Mechanisms and clinical relevance of the bidirectional relationship of viral infections with metabolic diseases

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Viruses have been present during all evolutionary steps on earth and have had a major effect on human history. Viral infections are still among the leading causes of death. Another public health concern is the increase of non-communicable metabolic diseases in the last four decades. In this Review, we revisit the scientific evidence supporting the presence of a strong bidirectional feedback loop between several viral infections and metabolic diseases. We discuss how viruses might lead to the development or progression of metabolic diseases and conversely, how metabolic diseases might increase the severity of a viral infection. Furthermore, we discuss the clinical relevance of the current evidence on the relationship between viral infections and metabolic disease and the present and future challenges that should be addressed by the scientific community and health authorities.

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Introduction

Viruses are infectious, non-autonomously replicating biological agents (arguably organisms) that exist in many varieties and have been present in all evolutionary steps of life on earth.[1] From smallpox to Spanish influenza, the HIV epidemic, and the SARS-CoV-2 pandemic, viruses and viral infections have had a major effect on societal development. The emergence and spread of old and new viral infections are associated with major transitions in the relationships of humans with the natural environment. We are now experiencing a new transition period reflecting the effect of environmental, technological, demographical, and behavioural changes occurring in human societies spread.[2] Changes in climate and land use are expected to force the movement of many species in new environments. This is predicted to facilitate viral sharing among previously isolated wildlife species, which will increase the likelihood of zoonotic spillover, especially in densely populated areas.[3] Based on datasets of large epidemics generated over the last four centuries and on the increasing rates of disease emergence from animal reservoirs related to environmental change, there is a high and steadily increasing probability of infectious disease epidemics in coming decades.[4] During the SARS-CoV-2 pandemic-related lockdown, a reduction in the prevalence of several respiratory viral infections was observed.[5] As we are now entering the post-pandemic phase, the prevalence of other viral and bacterial infections seems to have risen at least to the pre-pandemic level.[6–8]

During the last four decades, we have been experiencing the development of non-communicable global epidemics of metabolic diseases, characterised by continuously increasing prevalence of obesity, which, in conjunction with other environmental and genetic factors, might lead to type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and other metabolic sequelae.[9,10] The consequences of non-communicable epidemics on affected societies are already immense. Diabetes is the ninth leading cause of death and an important risk factor of four other top-ten leading causes of mortality (ischemic heart disease, stroke, chronic obstructive pulmonary disease, and kidney diseases).[8] Early during the SARS-CoV-2 pandemic, it became apparent that a strong association between metabolic diseases and SARS-CoV-2 severity and mortality exists,[11,12] which led to suggestions for adaptations in preventive and therapeutic strategies. Additionally, this still uncharacterised relationship rejuvenated the academic, clinical, and scientific interest in investigating the pathophysiological connections between viral infections and metabolic diseases, and their relevance for human health.

In this Review, we revisit the scientific evidence supporting the presence of a bidirectional relationship between several viral infections and metabolic diseases. Our aim is not to provide a comprehensive list of all the available data, but to present the current knowledge about some principle mechanisms explaining this relationship and to discuss the most intriguing new concepts. Regarding metabolic diseases, we will focus on diabetes, both type 1 (due to autoimmune or viral-induced β-cell dysfunction and destruction) and type 2 (primarily due to insulin resistance), and fatty liver disease. We have selected these metabolic diseases because of their high prevalence, their considerable health care burden, and the level of scientific data linking them with viral infections. In the first part of the Review, we focus on how viruses might promote the development of metabolic diseases by regulating glucose and lipid metabolism. We describe the most important mechanisms and provide representative examples of viruses that are causally related to the development or progression of metabolic diseases. The selected viruses for discussion either affect a large proportion of the general population (acutely or

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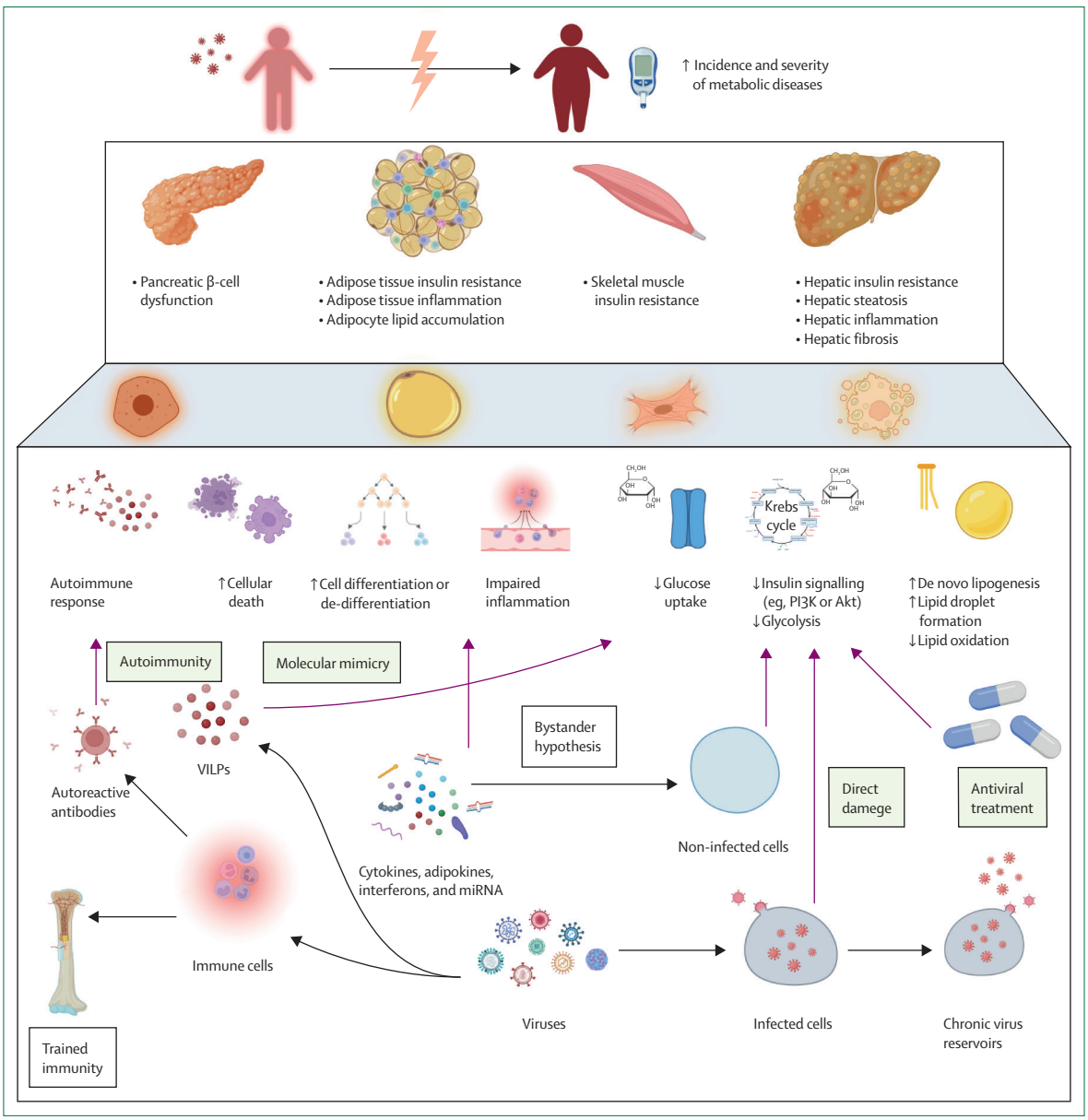

