Review Article | Open Access

THE DUAL IMPACT OF VIRAL INFECTIONS ON METABOLIC DISEASES: MECHANISMS AND CLINICAL PERSPECTIVES

[1*]Waqas Ahmed, M. Phil, [2]Saleem Basheer, M. Phil, [3]Asad Mehmood Raja, PhD, [4]Muhammad Mohsin, M. Phil, [5]Syed Mohsin Ali, M. Phil [6]Salman Ahmed, PhD

[1]Postgraduate trainee, Medical School, Shenzhen University, Shenzhen, Guangdong, China
[2]District Field Officer, Department of Biochemistry & Biotechnology, University of Gujrat, Punjab, Pakistan
[3]Laboratory Manager, Institute of Biochemistry & Biotechnology, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Punjab, Pakistan
[4]Postgraduate trainee, Institute of Biochemistry & Biotechnology, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Punjab, Pakistan
[5]Department of Biomedical Engineering & Sciences, School of Mechanical & Manufacturing Engineering, National University of Science & Technology (NUST), Islamabad, Pakistan
[6]Assistant Professor, Allama Iqbal Medical College, Lahore, Punjab, Pakistan

***Corresponding Author:** Waqas Ahmed (waqasahmed2023@email.szu.edu.cn)

Cite this article:
Ahmed W, Basheer S, Raja AM, Mohsin M, Ali SM, Ahmed S. The Dual Impact of Viral Infections on Metabolic Diseases: Mechanisms and Clinical Perspectives. AJMAHS. 2024; 2(2):38-57.

ABSTRACT

Throughout the evolutionary history of Earth, viruses have persisted and exerted significant influence on human civilization. Despite advancements in medicine, viral infections remain a leading cause of mortality. Concurrently, there has been a concerning rise in metabolic disorders over past years. Current review aims to reevaluate the systematic evidence to support the existence of robust two directional relationship among various viral infections and diseases of metabolism. We delve into how the viruses may contribute to onset or development of metabolic ailments and contrariwise, how these metabolic disorders can exacerbate viral infection severity. Additionally, this review analyzes the practical implications of the modern understanding of interplay among viral infections and disorders of metabolism, along with the difficulties faced by the technical personals and public health experts, both presently and in the foreseeable future.

Keywords: Metabolic diseases, viruses, evolution, medicine, clinical implications.

Introduction

Throughout the evolutionary timeline of Earth, viruses, an infectious agents, have played an integral role. Their impact on societal progress has been profound, spanning from historic scourges like smallpox and the Spanish influenza to contemporary crises like HIV and the ongoing SARS-CoV-2 pandemic. The occurrence and transmission of both established and novel viral infections are intricately tied to significant shifts in human interactions with the natural environment[1,2]. We are currently traversing a transitional phase marked by demographic, behavioral, environmental, and technological shifts, all of which influence viral dissemination. Predictions suggest that climate fluctuations and changes in land usage may facilitate the migration of diverse species into new habitats, heightening the probability of zoonotic spillover events, particularly, in heavily inhabited regions[3]. Centuries-worth data indicate a mounting likelihood of infectious disease outbreaks, exacerbated by environmental alterations that enable disease transmission from animal hosts. The implementation of lockdown measured throughout the pandemic of SARS-CoV-2 coincided with a decline among respiratory viral infections[4]. However, as we transition into the era after pandemic, the frequency of other infections appears to have reverted to levels before pandemic. Concurrently, there has been a surge in non-communicable metabolic disorders over the past decades, characterized by an escalating incidence of obesity, and its attendant complications, including non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes[5].

The repercussions of epidemics with non-communicable nature on affected communities are substantial, with diabetes ranking among the important causes of mortality and significantly contributing to deaths from other prevalent conditions. The onset of SARS-CoV-2 pandemic underscored the association between metabolic disorders and disease severity, prompting a reassessment of preventative and therapeutic approaches[2]. This resurgence in interest regarding the interplay between viral infections and metabolic ailments have revitalized scientific inquiry into their underlying physiological connections and implications from human well-being[6]. This review endeavors to revisit the evidence supporting a two directional association among viral infections and disorders of metabolism. Our objective is not to comprehensively catalog all available data but rather to illuminate the principal mechanisms diving this association and explore emerging concepts. Specifically, we scrutinize how viruses can modulate lipid and glucose metabolism, thereby influencing the onset or progression of metabolic disorders. Additionally, we investigate how metabolic dysregulation may exacerbate the transmission and severity of viral infections, with a particular emphasis on SARS-CoV-2 and influenza. Finally, we examine the clinical ramifications of these findings and outline the challenges confronting the scientific community and public health authorities moving forward.

1. Promotion of Metabolic Disorders by Viruses

Numerous research studies have revealed that viruses possess the ability to initiate metabolic disorders by influencing essential cellular functions. For example, they can control the survival of cells and critical mechanisms associated with cellular death, de-differentiation within viral metabolic and endocrine organs, and proliferation[7–10]. Moreover, viruses exert an impact on cellular metabolism of glucose through modulation of glucose transporters, changing the uptake of glucose, controlling signaling cellular mechanisms involved in sensing of cellular energy, and activating glycolysis within cells. Additionally, viruses have the capability to govern the metabolism of lipids by promoting the synthesis of fatty acids and lipids, formation of lipid droplets, and reducing oxidation of fatty acids. Many of these effects occur during virus replication within infected cells and result from direct viral actions intracellularly. The manipulation of lipid and glucose metabolism by viruses augments the availability of energy, thereby facilitating viral replication and spread. Furthermore, viruses are able to stimulate the secretion of peptides from affected cells that elicit systemic and local immune responses which target the host cells or their neighboring cells (known as the bystander hypothesis). Such effects may persevere even following clearance of virus, causing a progressive and irreversible damage to organs, reminiscent of autoimmune diseases subsequent to viral infection[11]. Furthermore, viruses can trigger the secretion of molecules such as adipocytokines, interferons and miRNAs, which modulate the function of both infected cells and cells in distant organs, potentially influencing glucose homeostasis[12]. Finally, viruses synthesize polypeptides homologous to immunomodulatory proteins, hormones, or growth factors, allowing them to mimic, cross-react, or antagonize host proteins, thereby affecting cell survival and metabolism through molecular mimicry[7].

Infectious spatiotemporal dynamics function in determining the chronicity and degree of the injury caused by viruses. Post-acute infection syndromes denote long-lasting disability after infection and were seen in numerous patients following viral infections, especially during pandemics (e.g., polio, SARS-CoV-2, varicella-zoster, Coxsackie, Ebola, Epstein-Barr, and dengue)[13,14]. Post-COVID-19 disease is associated with an enhanced frequency of cardiovascular conditions, obesity, dyslipidemia, and diabetes[15]. However, epidemiological evidence indicates that numerous other viral infection are also linked to a high risk of developing or exacerbating metabolic disorders. In some circumstances, the epidemiological associations are benefited by experimental proof, which generates reasonable hypotheses regarding potential reasons underlying the chronic complications of viruses, even following clearance of virus. In line with one hypothesis, the viruses may develop an infection stubborn in nature or leave the non-lethal antigens inside organs that can function as reservoirs for chronic pathogens[16–20]. Such pathogenic constituents may evade traditional methods of detection but still prompt chronic and subclinical inflammation.

Alternatively, viral infections could induce the synthesis of autoantibodies that gradually affect metabolic and endocrine functions with a significant interruption from the early infection. Another hypothesis proposes that trained innate immunity may contribute to the chronic infectious effects of virus on metabolism. Such stimuli may induce continuous metabolic and epigenetic variations in innate bone marrow progenitors and progenitor cells, and immune cells[21,22]. Subsequent unrelated infections or inflammatory stimuli may generate a second response of inflammation in susceptible organisms, with beneficial or detrimental effects. The trained innate immunity is seen following live attenuated vaccines, demonstrating its relevance as an immune memory mechanism following viral infection[23]. It remains uncertain whether acquired adaptive immunity following viral infection may provoke different inflammatory responses endorsing metabolic disorders on second stimulus exposure. Lastly, several viruses have been related with alterations in the dysfunction of gut and microbiome (dysbiosis), which may harm upcoming inflammatory response difficulties and secondary infections[24]. The dysbiosis is also seen in NAFLD, obesity, and type 2 diabetes and is linked to progression of disease. Lastly, although not directly caused by virus itself, antiviral or concomitant treatment may primarily contribute to metabolic rearrangement[25,26].

