1016/j.ejphar.2021.174121

122. Wang H, Yuan Z, Pavel MA, et al. The role of high cholesterol in age-related COVID19 lethality. *bioRxiv*. 2021. doi:10.1101/2020.05.09.086249
123. WK OH, Saso W. Multidrug treatment with nelfinavir and cepharanthine against COVID-19. *BioRxiv*.
124. Tikoo K, Patel G, Kumar S, et al. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. *Biochem Pharmacol*. 2015;93(3):343–351. doi:10.1016/j.bcp.2014.11.013
125. Semenzato L, Botton J, Drouin J, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. *Lancet Reg Health Eur*. 2021;8:100158. doi:10.1016/j.lanepe.2021.100158
126. Mancusi C, Grassi G, Borghi C, et al. Determinants of healing among patients with coronavirus disease 2019: the results of the SARS-RAS study of the Italian Society of Hypertension. *J Hypertens*. 2021;39(2):376–380. doi:10.1097/HJH.0000000000002666
127. Iaccarino G, Grassi G, Borghi C, et al. Age and Multimorbidity Predict Death Among COVID-19 Patients: results of the SARS-RAS Study of the Italian Society of Hypertension. *Hypertension*. 2020;76(2):366–372. doi:10.1161/HYPERTENSIONAHA.120.15324
128. RISk C, Treatments C. RAAS inhibitors are not associated with mortality in COVID-19 patients: findings from an observational multicenter study in Italy and a meta-analysis of 19 studies. *Vascul Pharmacol*. 2020;135:106805. doi:10.1016/j.vph.2020.106805
129. Barochiner J, Martinez R. Use of inhibitors of the renin-angiotensin system in hypertensive patients and COVID-19 severity: a systematic review and meta-analysis. *J Clin Pharm Ther*. 2020;45(6):1244–1252. doi:10.1111/jcpt.13246
130. Flacco ME, Acuti Martellucci C, Bravi F, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. *Heart*. 2020;106(19):1519–1524. doi:10.1136/heartjnl-2020-317336
131. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor effect on COVID-19 outcome: a Meta-analysis. *J Infect*. 2020;81(2):276–281. doi:10.1016/j.jinf.2020.05.052
132. Guo X, Zhu Y, Hong Y. Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension: a Meta-Analysis. *Hypertension*. 2020;76(2):e13–e14. doi:10.1161/HYPERTENSIONAHA.120.15572
133. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: a systematic review and meta-analysis. *Pharmacol Res*. 2020;158:104927. doi:10.1016/j.phrs.2020.104927
134. medRxiv. Available from: https://www.medrxiv.org/content/10. Acessed September 26, 2024.
135. Semenzato L, Botton J, Drouin J, et al. Antihypertensive Drugs and COVID-19 Risk: a Cohort Study of 2 Million Hypertensive Patients. *Hypertension*. 2021;77(3):833–842. doi:10.1161/HYPERTENSIONAHA.120.16314
136. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med*. 2020;382(25):2431–2440. doi:10.1056/NEJMoa2006923
137. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med*. 2020;382(25):2441–2448. doi:10.1056/NEJMoa2008975
138. Bramante CT, Ingraham NE, Murray TA, et al. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. *Lancet Healthy Longev*. 2021;2(1):e34–e41. doi:10.1016/S2666-7568(20)30033-7
139. Khunti K, Knighton P, Zaccardi F, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol*. 2021;9(5):293–303. doi:10.1016/S2213-8587(21)00050-4
140. Cheng X, Liu YM, Li H, et al. Metformin Is Associated with Higher Incidence of Acidosis, but Not Mortality, in Individuals with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab*. 2020;32(4):537–547e533. doi:10.1016/j.cmet.2020.08.013
141. Valencia I, Peiro C, Lorenzo O, Sanchez-Ferrer CF, Eckel J, Romacho T. DPP4 and ACE2 in Diabetes and COVID-19: therapeutic Targets for Cardiovascular Complications? *Front Pharmacol*. 2020;11(1161). doi:10.3389/fphar.2020.01161
142. Wargny M, Potier L, Gourdy P, et al. investigators C. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia*. 2021;64(4):778–794. doi:10.1007/s00125-020-05351-w
143. Strollo R, Maddaloni E, Dauriz M, Pedone C, Buzzetti R, Pozzilli P. Use of DPP4 inhibitors in Italy does not correlate with diabetes prevalence among COVID-19 deaths. *Diabetes Res Clin Pract*. 2021(171):108444. doi:10.1016/j.diabres.2020.108444
144. AstraZeneca. Update on the DARE-19 Phase III trial for Farxiga in COVID-19 Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-farxiga-covid-19-dare-19-phase-iii-trial.html. Acessed September 26, 2024.