Figure 1: **Principal mechanisms promoting acute and chronic metabolic derangement by viruses**
Viral entry and replication in cells of metabolic and endocrine organs can initially create direct damage that leads to cell death either by the activated immune system or by initiation of cell-autonomous death signalling pathways. Activated immune cells producing antibodies or cytokines and infected cells secreting biomolecules can also target non-infected cells both locally and in distant tissues (bystander hypothesis). Viral peptides with high homology with host proteins (eg, VILPs) might mimic or compete with their functions, thus affecting cell metabolism and survival (molecular mimicry). Autoreactive antibodies persisting after viral clearance can lead to permanent organ destruction (autoimmunity). Viral infections can induce changes in the haematopoietic stem and progenitor cells in the bone marrow that can generate a strong and fast response of the innate immune system in future inflammatory challenges (viral or metabolic) and be detrimental for metabolic health (maladaptive trained immunity). Viruses might establish a persistent infection, which serves as a chronic pathogen reservoir (chronic virus reservoirs). Medications used against viral infections might induce robust changes in glucose and lipid homeostasis (antiviral treatment). These mechanisms have been implicated in β-cell dysfunction, reduced cellular glucose uptake, increased insulin resistance, and enhanced fat accumulation by different viruses. Figure created with BioRender.com. VILP=viral insulin-like peptides.

chronically) or use distinct mechanisms for promoting metabolic diseases. In the second part of the Review, we present the reverse direction of this relationship, and specifically how metabolic derangement might facilitate viral infection spread and severity. In this second part, we present the mechanisms and include examples from SARS-CoV-2 and influenza infections, which are two of the most common and intensively studied viral respiratory infections. Lastly, we briefly discuss the relevance of the current evidence for clinical practice and focus on present and future challenges to be addressed by the scientific community and by health authorities.

How viruses might promote metabolic diseases

Several studies have shown that viruses might promote metabolic diseases by affecting important cell functions (figure 1). For instance, viruses can regulate cell survival and specific pathways pertinent to cell death, proliferation, or dedifferentiation in key endocrine and metabolic organs.[13–20] Furthermore, viruses are capable of controlling cell glucose metabolism by modulating glucose transporters altering glucose uptake, regulating signalling pathways involved in cellular energy sensing and stimulating glycolysis in infected cells.[13,14,21–25] Moreover, viruses can regulate lipid metabolism by increasing lipid and fatty acid synthesis and lipid droplet formation, and by decreasing fatty acid oxidation.[13,14,26,27]

Many of these effects are observed in infected cells during virus replication and derive from direct intracellular actions of the virus. The viral effect on glucose and lipid metabolism increases available energy which facilitates virus replication and propagation. Additionally, viruses can promote the release of peptides or proteins from infected cells that trigger both local and systemic immune responses targeting either the host cell or its neighbour cells (bystander hypothesis).[13,25,28] These effects might persist even after virus clearance, thereby leading to progressive irreversible organ damage, as is the case in autoimmune diseases following viral infection.[13,25,28] Viruses can also promote the release of molecules (eg, miRNAs, interferons, and adipocytokines) that manipulate the function both of the infected cell and cells in distant organs, which might participate in glucose or energy homeostasis.[29–34] Lastly, viruses produce polypeptides that share homology with endogenous immunomodulatory proteins, growth factors, or hormones, thus, either mimicking, cross-reacting, or antagonising host proteins to affect cellular metabolism and survival (molecular mimicry).[21,25,28,35–38]

The spatiotemporal dynamics of infections play a crucial role in the extent and chronicity of damage a virus can generate. Post-acute infection syndromes refer to chronic disability following an infectious disease and have been observed in many patients after viral infection (eg, SARS-CoV-2, coxsackie, influenza, varicella zoster, Epstein-Barr, Ebola, dengue, and polio) and are most visible in pandemics.[39,40] Post-COVID-19 disease is a more recent prevalent post-infection with an increased incidence of diabetes (hazard ratio [HR] 8·2), obesity (HR 9·5), dyslipidaemia (HR 9–10), and cardiovascular conditions (HR from 3·9 for heart failure up to 15·2 for hypertension).[41–43] However, epidemiologic evidence indicate that many other common viruses are also associated with an increased risk of development or progression of metabolic diseases (table 1). In few cases, the epidemiological links are further supported by experimental evidence that generate plausible hypotheses on the possible mechanisms involved in the chronic consequences of a viral infection, even after viral clearance. According to one hypothesis, viruses might establish a persistent infection or leave non-infectious antigens in organs, which will serve as chronic pathogen reservoirs.[13,14,29,30,69–72] These pathogens or pathogen-remnants might escape conventional detection methods, but still be able to induce chronic subclinical inflammation.[29,30,69–72] The viral infections could also lead to the production of autoantibodies affecting endocrine and metabolic function gradually and with a considerable delay from the initial infection.[13,25,28] According to another hypothesis, trained innate immunity might play a role in the chronic effects of a viral infection on metabolism. Specifically, microbial infections or other non-microbial inflammatory stimuli might elicit sustained epigenetic and metabolic changes in innate immune cells and bone marrow progenitors, including hematopoietic stem and progenitor cells.[73–76] A following unrelated infection or even a different inflammatory stimulus (eg, obesity-induced inflammation) might trigger a second profound inflammatory response in predisposed organisms, which can have either beneficial effects, such as a faster viral clearance, or detrimental ones, such as aggravating a pre-existing proinflammatory state (maladaptive trained immunity).[73,74,77] Notably, trained innate immunity has been observed after vaccination with live attenuated vaccines (eg, measles) indicating that this is a relevant mechanism of immune memory not only after bacterial, but also after viral infection.[78] Whether acquired adaptive immunity after viral infection might also trigger altered inflammatory responses promoting metabolic diseases upon exposure to a second stimulus (eg, either microbial infection or non-microbial inflammatory challenge) remains elusive. Lastly, several viruses (eg, influenza, enteroviruses, SARS-CoV-2, and HIV) have been associated with microbiome changes (dysbiosis) and gut dysfunction, which might impair future responses to inflammatory challenges and secondary infections.[79] Dysbiosis is also observed in obesity, type 2 diabetes, and non-alcoholic fatty liver disease, and has been related to disease progression.[80] Finally, not the virus per se, but the antiviral or concomitant treatment might be primarily responsible for metabolic derangement.[23,33,81–83]

In this Review, we provide representative examples and discuss emerging evidence on how specific viruses promote metabolic imbalance.

The potential effect of enteroviruses in β-cell dysfunction and type 1 diabetes

Viral infections, mostly enteroviruses, but also mumps, parainfluenza virus, human herpes virus 6, parechovirus, and rotaviruses have been associated with the development of diabetes due to β-cell destruction.[84,44] Many of these viruses share some common characteristics,[85] one being that they lead to highly prevalent infections, which usually occur at a young age. The timing of infection precedes or coincides with the peaks in development of islet autoantibodies that occur at age 2 for insulin autoantibodies and between 3–5 years of age for glutamic acid decarboxylase autoantibodies.[85,86] Despite the high prevalence of these