1.1. Enteroviruses

Various viral infections, primarily enteroviruses but also encompassing rotaviruses, mumps, human herpes virus 6, parainfluenza, and parechovirus, is linked to onset of diabetes because of the damage of β-cells. Several of such viral infections share mutual traits, particularly their propensity to cause widespread infections, often occurring during early childhood[27]. The infection timing frequently precedes or overlaps with the islet autoantibodies development, with insulin autoantibodies emerging around the age of 2 and glutamic acid decarboxylase autoantibodies between 3 and 5 years old[28]. The evidence supporting this association comes from epidemiological and histological studies, including correlations between RNA levels of Coxsackie virus B (CVB) among stool samples and the advancement to diabetes type 1, recognition of enteroviral islets RNA in individuals having newly diagnosed diabetes type 1, and presence of the enteroviral capsid protein VP1 among β-cells of diabetes type 1 donors. Remarkably, VP1 is found in a tiny concentration of islets, suggesting the gradual mechanism arising prior clinical manifestations[29–31].

Various receptors utilized by enteroviruses in order to enter cells, also show expression in β-cells of pancreas, with Coxsackie and adenovirus receptor (CAR) being the most significant[32]. A specific CAR (CAR-SIV) isoform on insulin granular surface may acts as entry point for viruses during recovery of membrane following insulin granule exocytosis[33]. Conversely, three primary mechanisms are proposed for β-cell damage induced by Coxsackie virus[34]. Initially, the replication of virus within β-cells may directly affect cell function and survival, resulting in apoptosis or necrosis. Moreover, enterovirus-

related products such as polyinosinic-polycytidylic acid may reduce the expression of β-cells-specific gene, potentially inducing β-cells differentiation, secretion of insulin induced by glucose through depletion of insulin granular stores and changing elements involved in membrane potential and calcium homeostasis. The other mechanism involves the stimulation of β-cells autoimmune response, facilitated by peptides secreted by injured β-cells that are accessed by antigen-presenting cells. This response leads to the destruction of β-cells by T-cells, along with MHC class I molecule expression. The third proposed mechanism depends on the molecular mimicry, where viral proteins contain sequence homology to islet autoantigen and glutamic acid decarboxylase 65 (GAD65), involved in process of inflammation causing diabetes type 1. Though, the extent of cross-reactivity among viral peptides and T-cell clones or autoimmune antibodies remain uncertain. Persistent infection with enterovirus in β-cells may exacerbate autoimmunity, with enteroviral protein or RNA identified in islet cells, gut mucosa, and mononuclear cells of patients having diabetes type 1[34]. Despite accumulating evidence from experiments and epidemiological studies, the hypothesis of enteroviral etiology in diabetes type 1 has not been definitively established due to inconsistencies among study findings. Struggles to eliminate virus through antiviral therapy or vaccination represent the eventual test for establishing interconnection between enteroviruses and diabetes type 1[29]. Vaccination strategies aims to prevent viral load, systemic spread, infiltration in pancreas, and potential undeviating effects on β-cells infected by virus, thereby inhibiting self-antigens release, triggering autoimmunity. Investigations in mice have demonstrated that the vaccines targeting six serotypes of CVB can encourage strong neutralizing antibodies and confer the immunity against CVB, potentially preventing diabetes induced by CVB. A clinical trial is assessing a vaccine which targets five CVB serotypes i.e., CVB1 to CVB5, among normal individuals. The achievement of these results relies on safety profile of the vaccine, which must be excellent to permit assessments in children and before CVB exposure[35]. Considering the infectious spatiotemporal dynamics and immune responses elicited by viruses will aid in developing more operative therapeutic approaches and assessment methods to measure disease progression and treatment efficacy.

1.2. Hepatitis C Virus

The infection with the hepatitis C virus (HCV) significantly raises the likelihood of developing type 2 diabetes, particularly in elder individuals with an advanced liver cirrhosis and diabetes history in family. This increased risk is largely due to heightened hepatic insulin resistance. HCV impairs glucose regulation by reducing hepatic uptake of glucose through downregulation of glucose transporter 2 and interfering with insulin signaling via promoting degradation of IRS-1 and IRS-2, thus inhibiting the P13K/Akt pathway[36]. Additionally, HCV may diminish insulin receptor expression and enhance the expression of genes involved in gluconeogenesis. Peripheral insulin resistance is also associated with HCV infection[37]. While the precise mechanisms are not

completely understood, one theory suggests that liver dysfunction alters circulating miRNAs, decreasing sensitivity of insulin in muscles and adipose tissues[38]. Additional theories indicate that HCV-induced oxidation stress and dysfunction of mitochondria lead to overexpression and release of pro-inflammatory cytokines, i.e., IL-6, IL-8, and TNF-α, which additionally worsen insulin resistance[39].

HCV infection is also implicated in diabetes because of dysfunction in β-cells. The virus replicates in β-cell of pancreas, reducing secretion of insulin and causing cell death. There are occasional reports of diabetes type 1 developing after infection by HCV or interferon therapy, indicating potential autoimmunity of pancreatic islets, though such findings are less constant compared to diabetes type 2. Contrariwise, diabetes type 2 in HCV patients is linked to quicker development to liver fibrosis and increased risk of developing decompensated liver cirrhosis and hepatocellular carcinoma[40,41]. The substantial impact of HCV infection on glucose metabolism is additionally supported by improvements in insulin sensitivity, secretion, and glycemic control following HCV eradication with effective direct-acting antiviral agents[42]. Eliminating HCV infection decreases the risk of diabetes type 2[43]. In addition to diabetes type 2, HCV infection is also related to liver steatosis, with severity depending on the genotype of HCV. The HCV genotype 3, which accounts for 20% HCV infections globally, is more effectively linked to steatosis than other genotypes, and the severity of steatosis correlates with intrahepatic HCV RNA levels[44,45]. The steatosis associated with genotype 3 may result from differences in the core protein's amino acid sequence, activating various steatogenic mechanisms. This genotype increases liver lipid accumulation by decreasing the assembly of very low-density lipoproteins through inhibiting transfer protein activity of microsomal triglycerides, encouraging lipogenesis through activation of SREBP-1c, and decreasing lipid β-oxidation through PPAR-α downregulation[46]. Particularly, HCV-induced steatosis is a negative predictor for continuous response of virus in early interferon-based therapy. Direct-acting antivirals targeting viral replication show effect in attaining sustained viral responses in HCV and hepatic steatosis[47]. While these antivirals can improve liver fibrosis, their impact on steatosis is mixed, with some studies reporting improvement and others noting progression, underscoring the need for further research.

HCV infection's impact on glucose and lipid metabolism can increase cardiovascular risk. Effects of HCV on atherosclerosis are well-documented. The virus can enhance permeability of endothelium, promote endothelial cellular death, stimulate the proliferation and migration of smooth muscle cells from tunica media to surface, and encourage the expression of soluble vascular cell adhesion molecule 1 through enhanced release of chemokines and cytokines, including TNF, IL-6, and IL-8. Direct-acting antiviral therapy has been related to a reduction in cardiovascular risks[48–50].