	Viral infectious disease	Metabolic disease	Metabolic disease incidence (95% CI)
Meta-analysis[44]	Enteroviruses	Type 1 diabetes	OR 9·8 (5·5–17·4)
Meta-analysis[45]	Enteroviruses	Type 1 diabetes	OR 5·75 (3·6–9·6)
Meta-analysis[46]	Enteroviruses	Type 1 diabetes	OR 7·78 (4·9–12·4)
Retrospective, population-based[47]	Enteroviruses	Type 1 diabetes	HR 1·48 (1·2–1·8)
Population-based, case-control[48]	Coxsackievirus B1	Type 1 diabetes	OR 1·7 (1·0–2·9)
Longitudinal, prospective, case-control, population-based[49]	Coxsackievirus B1	Type 1 diabetes	OR 1·5 (1·0–22·2)
Population-based[50]	Herpes simplex virus 2	Pre-diabetes	OR 1·59 (1·0–2·5)
Population-based[50]	Cytomegalovirus	Pre-diabetes	OR 1·33 (1·0–1·8)
Case-control, population-based[51]	Herpes simplex virus	Type 1 diabetes	OR 1·21 (1·0–1·5)
Meta-analysis[52]	Hepatitis C virus	Diabetes	OR 1·68 (1·2–2·2)
Cross-sectional, population-based[53]	Hepatitis C virus	Type 2 diabetes	OR 3·77 (1·8–7·9)
Longitudinal, prospective, case-control[54]	Hepatitis C virus	Type 2 diabetes	High-risk group: HR 11·58 (1·4–96·6); low-risk group: HR 0·48 (0·05–4·4)
Population-based[55]	Hepatitis C virus	Metabolic syndrome	PR 35% (30·6%–39·2%)
Population-based[55]	Hepatitis C virus	Diabetes	PR 17·5% (14·1%–20·9%)
Meta-analysis[56]	Hepatitis C virus (without cirrhosis)	Type 2 diabetes	OR 2·12 (1·6–2·8)
Meta-analysis[56]	Hepatitis C virus (with cirrhosis)	Type 2 diabetes	OR 6·82 (4·5–10·5)
Meta-analysis[57]	Hepatitis B virus	Diabetes	OR 1·33 (1·1–1·6)
Meta-analysis[58]	Hepatitis B virus	Type 2 diabetes	OR 1·99 (1·1–3·7)
Cross-sectional, case-control[59]	Hepatitis B virus	Type 2 diabetes	OR 5·39 (2·8–10·5)
Meta-analysis[60]	HIV	NAFLD	PR 34% (30–38%), PR 49% (34–63%)
Meta-analysis[60]	HIV	Liver fibrosis	PR 12% (10–14%), PR 23% (15–33%)
Meta-analysis[61]	HIV	NAFLD	PR 35% (29–42%)
Meta-analysis[61]	HIV	NASH	PR 42% (22–64%)
Meta-analysis[61]	HIV	Liver fibrosis	PR 22% (13–34%)
Cross-sectional, population-based[62]	HIV	NAFLD	PR 36·9%
Population-based[63]	HIV	NAFLD	PR 31%
Prospective, population-based[64]	HIV	NAFLD	PR 48%
Prospective, population-based[64]	HIV	Liver fibrosis	PR 15%
Meta-analysis[65]	HIV	Metabolic syndrome	PR 21·5% (15·1–26·9), relative risk 1·83 (1·0–3·4)
Population-based[66]	HIV	Diabetes	IRR 2·83 (1·6–5·1)
Meta-analysis[67]	Influenza A (H1N1)	Diabetes	PR 15% (12–17%)
Meta-analysis[67]	MERS-CoV	Diabetes	PR 54% (28–80%)
Population-based[41]	SARS-CoV-2	Diabetes	OR 8·2 (6·4–9·5)
Population-based[41]	SARS-CoV-2	Obesity	OR 9·5 (7·6–11·4)
Population-based[41]	SARS-CoV-2	Dyslipidaemia	OR 12·3 (8·2–16·2)
Retrospective, population-based[68]	SARS-CoV-2	Diabetes	IRR 1·28 (1·05–1·57)
Retrospective, population-based[42]	SARS-CoV-2	Diabetes	HR 1·40 (1·36–1·44)
Retrospective, population-based[43]	SARS-CoV-2	Dyslipidaemia	Composite dyslipidaemia outcomes: HR 1·24 (1·21–1·27)

HR=hazard risk ratio. IRR=incidence rate ratio. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatoheapatitis. OR=odds ratio. PR=prevalence rate.

Table 1: **Studies investigating the association of viral infections with incidence of metabolic diseases**

infections, only a small proportion of the population will eventually develop type 1 diabetes, suggesting that other factors, such as genetic background, timing of infection, and immune response, might play an important role. Of note, no convincing epidemiologic or experimental evidence exists for the involvement of these viruses in type 2 diabetes or steatosis. Most of these viruses are transmitted by the oral–faecal route; they can interact with immune cells and reach the pancreas to infect specifically pancreatic β cells.[85,86] Among different viruses, the strongest epidemiologic and experimental links with type 1 diabetes exist for enteroviruses. These consist of 15 species including enterovirus A71, echoviruses, polioviruses, and coxsackieviruses A and B.[87] Infections from echoviruses (serotypes 3, 4, 6, 9, 16, and 30) and coxsackievirus B (CVB; particularly serotypes CVB1 and CVB4) have been strongly associated with type 1 diabetes,[85] with most scientific evidence existing for CVB infections.[88]

The epidemiological and histological evidence includes associations between CVB RNA levels in stool samples with seroconversion and progression to type 1 diabetes, detection of enteroviral RNA in the islets of patients with new-onset type 1 diabetes more frequently than in controls, and detection of enteroviral capsid protein VP1 in the β cells of donors with type 1 diabetes.[71,89] Importantly, VP1 is detected in a small percentage of islets, which suggests a slow process probably occurring before the clinical manifestation of type 1 diabetes.[85]

Several receptors that enteroviruses might use to enter in the cell are also expressed in pancreatic β cells. The most important receptor seems to be the coxsackie and adenovirus receptor (CAR). An isoform of CAR (CAR-SIV) is expressed on the surface of insulin granules and might be used by viruses to enter the host cell during membrane recovery after insulin granules exocytosis.[90] Three main mechanisms have been suggested for coxsackie-virus induced damage of β cells. Firstly, virus replication in β cells might exert direct effects on cell function and survival. Coxsackieviruses can induce apoptosis via downregulation of anti-apoptotic proteins or induce necrosis by depletion of ATP.[15,16] Additionally, enterovirus-like products (ie, polyinosinic-polycytidylic acid [PolyI:C], which is a synthetic double-stranded RNA that is similar to the double-stranded RNA of some viruses) can decrease β cell-specific gene expression, indicating possible virus-induced β-cell dedifferentiation.[18] Furthermore, coxsackieviruses might block cap-dependent translation and reduce insulin content and glucose-induced insulin secretion by depleting insulin granule stores and by altering the expression of factors involved in Ca^{2+} homeostasis and membrane potential.[25,91] The second mechanism might involve the induction of a destructive autoimmune response against β cells. Peptides released by the damaged β cells are presented by antigen-presenting cells, whereas β cells induce the expression of MHC class I molecules to promote their destruction by T cells and facilitate the clearance of the virus.[28] This β cell loss can be crucial to maintain normoglycaemia, since β cells have restricted regenerative capacity. Additionally, neighbouring cells, such as islet α cells, pancreatic exocrine, endothelial, and neuronal cells might contribute with their infection and release of proinflammatory cytokines, to the activation of bystander islet-specific T cells in islets or lymph nodes, further fostering β-cell destruction (bystander effect).[25,28] The third mechanism that has been suggested is based on molecular mimicry. Viral proteins share homology in their sequence with glutamic acid decarboxylase 65 (GAD65) and IA-2 (ICA512), which are enriched in pancreatic islets. GAD65 and IA-2 are known islet autoantigens involved in inflammatory processes leading to type 1 diabetes.[25,28] However, cross-reactivity between these viral peptides, the autoimmune antibodies, or T-cell clones has so far not be detected, arguing against the considerable effect of this mechanism on autoimmune β-cell destruction.[37] Lastly, the observed chronicity of enterovirus infection in β cells and other organs might further contribute to autoimmunity. Specifically, persistent infection with enteroviruses has been detected in pancreatic islets and associated with virus-induced interferon alfa synthesis.[92] Enteroviral RNA or protein has been detected in pancreatic islet cells from autopsy specimens, in peripheral blood mononuclear cells, and in the gut mucosa of patients with type 1 diabetes.[69–71] Therefore, these organs might serve as chronic reservoirs of enteroviruses contributing to autoimmunity.

Despite accumulating experimental and epidemiological evidence, an enteroviral etiopathology of type 1 diabetes has not yet been proven, since the findings from studies do not unanimously agree. For example, some studies could not show an association between enteroviruses infection and islet autoimmunity or type 1 diabetes.[87] Late sampling or low virus titre might explain some of the negative results of these studies, but not all. Timing of infection also differs between studies with some suggesting either enterovirus infection long before seroconversion, close or shortly after seroconversion, or late after seroconversion by the time of diagnosis.[93] Furthermore, even positive findings do not necessarily prove causality. A key characteristic in type 1 diabetes is the expression of class I HLA, which is observed in pancreatic islets both with and without signs of enterovirus infection. Conversely, infection of islets with enterovirus do not always induce the expression of class I HLA.[93]

Efforts to eradicate the virus (eg, with vaccination or antiviral treatments) will be the ultimate test to prove causality between enteroviral infections and type 1 diabetes. The rationale behind the vaccination efforts is based on preventing viremia, systemic spreading, pancreas infiltration, and blocking possible early direct effects of virus on infected β cells, which might induce the release of self-antigens that trigger autoimmunity. Preclinical studies in mice have shown that vaccines comprising the six CVB serotypes can induce strong neutralising antibodies and can provide immunity against acute CVB infections, therefore inhibiting CVB-induced diabetes.[85] An ongoing phase I trial is currently evaluating such a vaccine targeting five serotypes (CVB1–CVB5) in healthy adults (NCT04690426). The success of such efforts depends on the safety profile, which is required to be excellent to allow vaccine evaluations as early in life as possible (in infancy) and before exposure to CVB. Understanding the spatiotemporal dynamics of infection and the protective or detrimental nature of the immune responses generated by viruses for β cell function and survival, will help develop more effective treatment strategies and help identify monitoring tools for assessing the course of the disease and treatment efficacy.

The effects of hepatitis C virus infection on insulin resistance, diabetes, and liver steatosis

Infection with hepatitis C virus (HCV) has been associated with an increased risk (odds ratio [OR] 1·8) for the development of type 2 diabetes.[52,94–96] This risk is even higher in older people with a family history of diabetes and with advanced liver cirrhosis.[97] The detrimental effects of HCV on glucose homeostasis are primarily attributed to increased hepatic insulin resistance. Specifically, HCV reduces hepatic glucose uptake from the circulation by downregulating the expression of glucose transporter 2.[22] Additionally, HCV directly impairs insulin signalling by inhibiting the PI3K/Akt pathway by increased IRS-1 and IRS-2 degradation.[24] Furthermore, HCV might decrease the expression of insulin receptor and increase the expression of gluconeogenic genes.[97] HCV infection is also associated with profound peripheral insulin resistance.[32] Although the mechanisms for HCV-induced insulin resistance have not been fully elucidated, an intriguing hypothesis suggests that hepatic dysfunction alters the profile of circulating miRNAs, thereby reducing insulin sensitivity of adipose and muscle tissues.[31] According to other hypotheses, insulin resistance is aggravated by increased oxidative stress and mitochondrial dysfunction induced by the HCV virus, which results in overexpression and secretion of pro-inflammatory cytokines, such as tumour necrosis factor (TNF) alpha, interleukin (IL) 6, and IL-8.[98] HCV infection has also been linked with diabetes due to β-cell dysfunction. Replication of HCV in pancreatic β cells diminish their insulin secretion and induces their death.[99,100] Sporadic reports of cases of patients developing type 1 diabetes following HCV infection or treatment with interferon, suggested possible induction of pancreatic islet autoimmunity. However, these findings have been less consistent and the epidemiological and mechanistic evidence is not as profound as for type 2 diabetes. Conversely, the presence of type 2 diabetes in patients with HCV infection has been associated with faster progression to fibrosis and a higher risk of decompensated cirrhosis and hepatocellular carcinoma.[97,101] The considerable effects of HCV on glucose homeostasis are further confirmed by the improvement reported after HCV elimination by new highly potent direct-acting antiviral agents.[102] Specifically, after HCV clearance, insulin sensitivity and secretion and consequently glycaemic control improve, whereas the risk of onset and progression of type 2 diabetes decreases.[99,102,103]

Apart from type 2 diabetes, HCV infection has been also associated with liver steatosis. The degree of steatosis is dependent on HCV genotype. HCV genotype 3 represents 20% of all HCV infections worldwide[104] and is not only more strongly associated with steatosis compared with the other genotypes, but the steatosis score also correlates positively with the intrahepatic HCV RNA titre.[105,106] Genotype 3-mediated steatosis might be related to differences in the amino-acid sequence of the core protein that leads to activation of multiple steatogenic mechanisms.[106] HCV genotype 3-mediated steatosis increases lipid accumulation in the liver by reducing very low density lipoprotein assembly by inhibition of microsomal triglyceride transfer protein activity, by inducing lipogenesis via SREBP-1c activation, and by reducing lipid β oxidation via PPAR-α downregulation.[26] Notably, steatosis induced by HCV infection is considered a negative predictor of sustained viral response in early HCV treatments that are interferon-based.[107] Direct-acting antivirals that target virus replication appear to be effective in achieving sustained virus response in patients with steatosis and HCV.[101] Direct-acting antivirals improve liver fibrosis, but contradictory results have been reported for steatosis with some studies showing improvement, whereas others have reported the progression of steatosis.[108–110] These discrepant findings emphasise the need for additional studies in this field.

Impaired glucose and lipid (or lipoprotein) metabolism, associated with HCV infection, can cause increased cardiovascular risk. Other direct and indirect effects of HCV on atherosclerosis induction have also been described.[101] HCV can indeed increase endothelial permeability, prompt endothelial cell apoptosis, promote the migration and proliferation of smooth muscle cells from the tunica media to the surface, and induce soluble vascular cell adhesion molecule 1 via increased cytokine and chemokine release (eg, IL-1, IL-6, and TNF).[111,112] Treatment with direct-acting antivirals have also here been associated with reduced risk of cardiovascular events.[113,114]

Identification of the Iridoviridae family of viruses as possible modulators of insulin and IGF-1 function by molecular mimicry

The Iridoviridae family consists of large double-stranded DNA viruses that commonly infect insects, reptiles, amphibians, and fish, often leading to death.[115] The genome of these viruses has also been detected in human plasma and enteric virome.[35,116] It has been shown that members of the Iridoviridae family encode sequences with high similarities to insulin and insulin-like growth factors 1 and 2 (IGF-1 and IGF-2).[35] These viral secreted peptides can bind to insulin or IGF-1 receptor and exert different functions. They can stimulate glucose uptake by increasing GLUT4 expression and Akt phosphrylation in white adipose tissue.[21] On the other hand, they may act as antagonists and thus inhibit cell proliferation and growth induced by IGF-1.[36] Thus, viral insulin-like peptides (VILPs) might represent a novel mechanism of molecular mimicry used by viruses to manipulate hormonal functions in humans. Nevertheless, it is still unclear whether and in which human cells VILP-containing viruses can enter and replicate. Additionally, it remains to be shown whether VILPs exert any other cellular effects apart from antagonising or mimicking the functions of insulin and IGF-1. For example, according to a recent

study, VILPs are capable of preventing ferroptosis and might have an important role in cell death.[38]