1.3. Iridoviridae

The iridoviridae family contains large double-stranded DNA viruses known to infect the insects, fish, reptiles, and amphibians, frequently causing fatal outcomes. Such viruses have also been identified in human plasma and the enteric virome[51]. Studies have shown that iridoviridae viruses possess sequences closely resembling those of insulin and insulin-like growth factors 1 and 2[52]. Such viral peptides can interact with IGF-1 or insulin receptors, influencing various biological processes. They may promote the uptake of glucose by enhancing the expression of GLUT4 and Akt phosphorylation in white adipose tissue[53]. Alternatively, they can function as antagonists, thereby inhibiting the cellular growth and proliferation usually stimulated by the IGF-1. As a result, viral insulin-like peptides (VILPs) may characterize a new form of molecular mimicry that viruses alter hormonal mechanisms in humans[54]. However, it remains uncertain which human cells may be infected by and support the replication of VILP-containing viruses. Additionally, it is yet to be determined if VILPs have other cellular effects beyond mimicking or inhibiting insulin and IGF-1 functions. For instance, recent research indicates that VILPs can prevent ferroptosis, suggesting they may play a crucial role in regulating cell death[54].

1.4. Human Immodeficiency Virus

Human immodeficiency virus (HIV) infection and the antiretroviral therapy (ART) have intense action on metabolism of lipids, adipose tissue characteristics, and spreading, closely related to metabolic diseases and hepatic steatosis. The metabolic issues linked to HIV largely stem from CD4+ T cell depletion and ongoing systemic inflammation. Without treatment, HIV often results in progressive loss of weight, or HIV wasting, because of decreased intake of energy, malabsorption, and heightened metabolic demands. Malabsorptions arises from loss of T cells of gut mucosa, which weakens the epithelial barrier of the gut, intensifies its permeability, and allows viruses and microbiota to translocate. The chronic inflammatory response further raises metabolic demands, leading to the loss of trunk fat and increased liver fat production, resulting in higher liver fat (steatosis) and elevated triglycerides in the blood[55]. In individuals with HIV, adipose tissue undergoes structural and functional changes, including decreased mitochondrial DNA content and reduced expression of critical genes like lipoprotein lipase, adiponectin, GLUT4, and PPARγ, which are crucial for energy and glucose regulation. Lower adipopectin levels can worsen liver steatosis and inflammation[56]. Additionally, adipose tissue may act as a HIV reservoir. HIV can be identified among CD4+ T cells within the adipose tissue stromal vascular fraction, leading to enhanced production of proinflammatory cytokines that promotes viral shedding[17]. This inflammatory environment in adipose tissue and systemically contributes to insulin resistance, enhancing the risk of hyperglycemia and liver steatosis.

Moreover, hepatic stellate cells, Kuppfer cells, and hepatocytes can be infected by HIV. Along with microbiota translocation, this interaction promotes further liver inflammation and fiboris[57].

One meta-analysis indicated that 34% HIV-infected individuals suffer from hepatic steatosis, and 12% have liver fibrosis greater than stage F2[56]. HIV also demonstrated how antiviral treatments can disrupt metabolic homeostasis. Early HIV treatments using combinations of three of more antiretroviral drugs often resulted in significant weight gain. However, these treatments also caused fat redistribution, with fat loss in the buttocks, face, and limbs, and fat gain in visceral and cervical areas, known as HIV-associated lipodystrophy[58]. Individuals with this condition showed significant lipid accumulation in the heart, muscles, and liver. Enhanced *de novo* synthesis of lipids and faster breakdown of lipids were major factors leading to lipodystrophy associated with HIV[25,58,59]. ARTs significantly impact function of adipose tissues, causing compromised synthesis and maturation of adipocytes, enhanced cellular death, and elevated production of proinflammatory cytokines. These treatments also alter the release of key hormonal controllers of lipid and energy homeostasis, such as decreased adiponectin and high ANGPTL3 and PCKS9[60]. These changes contribute to atherosclerosis, diabetes, and insulin resistance. Despite advancements in ART, weight gain remains a significant concern, necessitating monitoring of diabetes in many therapy settings. Although ARTs may have decreased hepatotoxicity, they can still endorse steatosis with increased body weight[61].

1.5. Herpesvirus

Herpesviruses are widespread among humans, but their role in metabolic diseases remains underexplored. An investigation tracked a cohort demonstrating that being seropositive for cytomegalovirus (CMV) and herpes simplex virus 2 (HSV-2) was linked with a higher likelihood of developing prediabetes or diabetes, after accounting for multiple confounding factors[62]. Notably, HSV-2 seropositivity was also linked to increased HbA1c levels. The initial seroprevalence in the study was 11% for the HSV-2 and 456% for the CMV. Providing that such infections typically happen early in life or during puberty period, and the serostatus of individuals remained largely unchanged in the period of follow-up, it is possible that these viruses have enduring actions on the metabolism, potentially contributing to onset or development of metabolic disorders. It is still unclear whether these chronic effects stem from persistent infections in certain organs or from changed immune responses on viral re-exposure. Another study found that respiratory infections might temporarily elevated plasma insulin levels without changing fasting glucose levels, indicating increased insulin resistance[63]. In mice model, the interferon-gamma (INF-γ) induced by CMV headed to the insulin receptor downregulation in skeletal muscles and a compensatory rise in secretion of insulin. This hyperinsulinemia induced by CMV directly improved functions of CD8+ effectors T cells, enhancing antiviral immunity but impairing glycemic control. This was particularly problematic in obese mice, where

CMV infection further exacerbated insulin resistance[63].

1.6. SARS-Cov-2

Epidemiological research has identified that individuals with metabolic diseases face a higher risk of severe COVID-19 and an elevated incidence of new-onset diabetes and diabetic ketoacidosis after SARS-CoV-2 infection. The increased risk of developing new-onset diabetes varies from 11% to 276% depending on factors such as age of the population studies, the severity of infection, the risk assessment period, and the compared groups used[64]. Investigations show a stronger correlation between new-onset diabetes and severe COVID-19 in older adults compared to younger individuals with milder cases. Hospitalization due to COVID-19 may reveal pre-existing diabetes among individuals who do not undergo regular check-ups, as indicated by a decrease in new-onset diabetes risk over time following COVID-19 diagnosis[64]. Many studies have compared infected individuals with those who were not severely ill but severe infection and hospitalization can independently enhance the diabetes incidence. A 2020 study noted a similar rise in new-onset diabetes risk following hospitalization for COVID-19 and pneumonia[65]. The two directional association between COVID-19 and metabolic disorders is still being understood with some studies yielding contradictory results. Various pathophysiological mechanisms might be at play[66]. β-cells are vulnerable to the SARS-CoV-2 infection, leading to degranulation, apoptosis, compromised secretion of insulin, and transdifferentiation or dedifferentiation[67]. Though, mRNA of SARS-CoV-2 is present in tiny concentration in pancreas and for a small duration in contrast to other cells, suggesting that this may not completely account for rise in new-onset diabetes[68]. The broad cellular tropism of SARS-CoV-2 implies that the other endocrine organs could also lead to metabolic deregulations. Adipocytes, which can be infected by the virus, might serve as reservoirs, producing proinflammatory cytokines and attracting macrophages over time[69]. Furthermore, adipocytes synthesize plasminogen activator inhibitor-1 (PAI-1), which prevents fibrinolysis and its significantly elevated in COVID-19 patients, potentially causing coagulopathy. The mRNA of SARS-CoV-2 is obstinately and highly detected in hypothalamus. The infection might also increase GP73 production, stimulating hepatic gluconeogenesis and raising blood glucose levels in mice[70].

Indirect factors also lead to hyperglycemia and new-onset diabetes. Pandemic-related lifestyle modifications, such as weight gain and reduced access to preventing care, could exacerbate pre-existing metabolic conditions. Acute severe illness can induce stress-related hyperglycemia through enhanced breakdown of lipids and free fatty acids in circulation. Commonly used treatments for treating COVID-19, such as steroid, can also trigger or worsen hyperglycemia[71,72]. Further mechanistic studies are necessary to investigate the potential causal links between COVID-19 and metabolic diseases.

2. Effect of Metabolic Disorders with Viral Infections Severity

A significant body of epidemiological research shows a robust correlation among metabolic disorders and both the severity and frequency of different viral infections. Nonetheless, the specific nature of these correlations can be ambiguous, leaving uncertainty about whether metabolic disorders enhance the infection risk for all viruses. Equally, there is strong evidence supporting a causal link among metabolic disorders and severity and outcomes of infectious diseases.