The effects of HIV and its treatment on fat distribution, liver steatosis, and metabolic syndrome

HIV infection and antiretroviral therapy (ART) have profound effects on lipid metabolism, adipose tissue quantity, morphology, and distribution, and are strongly associated with liver steatosis and metabolic syndrome.[23,83] The metabolic effects of HIV are primarily attributed to CD4+ T cell depletion and the induction of a chronic systemic inflammation. An untreated HIV infection is characterised by progressive weight loss (HIV wasting) due to reduced energy intake, malabsorption, and elevated metabolic requirements. Malabsorption results from the depletion of gut mucosal T cells, which impairs the maintenance of the gut epithelial barrier, increases its permeability, and thus, facilitates the translocation of viruses and microbiota.[117,118] The increase in metabolic requirements is further triggered by the persistent inflammatory response. Trunk fat is primarily lost, whereas de novo hepatic lipogenesis is increased resulting both in higher fat accumulation in the liver (steatosis) and in higher circulating triglycerides.[27] Changes in adipose tissue structure and function include lower mitochondrial DNA content and downregulated gene expression of important factors (eg, adiponectin, PPARγ, GLUT4, and lipoprotein lipase), which regulate systemic energy and glucose homeostasis.[23] The reduction in adiponectin might further aggravate hepatic steatosis and inflammation.[60,119] Furthermore, adipose tissue might function as an important HIV reservoir. Replication-competent HIV can be detected in CD4+ T cells from the stromal vascular fraction of adipose tissue in untreated and ART-treated patients, leading to increased expression of proinflammatory cytokines, which in turn further supports viral shedding.[29,30] Furthermore, the higher adipose-tissue and systemic inflammatory environment increases insulin resistance, which will promote hyperglycaemia and liver steatosis. Additionally, hepatocytes, Kupffer cells, and hepatic stellate cells are permissive to HIV and viral infection, and together with microbiota translocation, co-interact to promote further inflammation and fibrogenesis in the liver.[120] In this context, a meta-analysis has shown that 34% of people living with HIV have liver steatosis (non-alcoholic fatty liver disease) and 12% have greater than F2 stage fibrosis in liver histology.[60]

HIV is also a notable example of how antiviral treatments themselves might perturb metabolic homeostasis. The first treatments of patients with HIV included combinations of three or more antiretroviral medications (nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors), which resulted in most patients gaining considerable body weight. However, alterations in fat distribution were observed, with lipoatrophy of the limbs, face, and buttocks and lipohypertrophy of the cervical and visceral area, a condition named HIV-associated lipodystrophy.[23] Patients with HIV-associated lipodystrophy showed considerable hepatic, intramyocellular, and intramyocardial lipid accumulation.[23,81,83] Increased de novo lipogenesis combined with accelerated lipolysis were key factors contributing to HIV-associated lipodystrophy. ARTs led to robust changes in adipose tissue function including impaired adipogenesis and maturation, increased apoptosis, and increased proinflammatory cytokine production.[23] Additionally, ARTs affected the secretion of important hormonal regulators of energy and lipid homeostasis (eg, reduced adiponectin and increased PCSK9 and ANGPTL3).[33] All these effects contributed to insulin resistance, diabetes, and atherosclerosis. To date, weight gain under ART remains a major concern even with the most advanced drugs, requiring diabetes monitoring in several treatment settings.[121] Furthermore, ARTs might show low hepatotoxicity, but could still promote steatosis with the increase of body weight.[122]

The potential role of herpesviruses in the regulation of glucose homeostasis

Herpesviruses are among the most prevalent human viruses, but paradoxically, their relationship with metabolic diseases has been severely under-investigated. A study in a large cohort, which was followed for 6·5 years, found that herpes simplex virus 2 (HSV-2) and cytomegalovirus (CMV) seropositivities were associated with prediabetes or diabetes incidence (OR 1·59 for HSV-2 and OR 1·33 for CMV) after adjusting for multiple possible confounders.[50] Notably for HSV-2, the serostatus was also positively associated with HbA1c. Baseline seroprevalence for HSV-2 in the study was 11% and for 456% for CMV. Given that most of these infections occur early in life or in puberty, and that in most of the participants in this study the serostatus (either positive or negative) was maintained during the follow-up period, it is plausible that common viruses exert important chronic effects on human metabolism and therefore facilitate the development or progression of metabolic diseases. Whether a persistent infection due to the presence of a viral reservoir in an organ, or an altered immune response upon re-exposure to the virus play a role in promoting chronic effects, remains unclear. A study reported that respiratory infections were associated with a transient plasma insulin increase with no changes in fasting glucose, suggesting increased insulin resistance in humans.[34] In mice, CMV-induced IFN-γ led to downregulation of insulin receptor in skeletal muscle and a compensatory increased in insulin secretion. CMV-induced hyperinsulinemia directly stimulated CD8+ effector T cell function, thus promoting antiviral immunity at the expense of glycaemic control, which was lost in obese mice infected with CMV due to the further aggravation of insulin resistance.[34]

The potential effects of COVID-19 on metabolic diseases

Most epidemiological studies have reported both an increased risk of severe COVID-19 in patients with metabolic diseases and higher rates of new-onset diabetes and diabetic ketoacidosis following a SARS-CoV-2 infection.[11,12,42,43] The increased risk for new-onset diabetes has been reported to be between 11% and 276% and appears to depend on the age of the study population, severity of the clinical course of the infection, timing of risk assessment, and type of comparator groups.[123]