2.1. Immune Response Impairment

Individuals with diabetes, insulin resistance, or obesity undergo notable variations in their adaptive and innate immune systems. In type 2 diabetes, innate immune functions such as chemotaxis and neutrophil phagocytosis are impaired[73]. Natural killer (NK) cells exhibit decreased activity, and macrophages gather in the adipose tissues, become proinflammatory[74]. The maladaptive-trained immunity leads to myeloid cells having enhanced proinflammatory responses on subsequent exposures. Concerning the adaptive immune system, the obesity results in a decrease in natural killer T cells in adipose tissue, while B cells proliferate and secrete more proinflammatory cytokines[75]. Multiomics investigates of various specimens i.e., blood, nasal, and stool swabs, reveal that individuals having resistance of insulin exhibit delayed immune responses to viral infections[76]. Hyperglycemia is a key factor in the dysfunction of memory CD8 T cells during viral infections in diabetes[77]. In obese mouse models, influenza infection impairs the function of T-cells because of oxidative stress, leading to decreased production of TNF-α and IFN-γ, and an insufficient B cell response. Such changes cause delayed and weakened immune responses, faster replication of virus, prolonged shedding of virus, more severe pulmonary damage, and enhanced mortality. Obese mice also exhibit a delayed immune response along with decreased type I interferon levels, encouraging viral diversity and potentially leading to more virulent influenza strains[78–80].

For individuals having SARS-CoV-2 and obesity, increased levels of IL-6 and leptin produced by the adipose tissue may augment the cytokine storm risk. Elevated levels of glucose are linked to a decrease in the T follicular regulatory cells and impaired monocyte and T cell function through glycolysis or HIF-1α -dependent mechanisms[81–83]. Overall, changed immune system functions in metabolic disorders cause patients to delayed and insufficient immune responses to viral infections, heightening risk of developing cytokine storm.

2.2. Entry of Virus into the Body

A healthy mucosa of gut epithelium is essential for blocking the passage of virulent viruses from gut lumen into bloodstream. Certain bacteria in gut can strengthen this barrier or produce compounds that kill viruses. In conditions including NAFLD, type 2 diabetes, and obesity, the gut microbiome undergoes significant

changes, known as dysbiosis, increasing the permeability of intestine[84]. This "leaky gut" condition may heighten the risk of systemic infections through viral transport and bacterial superinfections due to an impaired immune response after a viral infection. Infection by SARS-CoV-2 has also been related with alterations in the gut microbiome, and these changes can persist even after recovery. The configuration of microbiota in gut during SARS-CoV-2 infection has been linked to levels of inflammatory chemokines and cytokines[85]. Additionally, other aspects of metabolic diseases can influence viral entry in the cell. For instance, 1, 5-anhydro-D-glucitol, a glucose-like metabolite, which can attach to SARS-CoV-2 spike protein and prevent viral entrance into host cells, is found in low levels in diabetes type 2 patients. This deficiency may contribute to their increased risk of severe SARS-CoV-2 infection[86]. Furthermore, adipose tissue can function as a long-term pathogen reservoirs, suggesting that individuals having obesity and elevated amounts of adipose tissue might be more vulnerable to chronic effects on certain infections[73]. This area requires further research to fully understand the implications.

2.3. Endothelial Dysfunction

Vascular endothelial cells are essential for a variety of functions, including maintaining the integrity of blood vessels, nutrient transport, regulating the flow of blood through vasoconstriction and vasodilation, regulating blood clotting, and moderating inflammatory responses. In diabetes type 2, endothelial dysfunction is characterized by heightened oxidation stress, increased levels of proinflammatory and prothrombotic factors, elevated vasoconstrictors, reduced vasodilators, and diminished activity of nitric oxide synthase. This condition leads to increased inflammation and vasoconstriction, and in combination with hyperactivity of platelets, can contribute to atherosclerosis and thrombosis[87]. As a result, people with type 2 diabetes are at a higher risk for vascular complications, which can be further exacerbated during infections[88]. In addition to promoting thrombosis, endothelial dysfunction negatively impacts pulmonary function by altering inflammatory responses. During influenza A virus infection, endothelial cells in lungs are important cytokine manufacturers. High glucose levels trigger a proinflammatory cytokine response in endothelial cells, which impairs the junctional complex in epithelium and damage the pulmonary epithelial-endothelial barrier[89]. Likewise, SARS-CoV-2 infections is also linked with endothelial cell infection and subsequent pulmonary and vascular endotheliitis, which correlate considerably to COVID-19 related mortality. Consequently, pre-existing dysfunction in endothelium may worsen the viral infection severity by enhancing the risk of thrombosis and exacerbating pulmonary damage through intensified inflammatory responses[90].

3. Clinical Significance

The pandemic of COVID-19 has initiated noteworthy discussions on how to adapt the management of metabolic diseases during such

widespread health crises. Recommendations consistently highlight the necessity of metabolic maintenance. This need has intensified during the pandemic due to increased sedentary behavior, poorer dietary habits, and reduced access to healthcare providers. The pandemic has also underscored the two directional association among infectious diseases and metabolic disorders[91]. As future pandemics and epidemics are anticipated to become common, it is essential to better understand this relationship, develop operative approaches for prevention to mitigate the threat of developing or worsening metabolic disorders following infections, reduce the severity of infections among metabolic disorder patients, and optimize their treatment approaches. The long-term function of viral infections on metabolism, even after the virus is no longer detectable and their role in the growth or exacerbation of metabolic disorders, are not well-studied. This applies to both highly pathogenic viruses and those that are predominant in community with typically mild or subclinical diseases, such as herpesviruses or minimally symptomatic SARS-CoV-2. Many viral infections result in post-acute infection syndromes, which share common symptoms and suggest similar underlying mechanisms[13]. However, these syndromes are often under-recognized in clinical setting, lack clear criteria for diagnosis, and have no specific strategies for therapy. The mechanisms by which metabolic disorders may have an enhanced post-viral squeal risk, or how post-viral sequel might encourage or worsen metabolic disease, remain mainly unidentified. To advance the optimization of post-viral treatment, it is necessary to develop clear diagnostic criteria, educate healthcare providers, establish guidelines for monitoring, and evaluate various treatments.

Precision medicine has identified subcategories of patients having a similar disease but diverse disease courses. For example, in diabetes type 2, five subclasses with distinct disease progressions and risks for complications have been recognized[92]. Though, it is unclear whether the phenotypes are also linked to high infection severity and vulnerability, the post-acute infection syndrome development, or the metabolic disturbance risk throughout and subsequently after infection. Future research should focus on recognizing novel subdivisions of individuals having metabolic diseases who are at higher risk of complications during and after infections, or contrariwise, those at higher threat of emerging metabolic diseases after viral infections. For instance, epidemiological studies following infection with SARS-CoV-2 have shown that new-onset diabetes risk varies based on age, gender, socioeconomic factors, time since infection, pre-existing metabolic conditions, hospitalization status, and comorbidities[93,94]. Since it is impractical to assess the entire affected individuals, such studies can help prioritize monitoring the growth or advancement of metabolic disorders in high-risk groups. Identifying these categories can reduce the failure rates, cost, and time in clinical investigations, which may emphasize on preventing actions or interventions to decrease the danger of metabolic disease post-infection or on approaches to reduce the severity of infections in those with metabolic disorders.

There is inadequate evidence on the role of lifestyle interferences or treatments that target metabolic disorders on severity and vulnerability of infections. Utmost results comes from epidemiological investigations, which contain limitations because of confounding factors such as age, comorbid conditions, and interval of metabolic disorders, and comorbidities. More randomized trials, for example those conducted for metformin and dapagliflozin among SARS-CoV-2-infected individuals, are needed to assess the effects of anti-hyperlipidemic, anti-diabetic, and anti-obesity therapies on severity and vulnerability of infections[95,96]. Similarly, preclinical studies on common infections among animal models of NAFLD, diabetes, or obesity, and effects different interventions, can deliver significant systematic understandings. Likewise, clinical and preclinical investigations should also emphasize on assessment of the impact of vaccines and antiviral therapies on the development and progression of metabolic diseases.