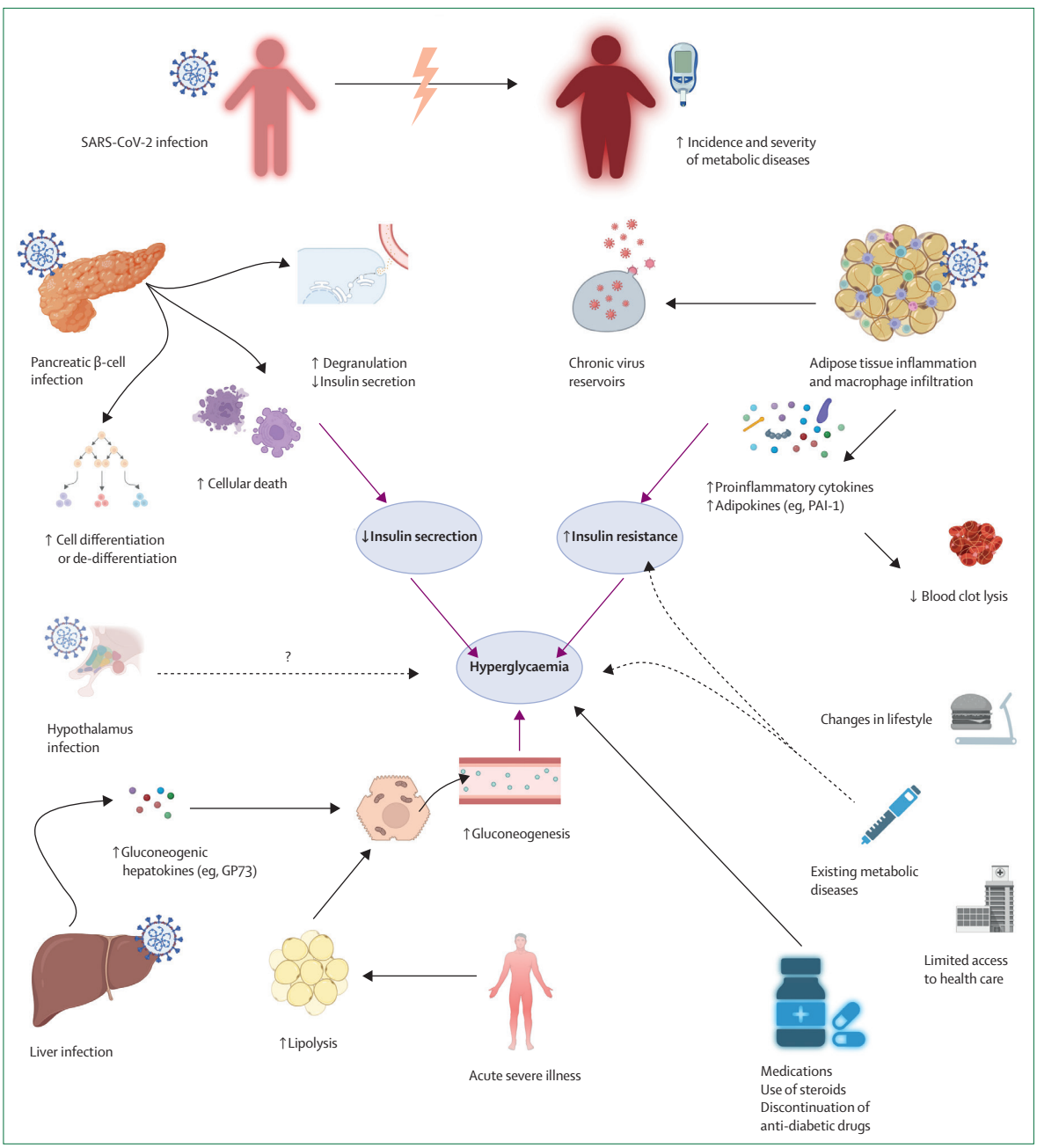

Figure 2: **Factors contributing to the development or aggravation of diabetes in patients with SARS-CoV-2 infection**
SARS-CoV-2 can enter and exert direct effects on organs leading to hyperglycaemia. In the pancreas, SARS-CoV-2 infection might affect β-cell function resulting in lower insulin secretion. In adipose tissue, SARS-CoV-2 infection might aggravate inflammation and change lipid metabolism, thus increasing insulin resistance, whereas it might stimulate the release of proteins that promote coagulation. In the liver, SARS-CoV-2 infection might induce gluconeogenesis contributing to higher blood glucose levels. Several other factors might indirectly promote hyperglycaemia, such as changes in lifestyle during the pandemic characterised by an unhealthy diet and reduced body activity can further contribute to metabolic dysfunction. Limited access to health care might delay the diagnosis of diabetes or the optimisation of its treatment. Some medications for the treatment of SARS-CoV-2 infection (eg, steroids) might induce or aggravate hyperglycaemia. Figure created with BioRender.com.

Specifically, studies in older adults or in patients with more severe infection, reported stronger associations with new-onset diabetes than in younger populations with milder disease course. It is also possible that hospitalisation due to COVID-19 led to the diagnosis of pre-existing diabetes in people who did not routinely conduct health check-ups.[123] This assumption is further supported by the reduction of the risk for new-onset diabetes with increasing follow-up time from the diagnosis of a COVID-19 infection.[123] Lastly, many studies have used people that have not been infected or have not been severely ill as comparative study groups. However, severe illness and hospitalisation can increase the incidence of diabetes, irrespective of the cause.[124] In this context, one study from 2020, reported a similar increase in the risk of new-onset diabetes following hospitalisation due to COVID-19 when compared with the risk following hospitalisation due to pneumonia.[124]

Although we are only beginning to understand the extent and clinical relevance of this detrimental bidirectional relationship for which contradictory findings from studies have been reported,[125] various pathophysiological mechanisms and factors might play a role (figure 2). First, β cells are permissive to infection with SARS-CoV-2, which has been associated with degranulation, impaired insulin-secretion, dedifferentiation or transdifferentiation, and cell death.[17,19,126] However, SARS-CoV-2 mRNA in the pancreas is detected only in small quantities and for a short period of time compared with other tissues.[127] Thus, this finding might not fully explain the higher numbers of new onset diabetes. SARS-CoV-2 has a broad tissue tropism suggesting that other endocrine organs might contribute to metabolic dysregulations. For example, adipocytes are also permissive to infection and it has been suggested that adipose tissue serves as a virus reservoir that over a prolonged time, gives rise to the production of proinflammatory cytokines and infiltrating macrophages.[72,128,129] Additionally, adipocytes produce plasminogen activator inhibitor-1 (PAI-1) that inhibits fibrinolysis. PAI-1 is considerably increased in patients with COVID-19 disease and attenuates clot lysis,[130] which might contribute to coagulopathy. Furthermore, SARS-CoV-2 mRNA is detected persistently and in high concentrations in the hypothalamus, which is a key organ for the regulation of the endocrine system and energy homeostasis.[127] Moreover, SARS-CoV-2 infection might enhance the production and secretion of GP73, which can stimulate hepatic gluconeogenesis to increase blood glucose levels in mice.[131] Apart from these direct effects, several indirect effects might contribute to hyperglycaemia and new-onset diabetes. For example, changes in lifestyle leading to weight gain combined with reduced access to preventive care during the pandemic, could have further aggravated a pre-existing abnormal or borderline metabolic state in several individuals.[11,12] Moreover, acute severe illness can lead to stress-induced hyperglycaemia due to increased lipolysis and circulating free fatty acids.[11] Medications, such as steroids that have been commonly used to treat COVID-19 infection, can also induce or further aggravate hyperglycaemia.[11,12] Nevertheless, it is important to highlight that more mechanistic data to investigate a potential causality between the observed bidirectional associations between COVID-19 infection (and other infections) and metabolic diseases are needed.

How metabolic diseases might affect infection severity of viral infections

Ample epidemiological evidence suggests a robust association of metabolic diseases with the incidence and severity of several viral infections (table 2). The direction of such associations is not always clear, thus, it remains elusive whether and for which viruses metabolic diseases increase the risk of infection. Conversely, convincing findings do exist for the causal association of metabolic diseases with infectious disease severity and outcome. We present some of the most important factors predisposing patients with metabolic disease to severe viral infections (figure 3).

Impaired immune response in metabolic diseases

People with obesity, insulin resistance, or diabetes display considerable alterations in both innate and adaptive immune system functions. Regarding the innate immune system, impaired chemotaxis, and phagocytosis of neutrophils have been observed in patients with type 2 diabetes.[161] Moreover, natural killer cells show reduced activity, whereas macrophages accumulate in the adipose tissue and develop a proinflammatory phenotype.[162] Maladaptive-trained immunity also generates myeloid cells with increased proinflammatory capacity upon exposure to a second challenge.[73] Regarding the adaptive immune system, in obesity, natural killer T cell numbers decrease in the adipose tissue, whereas B cells accumulate in adipose tissue and secrete more proinflammatory cytokines.[162,163]

Notably, in longitudinal multiomics analyses of diverse biospecimens (blood, nasal, and stool swabs), people with insulin resistance presented a delayed immune response following respiratory viral infections compared with people with normal insulin sensitivity.[164] Hyperglycaemia appears to also be an important mediator of diabetes-induced memory CD8 T-cell dysfunction in viral infections.[165] Furthermore, in mouse models of obesity, infection with influenza virus compromised T-cell function due to oxidative stress and led to lower TNF-α, lower IFN-γ production, and inadequate B cell response.[166–168] These alterations contributed to a delayed and impaired immune response after infection that resulted in faster viral replication, longer viral shedding, greater lung damage, and increased mortality in mice.[166–168] Delayed immune response with low type I interferon responses observed in obese mice, facilitates the generation of viral diversity and might contribute to the emergence of more virulent influenza virus populations.[169]