4. Conclusion

Significant knowledge gaps persist about the mechanisms underlying the intricate association between metabolic disorders and viral infections. These gaps encompass understanding the specific types of viruses or metabolic subtypes involved, delineating between the immediate and prolonged impacts of viral infections on the metabolic well-being, and pinpointing most effective therapeutic or preventive interventions to mitigate the metabolic disorder risk onset or worsening, as well as the susceptibility to severe infection among individuals with metabolic disorders. These gaps in understanding may arise from a limited scientific grasp of the connections among viruses and metabolic conditions. The pandemic of COVID-19 has brought about heightened awareness among the public concerning preventive measure against infectious diseases and the vulnerability of individuals at elevated risk of severe or life-threatening complications. Furthermore, it has catalyzed interdisciplinary discussions and collaborative research endeavors among experts from various fields, including diabetologists, cardiologists, immunologists, endocrinologists, and infectiologists. Moving onward, it will be imperative to educate a different cohort of experts, healthcare professionals, and clinicians who possess a comprehensive understanding of both infectious diseases and metabolic disorders. Such interdisciplinary training can advance our comprehension of intricate scientific inquires spanning diverse specialties, raise awareness among healthcare providers and the general public, and facilitate the development of more efficacious preventing and therapeutic approaches to enhance overall health.

References

1. Domingo E. Introduction to virus origins and their role in biological evolution. Virus as Popul [Internet]. 2020 [cited 2024 May 27];1–33. Available from: /pmc/articles/PMC7173561/
2. Patterson GE, McIntyre KM, Clough HE, Rushton J. Societal Impacts of Pandemics: Comparing COVID-19 With History to Focus Our Response. Front Public Heal [Internet]. 2021 Apr 12 [cited

2024 May 27];9:630449. Available from: /pmc/articles/PMC8072022/
3. Hermans K, McLeman R. Climate change, drought, land degradation and migration: exploring the linkages. Curr Opin Envir Sustain. 2021 Jun 1;50:236–44.
4. Oraby T, Tyshenko MG, Maldonado JC, Vatcheva K, Elsaadany S, Alali WQ, et al. Modeling the effect of lockdown timing as a COVID-19 control measure in countries with differing social contacts. Sci Rep. 2021;11:3354.
5. Chew NWS, Ng CH, Tan DJH, Kong G, Lin C, Chin YH, et al. The global burden of metabolic disease: Data from 2000 to 2019. Cell Metab [Internet]. 2023 Mar 7 [cited 2024 May 27];35(3):414–28. Available from: https://pubmed.ncbi.nlm.nih.gov/36889281/
6. Chen P, Wu M, He Y, Jiang B, He M-L. Metabolic alterations upon SARS-CoV-2 infection and potential therapeutic targets against coronavirus infection. Sig Transduct Target Ther. 2023;8:237.
7. Girdhar K, Powis A, Raisingani A, Chrudinová M, Huang R, Tran T, et al. Viruses and Metabolism: The Effects of Viral Infections and Viral Insulins on Host Metabolism. Annu Rev Virol. 2021;8(1):373–91.
8. Colli ML, Nogueira TC, Allagnat F, Cunha DA, Gurzov EN, Cardozo AK, et al. Exposure to the viral by-product dsRNA or Coxsackievirus B5 triggers pancreatic beta cell apoptosis via a Bim / Mcl-1 imbalance. PLoS Pathog [Internet]. 2011 Sep [cited 2024 May 27];7(9):e1002267. Available from: https://pubmed.ncbi.nlm.nih.gov/21977009/
9. Ylipaasto P, Smura T, Gopalacharyulu P, Paananen A, Seppänen-Laakso T, Kaijalainen S, et al. Enterovirus-induced gene expression profile is critical for human pancreatic islet destruction. Diabetologia [Internet]. 2012 Dec [cited 2024 May 27];55(12):3273–83. Available from: https://pubmed.ncbi.nlm.nih.gov/22983635/
10. Tang X, Uhl S, Zhang T, Xue D, Li B, Vandana JJ, et al. SARS-CoV-2 infection induces beta cell transdifferentiation. Cell Metab [Internet]. 2021 Aug 3 [cited 2024 May 27];33(8):1577-1591.e7. Available from: https://pubmed.ncbi.nlm.nih.gov/34081913/
11. Girdhar K, Powis A, Raisingani A, Chrudinova M, Huang R, Tran T, et al. Viruses and Metabolism: The Effects of Viral Infections and Viral Insulins on Host Metabolism. Annu Rev Virol [Internet]. 2021 Sep 9 [cited 2024 May 27];8(1):373–91. Available from: /pmc/articles/PMC9175272/
12. Mertowska P, Smolak K, Mertowski S, Grywalska E. Immunomodulatory Role of Interferons in Viral and Bacterial Infections. Int J Mol Sci [Internet]. 2023 Jun 1 [cited 2024 May 27];24(12):10115. Available from: /pmc/articles/PMC10298684/
13. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med [Internet]. 2022 May 1 [cited 2024 May 27];28(5):911–23. Available from: https://pubmed.ncbi.nlm.nih.gov/35585196/
14. Stefano GB. Historical Insight into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID. Med Sci Monit [Internet]. 2021 Feb 26 [cited 2024 May 27];27:e931447. Available from: https://www.medscimonit.com/abstract/full/idArt/931447
15. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021;594(7862):259–64.
16. Girdhar K, Powis A, Raisingani A, Chrudinova M, Huang R, Tran T, et al. Viruses and Metabolism: The Effects of Viral Infections and Viral Insulins on Host Metabolism. Annu Rev Virol [Internet]. 2021 Sep 29 [cited 2024 May 27];8(1):373–91. Available from: https://pubmed.ncbi.nlm.nih.gov/34586876/
17. Couturier J, Suliburk JW, Brown JM, Luke DJ, Agarwal N, Yu X, et al. Human adipose tissue as a reservoir for memory CD4+ T cells and HIV. AIDS [Internet]. 2015 Mar 27 [cited 2024 May 27];29(6):667–74. Available from: https://pubmed.ncbi.nlm.nih.gov/25849830/

18. Oikarinen M, Tauriainen S, Oikarinen S, Honkanen T, Collin P, Rantala I, et al. Type 1 diabetes is associated with enterovirus infection in gut mucosa. Diabetes [Internet]. 2012 Mar [cited 2024 May 27];61(3):687–91. Available from: https://pubmed.ncbi.nlm.nih.gov/22315304/
19. Schulte BM, Bakkers J, Lanke KHW, Melchers WJG, Westerlaken C, Allebes W, et al. Detection of enterovirus RNA in peripheral blood mononuclear cells of type 1 diabetic patients beyond the stage of acute infection. Viral Immunol [Internet]. 2010 Feb 1 [cited 2024 May 27];23(1):99–104. Available from: https://pubmed.ncbi.nlm.nih.gov/20121407/
20. Ryan PMD, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019? Obes (Silver Spring) [Internet]. 2020 Jul 1 [cited 2024 May 27];28(7):1191–4. Available from: https://pubmed.ncbi.nlm.nih.gov/32314868/
21. Chavakis T, Wielockx B, Hajishengallis G. Inflammatory Modulation of Hematopoiesis: Linking Trained Immunity and Clonal Hematopoiesis with Chronic Disorders. Annu Rev Physiol [Internet]. 2022 [cited 2024 May 27];84:183–207. Available from: https://pubmed.ncbi.nlm.nih.gov/34614373/
22. Li X, Wang H, Yu X, Saha G, Kalafati L, Ioannidis C, et al. Maladaptive innate immune training of myelopoiesis links inflammatory comorbidities. Cell [Internet]. 2022 May 12 [cited 2024 May 27];185(10):1709–27. Available from: https://pubmed.ncbi.nlm.nih.gov/35483374/
23. Geckin B, Konstantin Föhse F, Domínguez-Andrés J, Netea MG. Trained immunity: implications for vaccination. Curr Opin Immunol [Internet]. 2022 Aug 1 [cited 2024 May 27];77:102190. Available from: https://pubmed.ncbi.nlm.nih.gov/35597182/
24. Harper A, Vijayakumar V, Ouwehand AC, ter Haar J, Obis D, Espadaler J, et al. Viral Infections, the Microbiome, and Probiotics. Front Cell Infect Microbiol [Internet]. 2021 Feb 12 [cited 2024 May 27];10:596166. Available from: https://pubmed.ncbi.nlm.nih.gov/33643929/
25. Luzi L, Perseghin G, Tambussi G, Meneghini E, Scifo P, Pagliato E, et al. Intramyocellular lipid accumulation and reduced whole body lipid oxidation in HIV lipodystrophy. Am J Physiol Endocrinol Metab [Internet]. 2003 Feb 1 [cited 2024 May 27];284(2):E274-80. Available from: https://pubmed.ncbi.nlm.nih.gov/12388139/
26. Nguyen NN, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, et al. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. Metabolism [Internet]. 2022 Jun 1 [cited 2024 May 27];131:155196. Available from: https://pubmed.ncbi.nlm.nih.gov/35367460/
27. Isaacs SR, Foskett DB, Maxwell AJ, Ward EJ, Faulkner CL, Luo JYX, et al. Viruses and Type 1 Diabetes: From Enteroviruses to the Virome. Microorganisms [Internet]. 2021 Jul 1 [cited 2024 May 27];9(7):1519. Available from: /pmc/articles/PMC8306446/
28. Lugar M, Eugster A, Achenbach P, Von Dem Berge T, Berner R, Besser REJ, et al. SARS-CoV-2 Infection and Development of Islet Autoimmunity in Early Childhood. JAMA [Internet]. 2023 Sep 26 [cited 2024 May 27];330(12):1151–60. Available from: https://pubmed.ncbi.nlm.nih.gov/37682551/
29. Nekoua MP, Alidjinou EK, Hober D. Persistent coxsackievirus B infection and pathogenesis of type 1 diabetes mellitus. Nat Rev Endocrinol. 2022;18(8):503–16.
30. Isaacs SR, Roy A, Dance B, Ward EJ, Foskett DB, Maxwell AJ, et al. Enteroviruses and risk of islet autoimmunity or type 1 diabetes: systematic review and meta-analysis of controlled observational studies detecting viral nucleic acids and proteins. Lancet Diabetes Endocrinol [Internet]. 2023 Aug 1 [cited 2024 May 27];11(8):578–92. Available from: https://pubmed.ncbi.nlm.nih.gov/3739083

9/
31. Richardson SJ, Leete P, Bone AJ, Foulis AK, Morgan NG. Expression of the enteroviral capsid protein VP1 in the islet cells of patients with type 1 diabetes is associated with induction of protein kinase R and downregulation of Mcl-1. Diabetologia [Internet]. 2013 Jan [cited 2024 May 27];56(1):185–93. Available from: https://pubmed.ncbi.nlm.nih.gov/23064357/
32. Wells AI, Coyne CB. Enteroviruses: A Gut-Wrenching Game of Entry, Detection, and Evasion. Viruses [Internet]. 2019 May 1 [cited 2024 May 27];11(5):460. Available from: /pmc/articles/PMC6563291/
33. Omar-Hmeadi M, Idevall-Hagren O. Insulin granule biogenesis and exocytosis. Cell Mol Life Sci [Internet]. 2021 Mar 1 [cited 2024 May 27];78(5):1957–70. Available from: https://link.springer.com/article/10.1007/s00018-020-03688-4
34. Roivainen M, Rasilainen S, Ylipaasto P, Nissinen R, Ustinov J, Bouwens L, et al. Mechanisms of coxsackievirus-induced damage to human pancreatic beta-cells. J Clin Endocrinol Metab [Internet]. 2000 Jan [cited 2024 May 27];85(1):432–40. Available from: https://pubmed.ncbi.nlm.nih.gov/10634421/
35. Carré A, Vecchio F, Flodström-Tullberg M, You S, Mallone R. Coxsackievirus and Type 1 Diabetes: Diabetogenic Mechanisms and Implications for Prevention. Endocr Rev [Internet]. 2023 Jul 11 [cited 2024 May 27];44(4):737–51. Available from: https://pubmed.ncbi.nlm.nih.gov/36884282/
36. Pol S, Lagaye S. The remarkable history of the hepatitis C virus. Genes Immun [Internet]. 2019 May 1 [cited 2024 May 28];20(5):436–46. Available from: https://pubmed.ncbi.nlm.nih.gov/31019253/
37. Gomes D, Sobolewski C, Conzelmann S, Schaer T, Lefai E, Alfaiate D, et al. ANGPTL4 is a potential driver of HCV-induced peripheral insulin resistance. Sci Rep. 2023;13:6767.
38. Singhal A, Agrawal A, Ling J. Regulation of insulin resistance and type II diabetes by hepatitis C virus infection: A driver function of circulating miRNAs. J Cell Mol Med [Internet]. 2018 Apr 1 [cited 2024 May 28];22(4):2071–85. Available from: https://pubmed.ncbi.nlm.nih.gov/29411512/
39. Maqbool MA, Imache MR, Higgs MR, Carmouse S, Pawlotsky J-M, Lerat H. Regulation of hepatitis C virus replication by nuclear translocation of nonstructural 5A protein and transcriptional activation of host genes. J Virol [Internet]. 2013 May 15 [cited 2024 May 28];87(10):5523–39. Available from: https://pubmed.ncbi.nlm.nih.gov/23468497/
40. Hammerstad SS, Grock SF, Lee HJ, Hasham A, Sundaram N, Tomer Y. Diabetes and Hepatitis C: A Two-Way Association. Front Endocrinol [Internet]. 2015 Sep 14 [cited 2024 May 28];6:134. Available from: https://pubmed.ncbi.nlm.nih.gov/26441826/
41. Mazzaro C, Quartuccio L, Adinolfi LE, Roccatello D, Pozzato G, Nevola R, et al. A Review on Extrahepatic Manifestations of Chronic Hepatitis C Virus Infection and the Impact of Direct-Acting Antiviral Therapy. Viruses [Internet]. 2021 Nov 9 [cited 2024 May 28];13(11):2249. Available from: https://www.mdpi.com/1999-4915/13/11/2249/htm
42. Cheng CH, Chu CY, Chen HL, Lin IT, Wu CH, Lee YK, et al. Virus Elimination by Direct-Acting Antiviral Agents Impacts Glucose Homeostasis in Chronic Hepatitis C Patients. Front Endocrinol [Internet]. 2022 Jan 13 [cited 2024 May 28];12:799382. Available from: www.frontiersin.org
43. Chen Y, Ji H, Shao J, Jia Y, Bao Q, Zhu J, et al. Different Hepatitis C Virus Infection Statuses Show a Significant Risk of Developing Type 2 Diabetes Mellitus: A Network Meta-Analysis. Dig Dis Sci [Internet]. 2020 Jul 1 [cited 2024 May 28];65(7):1940–50. Available from: https://pubmed.ncbi.nlm.nih.gov/31758432/
44. Welzel TM, Bhardwaj N, Hedskog C, Chodavarapu K, Camus G, McNally J, et al. Global epidemiology of HCV subtypes and resistance-associated substitutions

evaluated by sequencing-based subtype analyses. J Hepatol [Internet]. 2017 Aug 1 [cited 2024 May 28];67(2):224–36. Available from: https://pubmed.ncbi.nlm.nih.gov/28343981/