	Metabolic disease	Viral infectious disease	Infection incidence (95% CI)	Infection–related severity (95% CI)	Infection–related mortality (95% CI)
Meta-analysis[132]	Metabolic diseases	Hospital-acquired influenza	OR 8·1 (2·5–26·6)	..	..
Meta-analysis[132]	Diabetes	Hospital-acquired influenza	OR 1·2 (1·0–1·4)	..	..
Longitudinal, prospective, population-based[133]	Type 1 diabetes	Lower respiratory tract infection	OR 1·42 (1·0–2·1)	..	..
Longitudinal, prospective, population-based[133]	Type 2 diabetes	Lower respiratory tract infection	OR 1·32 (1·1–1·5)	..	..
Meta-analysis[134]	Morbid obesity	Influenza A (H1N1)	..	RR 4·4 (1·8–10·4)	..
Case-control, population-based[135]	Obesity	Influenza A (H1N1)	..	OR 9·1 (4·4–18·7)	..
Case-control, population-based[135]	Diabetes	Influenza A (H1N1)	..	OR 1·5 (0·8–2·8)	..
Case-control, population-based[136]	Obesity	Influenza A (H1N1)	..	..	OR 3·1 (1·5–6·6)
Case-control, population-based[136]	Morbid obesity	Influenza A (H1N1)	..	OR 4·7 (1·3–17·2)	OR 7·6 (2·1–27·9)
Retrospective[137]	Diabetes	Influenza A (H1N1)	PR 3·10 (2·0–4·7)	OR 4·29 (1·3–14·3)	..
Meta-analysis[138]	Obesity	SARS-CoV-2	..	Hospitalisation: OR 2·36 (1·4–4·1); ICU admission: OR 2·32 (1·4–3·9), IMV support: OR 2·63 (1·3–5·3)	OR 1·49 (1·2–1·9)
Retrospective, population-based[139]	Obesity	SARS-CoV-2	..	Mechanical support class I obesity: OR 1·54 (1·3–1·8); class II: OR 1·88 (1·5–2·3); class III: OR 2·08 (1·7–2·6)	Class III obesity: HR 1·26 (1·0–1·6)
Retrospective, population-based[140]	Obesity	SARS-CoV-2	..	Overweight: OR 1·39 (1·13–1·71); obesity stage I: OR 1·70 (1·34–2·16); obesity stage II: OR 3·38 (2·60–4·40)	..
Meta-analysis[141]	Diabetes	SARS-CoV-2	..	..	OR 1·75 (1·3–2·36)
Meta-analysis[142]	Diabetes	SARS-CoV-2	..	OR 2·75 (2·09–3·62)	OR 1·90 (1·37–2·64)
Meta-analysis[143]	Diabetes	SARS-CoV-2	..	..	OR 2·63 (2·1–3·3)
Meta-analysis[143]	Obesity	SARS-CoV-2	..	..	OR 1·72 (1·0–2·9)
Population-based[144]	Hyperglycaemia	SARS-CoV-2	..	..	HR 1·80 (1·0–3·2)
Population-based[145]	Diabetes	SARS-CoV-2	..	Oxygen treatment: OR 1·35 (1·1–1·7); ventilator use: OR 1·93 (1·3–2·9)	OR 2·66 (1·9–3·73)
Population-based[146]	Type 1 diabetes	SARS-CoV-2	..	..	HR 2·23 (1·47–3·30)
Population-based[146]	Type 2 diabetes	SARS-CoV-2	..	..	HR 1·61 (1·47–1·77)
Population-based[147]	Type 1 diabetes	SARS-CoV-2	..	..	OR 3·51 (3·16–3·90)
Population-based[147]	Type 2 diabetes	SARS-CoV-2	..	..	OR 2·03 (1·97–2·09)
Retrospective[148]	Type 2 diabetes	SARS-CoV-2	..	OR 2·24 (1·84–2·73)	..
Retrospective, population-based[149]	Type 1 diabetes	SARS-CoV-2	..	OR 2·40 (1·8–3·2)	..
Retrospective, population-based[149]	Type 2 diabetes	SARS-CoV-2	..	OR 1·37 (1·28–1·47)	..
Retrospective, population-based[150]	Type 2 diabetes	SARS-CoV-2	..	..	HR 1·23 (1·14–1·32)
Retrospective, population-based[151]	Metabolic syndrome	SARS-CoV-2	OR 7·00 (6·1–8·0)	..	..
Retrospective, population-based[151]	Diabetes	SARS-CoV-2	OR 1·41 (1·3–1·5)	..	..
Retrospective, population-based[151]	Obesity	SARS-CoV-2	OR 2·20 (2·1–2·3)	..	..
Retrospective, population-based[151]	Hyperlipidaemia	SARS-CoV-2	OR 1·70 (1·6–1·7)	..	..
Retrospective, population-based[151]	NASH	SARS-CoV-2	OR 4·93 (4·1–6·0)	..	..
Meta-analysis[152]	Type 2 diabetes	SARS-CoV-2	OR 10·8 (10·3–11·4)	..	..

(Table 2 continues on next page)

	Metabolic disease	Viral infectious disease	Infection incidence (95% CI)	Infection–related severity (95% CI)	Infection–related mortality (95% CI)
(Continued from previous page)					
Meta-analysis[152]	Type 2 diabetes	Hepatitis C virus	OR 3·6 (2·7–4·9)	..	..
Meta-analysis[152]	Type 2 diabetes	HHV8	OR 2·7 (1·3–5·4)	..	..
Meta-analysis[152]	Type 2 diabetes	Influenza A (H1N1)	OR 2·1 (1·7–2·5)	..	..
Meta-analysis[152]	Type 2 diabetes	Hepatitis B virus	OR 1·6 (1·2–2·1)	..	..
Meta-analysis[152]	Type 2 diabetes	HSV1	OR 1·5 (1·1–2·0)	..	..
Meta-analysis[152]	Type 2 diabetes	Cytomeaglovirus	OR 3·5 (0·6–18·3)	..	..
Meta-analysis[152]	Type 2 diabetes	TTV	OR 2·9 (1·0–8·7)	..	..
Meta-analysis[152]	Type 2 diabetes	Parvovirus B19	OR 2·6 (0·7–9·1)	..	..
Meta-analysis[152]	Type 2 diabetes	Coxsackievirus B	OR 0·7 (0·3–1·5)	..	..
Meta-analysis[153]	Type 2 diabetes	Hepatitis C virus	OR 3·5 (2·5–4·8)	..	..
Meta-analysis[154]	Insulin resistance	Hepatitis C virus	..	RR 1·63 (1·3–2·0)	..
Meta-analysis[155]	Diabetes	SARS-CoV-2	..	..	RR 1·54 (1·4–1·6)
Meta-analysis[155]	Obesity	SARS-CoV-2	..	..	RR 1·45 (1·3–1·6)
Meta-analysis[156]	Diabetes	Varicella zoster virus	IRR 1·60 (1·3–1·9)	..	..
Meta-analysis[157]	Diabetes	Varicella zoster virus	RR 1·38 (1·2–1·6)	..	..
Meta-analysis[158]	Diabetes	Dengue virus	..	OR 4·38 (2·6–7·4)	..
Meta-analysis[159]	Diabetes	Dengue virus	..	OR 2·88 (1·7–4·8)	..
Meta-analysis[160]	Diabetes	Dengue virus	..	..	OR 3·70 (1·2–11·4)

HR=hazard risk ratio. IMV=intermittent mandatory ventilation. IRR=incidence rate ratio. OR=odds ratio. PR=prevalence rate. RR=relative risk.