45. Siphepho PY, Liu YT, Shabangu CS, Huang JF, Huang CF, Yeh ML, et al. The Impact of Steatosis on Chronic Hepatitis C Progression and Response to Antiviral Treatments. Biomedicines [Internet]. 2021 Oct 17 [cited 2024 May 28];9(10):1491. Available from: https://www.mdpi.com/2227-9059/9/10/1491/htm
46. Amako Y, Munakata T, Kohara M, Siddiqui A, Peers C, Harris M. Hepatitis C virus attenuates mitochondrial lipid β-oxidation by downregulating mitochondrial trifunctional-protein expression. J Virol. 2015;89(9):4092–101.
47. Bhattacharjee C, Singh M, Das D, Chaudhuri S, Mukhopadhyay A. Current therapeutics against HCV. Virusdisease. 2021;32(2):228–243.
48. Salama II, Raslan HM, Abdel-Latif GA, Salama SI, Sami SM, Shaaban FA, et al. Impact of direct-acting antiviral regimens on hepatic and extrahepatic manifestations of hepatitis C virus infection. World J Hepatol [Internet]. 2022 [cited 2024 May 28];14(6):1053–73. Available from: https://pubmed.ncbi.nlm.nih.gov/35978668/
49. Muñoz-Hernández R, Ampuero J, Millán R, Gil-Gómez A, Rojas Á, Macher HC, et al. Hepatitis C Virus Clearance by Direct-Acting Antivirals Agents Improves Endothelial Dysfunction and Subclinical Atherosclerosis: HEPCAR Study. Clin Transl Gastroenterol [Internet]. 2020 Aug 1 [cited 2024 May 28];11(8):e00203. Available from: https://pubmed.ncbi.nlm.nih.gov/32955194/
50. Su X, Zhao X, Deng JL, Li SN, Du X, Dong JZ, et al. Antiviral treatment for hepatitis C is associated with a reduced risk of atherosclerotic cardiovascular outcomes: A systematic review and meta-analysis. J Viral Hepat [Internet]. 2021 Apr 1 [cited 2024 May 28];28(4):664–71. Available from: https://pubmed.ncbi.nlm.nih.gov/33452699/
51. Kramná L, Kolářová K, Oikarinen S, Pursiheimo JP, Ilonen J, Simell O, et al. Gut virome sequencing in children with early islet autoimmunity. Diabetes Care [Internet]. 2015 May 1 [cited 2024 May 28];38(5):930–3. Available from: https://pubmed.ncbi.nlm.nih.gov/25678103/
52. Altindis E, Cai W, Sakaguchi M, Zhang F, GuoXiao W, Liu F, et al. Viral insulin-like peptides activate human insulin and IGF-1 receptor signaling: A paradigm shift for host-microbe interactions. Proc Natl Acad Sci U S A [Internet]. 2018 Mar 6 [cited 2024 May 28];115(10):2461–6. Available from: https://pubmed.ncbi.nlm.nih.gov/29467286/
53. Chrudinová M, Moreau F, Noh HL, Páníková T, Žáková L, Friedline RH, et al. Characterization of viral insulins reveals white adipose tissue-specific effects in mice. Mol Metab [Internet]. 2021 Feb 1 [cited 2024 May 28];44:101121. Available from: https://pubmed.ncbi.nlm.nih.gov/33220491/
54. Belavgeni A, Maremonti F, Tonnus W, Stadtmüller M, Gavali S, Mallais M, et al. vPIF-1 is an insulin-like antiferroptotic viral peptide. Proc Natl Acad Sci U S A [Internet]. 2023 [cited 2024 May 28];120(21):e2300320120. Available from: https://pubmed.ncbi.nlm.nih.gov/37186845/
55. Mataramvura H, Bunders MJ, Duri K. Human immunodeficiency virus and antiretroviral therapy-mediated immune cell metabolic dysregulation in children born to HIV-infected women: potential clinical implications. Front Immunol. 2023;14:1182217.
56. Kalligeros M, Vassilopoulos A, Shehadeh F, Vassilopoulos S, Lazaridou I, Mylonakis E, et al. Prevalence and Characteristics of Nonalcoholic Fatty Liver Disease and Fibrosis in People Living With HIV Monoinfection: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol [Internet]. 2023 Jul 1 [cited 2024 May 28];21(7):1708–22. Available from: https://pubmed.ncbi.nlm.nih.gov/36642292/

57. Zhang L, Bansal MB. Role of Kupffer Cells in Driving Hepatic Inflammation and Fibrosis in HIV Infection. Front Immunol [Internet]. 2020 Jun 16 [cited 2024 May 28];11:1086. Available from: https://pubmed.ncbi.nlm.nih.gov/32612603/
58. Koethe JR. Adipose Tissue in HIV Infection. Compr Physiol [Internet]. 2017 Oct 1 [cited 2024 May 28];7(4):1339–57. Available from: https://pubmed.ncbi.nlm.nih.gov/28915327/
59. Polyzos SA, Perakakis N, Mantzoros CS. Fatty liver in lipodystrophy: A review with a focus on therapeutic perspectives of adiponectin and/or leptin replacement. Metabolism [Internet]. 2019 Jul 1 [cited 2024 May 28];96:66–82. Available from: https://pubmed.ncbi.nlm.nih.gov/31071311/
60. Bouzoni E, Perakakis N, Connelly MA, Angelidi AM, Pilitsi E, Farr O, et al. PCSK9 and ANGPTL3 levels correlate with hyperlipidemia in HIV-lipoatrophy, are regulated by fasting and are not affected by leptin administered in physiologic or pharmacologic doses. Metabolism [Internet]. 2022 Sep 1 [cited 2024 May 28];134:155265. Available from: https://pubmed.ncbi.nlm.nih.gov/35820631/
61. Yen DW, Sherman KE. Causes and outcomes of hepatic fibrosis in persons living with HIV. Curr Opin HIV AIDS. 2022;17(6):359–67.
62. Woelfle T, Linkohr B, Waterboer T, Thorand B, Seissler J, Chadeau-Hyam M, et al. Health impact of seven herpesviruses on (pre)diabetes incidence and HbA1c: results from the KORA cohort. Diabetologia [Internet]. 2022 Aug 1 [cited 2024 May 28];65(8):1328–38. Available from: https://pubmed.ncbi.nlm.nih.gov/35538159/
63. Šestan M, Marinović S, Kavazović I, Cekinović Đ, Wueest S, Turk Wensveen T, et al. Virus-Induced Interferon-γ Causes Insulin Resistance in Skeletal Muscle and Derails Glycemic Control in Obesity. Immunity [Internet]. 2018 Jul 17 [cited 2024 May 28];49(1):164–77. Available from: https://pubmed.ncbi.nlm.nih.gov/29958802/
64. Harding JL, Oviedo SA, Ali MK, Ofotokun I, Gander JC, Patel SA, et al. The bidirectional association between diabetes and long-COVID-19 - A systematic review. Diabetes Res Clin Pr [Internet]. 2023 Jan 1 [cited 2024 May 28];195:110202. Available from: https://pubmed.ncbi.nlm.nih.gov/36496030/
65. Holman N, Barron E, Young B, Gregg EW, Khunti K, Valabhji J, et al. Comparative Incidence of Diabetes Following Hospital Admission for COVID-19 and Pneumonia: A Cohort Study. Diabetes Care. 2023;46(5):938–43.
66. Laurenzi A, Caretto A, Molinari C, Mercalli A, Melzi R, Nano R, et al. No Evidence of Long-Term Disruption of Glycometabolic Control After SARS-CoV-2 Infection. J Clin Endocrinol Metab. 2022;107(3):e1009–19.
67. Ibrahim S, Monaco GSF, Sims EK. Not so sweet and simple: impacts of SARS-CoV-2 on the β cell. Islets [Internet]. 2021 [cited 2024 May 29];13(3–4):66–79. Available from: /pmc/articles/PMC8281101/
68. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature [Internet]. 2022 Dec 22 [cited 2024 May 29];612(7941):758–63. Available from: https://pubmed.ncbi.nlm.nih.gov/36517603/
69. Zickler M, Stanelle-Bertram S, Ehret S, Heinrich F, Lange P, Schaumburg B, et al. Replication of SARS-CoV-2 in adipose tissue determines organ and systemic lipid metabolism in hamsters and humans. Cell Metab [Internet]. 2022 Jan 4 [cited 2024 May 29];34(1):1–2. Available from: https://pubmed.ncbi.nlm.nih.gov/34895500/
70. Wan L, Gao Q, Deng Y, Ke Y, Ma E, Yang H, et al. GP73 is a glucogenic hormone contributing to SARS-CoV-2-induced hyperglycemia. Nat Metab [Internet]. 2022 Jan 1 [cited 2024 May 29];4(1):29–43. Available from: https://pubmed.ncbi.nlm.nih.gov/34992299/
71. Hartmann-Boyce J, Rees K, Perring JC, Kerneis SA, Morris EM, Goyder C, et al. Risks of and From SARS-CoV-2 Infection

and COVID-19 in People With Diabetes: A Systematic Review of Reviews. Diabetes Care [Internet]. 2021 Dec 1 [cited 2024 May 29];44(12):2790–811. Available from: https://pubmed.ncbi.nlm.nih.gov/34711637/

72. Khunti K, Valabhji J, Misra S. Diabetes and the COVID-19 pandemic. Diabetologia [Internet]. 2023 Feb 1 [cited 2024 May 29];66(2):255–66. Available from: https://pubmed.ncbi.nlm.nih.gov/36418578/
73. Erener S. Diabetes, infection risk and COVID-19. Mol Metab [Internet]. 2020 Sep 1 [cited 2024 May 29];39:101044. Available from: https://pubmed.ncbi.nlm.nih.gov/32585364/
74. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature [Internet]. 2017 Feb 8 [cited 2024 May 29];542(7640):177–85. Available from: https://pubmed.ncbi.nlm.nih.gov/28179656/
75. Hotamisligil GS. Foundations of Immunometabolism and Implications for Metabolic Health and Disease. Immunity [Internet]. 2017 Sep 19 [cited 2024 May 29];47(3):406–20. Available from: https://pubmed.ncbi.nlm.nih.gov/28930657/
76. Zhou W, Sailani MR, Contrepois K, Zhou Y, Ahadi S, Leopold SR, et al. Longitudinal multi-omics of host-microbe dynamics in prediabetes. Nature [Internet]. 2019 May 30 [cited 2024 May 29];569(7758):663–71. Available from: https://pubmed.ncbi.nlm.nih.gov/31142858/
77. Kavazović I, Krapić M, Beumer-Chuwonpad A, Polić B, Wensveen TT, Lemmermann NA, et al. Hyperglycemia and Not Hyperinsulinemia Mediates Diabetes-Induced Memory CD8 T-Cell Dysfunction. Diabetes [Internet]. 2022 Apr 1 [cited 2024 May 29];71(4):706–21. Available from: https://pubmed.ncbi.nlm.nih.gov/35044446/
78. Karlsson EA, Sheridan PA, Beck MA. Diet-induced obesity impairs the T cell memory response to influenza virus infection. J Immunol [Internet]. 2010 Mar 15 [cited 2024 May 29];184(6):3127–33. Available from: https://pubmed.ncbi.nlm.nih.gov/20173021/
79. Paich HA, Sheridan PA, Handy J, Karlsson EA, Schultz-Cherry S, Hudgens MG, et al. Overweight and obese adult humans have a defective cellular immune response to pandemic H1N1 influenza A virus. Obes (Silver Spring) [Internet]. 2013 [cited 2024 May 29];21(11):2377–86. Available from: https://pubmed.ncbi.nlm.nih.gov/23512822/
80. Honce R, Karlsson EA, Wohlgemuth N, Estrada LD, Meliopoulos VA, Yao J, et al. Obesity-Related Microenvironment Promotes Emergence of Virulent Influenza Virus Strains. MBio [Internet]. 2020 Mar 1 [cited 2024 May 29];11(2):e03341-19. Available from: https://pubmed.ncbi.nlm.nih.gov/32127459/
81. Maurya R, Sebastian P, Namdeo M, Devender M, Gertler A. COVID-19 Severity in Obesity: Leptin and Inflammatory Cytokine Interplay in the Link Between High Morbidity and Mortality. Front Immunol. 2021;12:649359.
82. Chung TH, Kim JK, Kim JH, Lee YJ. Fatty Liver Index as a Simple and Useful Predictor for 10-year Cardiovascular Disease Risks Determined by Framingham Risk Score in the General Korean Population. J Gastrointestin Liver Dis [Internet]. 2021 Jun 1 [cited 2024 May 29];30(2):221–6. Available from: https://pubmed.ncbi.nlm.nih.gov/34174059/
83. Codo AC, Davanzo GG, Monteiro L de B, de Souza GF, Muraro SP, Virgilio-da-Silva JV, et al. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis. Cell Metab [Internet]. 2020 Sep 1 [cited 2024 May 29];32(3):498–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32877692/
84. Hu H, Lin A, Kong M, Yao X, Yin M, Xia H, et al. Intestinal microbiome and NAFLD: molecular insights and therapeutic perspectives. J Gastroenterol [Internet]. 2020 Feb 1 [cited 2024 May

29];55(2):142–58. Available from: https://pubmed.ncbi.nlm.nih.gov/31845054/
85. Yeoh YK, Zuo T, Lui GCY, Zhang F, Liu Q, Li AYL, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut [Internet]. 2021 Apr 1 [cited 2024 May 29];70(4):698–706. Available from: https://pubmed.ncbi.nlm.nih.gov/33431578/
86. Shihui SunTong L, Xiao X, Li M, Fang S, Ma E, Yu X, et al. A glucose-like metabolite deficient in diabetes inhibits cellular entry of SARS-CoV-2. Nat Metab. 2022;4(5):547–58.
87. Dubsky M, Veleba J, Sojakova D, Marhefkova N, Fejfarova V, Jude EB. Endothelial Dysfunction in Diabetes Mellitus: New Insights. Int J Mol Sci [Internet]. 2023 Jul 1 [cited 2024 May 29];24(13):10705. Available from: /pmc/articles/PMC10341633/
88. Jung CH, Mok JO. Recent Updates on Vascular Complications in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab (Seoul) [Internet]. 2020 [cited 2024 May 29];35(2):260–271. Available from: /pmc/articles/PMC7386121/
89. Bauer L, Rijsbergen LC, Leijten L, Benavides FF, Noack D, Lamers MM, et al. The pro-inflammatory response to influenza A virus infection is fueled by endothelial cells. Life Sci Alliance. 2023;6(7):e202201837.
90. Xu S, Ilyas I, Weng J. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin. 2023;44:695–709.
91. Ayres JS. A metabolic handbook for the COVID-19 pandemic. Nat Metab. 2020;2(7):572–85.
92. Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. Lancet Diabetes Endocrinol [Internet]. 2019 Jun 1 [cited 2024 May 29];7(6):442–51. Available from: https://pubmed.ncbi.nlm.nih.gov/31047901/
93. Zhang T, Mei Q, Zhang Z, Walline JH, Liu Y, Zhu H, et al. Risk for newly diagnosed diabetes after COVID-19: a systematic review and meta-analysis. BMC Med. 2022;20(1):444.
94. Lai H, Yang M, Sun M, Pan B, Wang Q, Wang J, et al. Risk of incident diabetes after COVID-19 infection: A systematic review and meta-analysis. Metabolism [Internet]. 2022 Dec 1 [cited 2024 May 29];137:155330. Available from: https://pubmed.ncbi.nlm.nih.gov/36220361/
95. Kosiborod MN, Esterline R, Furtado RHM, Oscarsson J, Gasparyan SB, Koch GG, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol [Internet]. 2021 Sep 1 [cited 2024 May 29];9(9):586–94. Available from: https://pubmed.ncbi.nlm.nih.gov/34302745/
96. Bramante CT, Huling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. N Engl J Med [Internet]. 2022 Aug 18 [cited 2024 May 29];387(7):599–610. Available from: https://pubmed.ncbi.nlm.nih.gov/36070710/