Table 2: **Studies investigating the association of metabolic diseases with viral infection incidence and severity**

In people with obesity and SARS-CoV-2, high leptin and IL-6 production by adipose tissue might increase the risk of a cytokine storm.[170] Additionally, high glucose levels correlate with a reduction in T follicular regulatory cells and with the disruption of T cell and monocyte function via a HIF-1a or glycolysis-dependent mechanism.[171,172] Altogether, an altered immune system function in metabolic diseases predispose patients to an inadequate and delayed immune response to viral infections, followed by an increased risk of developing a cytokine storm.

Mechanisms facilitating viral entry into the body

An intact gut mucosal epithelium is an important barrier against transportation of pathogenic viruses from the lumen to the circulatory system. Some gut bacteria might further enhance mucosal barrier function or produce antimicrobial compounds with virucidal properties.[79] In obesity, type 2 diabetes and NAFLD, considerable alterations in the gut microbiome have been observed (dysbiosis), which increase intestinal permeability.[173,174] This leaky gut model can increase susceptibility to either systemic infections due to viral transportation, or bacterial superinfections due to dysfunctional immune system responses caused by the preceding viral infection.[175] Changes in the gut microbiome composition have also been observed during SARS-CoV2 infection and persisted after disease resolution. The concentrations of inflammatory cytokines and chemokines correlated with gut microbiota composition in SARS-CoV-2 infection.[176] Furthermore, other factors present in metabolic diseases might affect virus entry at the cellular level. For example, it was reported that the glucose-like metabolite 1,5-anhydro-D-glucitol can bind directly to the SARS-CoV-2 spike protein and inhibit virus entry to the host cell. Patients with type 2 diabetes have low levels of 1,5-anhydro-D-glucitol, which might explain why they are prone to more severe infection with SARS-CoV-2.[177] Finally, as mentioned earlier, adipose tissue can serve as a chronic reservoir for several pathogens.[13,14,29,30,72] Therefore, whether people with obesity and high adipose tissue mass are more susceptible to the chronic effects of specific viral infections needs further investigation.

Pre-existing endothelial dysfunction or coagulopathy and severe disease during viral infection

Vascular endothelial cells have pleiotropic functions and are important for maintaining vascular integrity, transporting nutrients, regulating blood flow by vaso-constriction and vasodilatation, controlling coagulation, and modulating inflammatory response. In type 2 diabetes, endothelial dysfunction is characterised by increased oxidative stress, expression of proinflammatory, pro-thrombotic factors and vasoconstrictors, decreased levels of vasodilators, and decreased activity of nitric oxide synthase.[178] Thus, endothelial dysfunction increases vasoconstriction and inflammation, and together with platelet hyperactivity, might promote thrombosis and atherosclerosis.[178] Consequently,

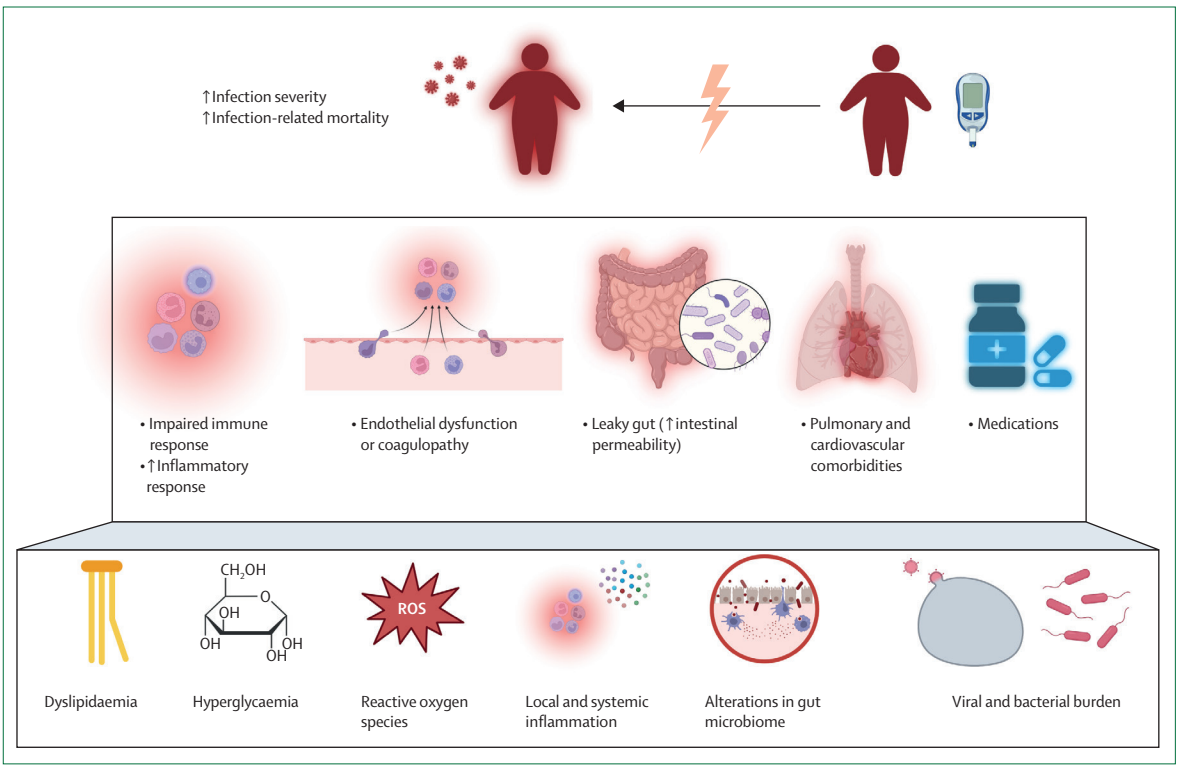

Figure 3: **Factors affecting infection severity and infection-related mortality in patients with metabolic diseases**
Hyperglycaemia, dyslipidaemia, increased reactive oxygen species, and chronic subclinical inflammation lead to considerable alterations in both the innate and adaptive immune systems, which are important for delayed impaired immune response and higher risk for a cytokine storm during viral infection, in patients with metabolic diseases. Endothelial dysfunction, platelet activation, and coagulopathy can also increase the risk of thrombosis and microvascular complications. Furthermore, high glucose predisposes endothelial cells to a more profound inflammatory response during viral infection that can impair the pulmonary epithelial-endothelial barrier, thus causing severe lung damage. In metabolic diseases, profound changes in gut microbiome increase its intestinal permeability, which potentially facilitates viral or bacterial entry and thus, the risk of viral infection or bacterial superinfection (leaky gut). Patients with metabolic syndromes often have already established structural and functional lung abnormalities, and macrovascular and microvascular complications (pulmonary and cardiovascular comorbidities) that can be further aggravated or manifest overtly during stress and hypoxic conditions caused by viral infections. Last, medications that are commonly used to treat metabolic diseases can have an effect on the course of viral infections or conversely, medications that are commonly used during infection might further aggravate metabolic diseases or lead more frequently to drug-induced liver injury. Figure created with BioRender.com.

patients with type 2 diabetes are predisposed to an increased risk of vascular complications that can be further aggravated during infection. Apart from the development of thrombosis, endothelial dysfunction has been shown to impair pulmonary function by modulating inflammatory responses. Specifically, pulmonary endothelial cells are the major cytokine producers in the lung during influenza A virus infection.[179] Exposure of endothelial cells to high glucose further induces a proinflammatory cytokine response that contributes to the impairment of the epithelial junctional complex and to the damage of the pulmonary epithelial–endothelial barrier.[180] Similarly, endothelial cell infection and pulmonary and vascular endothelitis have been observed in SARS-CoV-2 infection, and correlate statistically significantly with COVID-19 associated death.[181] Therefore, pre-existing endothelial dysfunction might increase the severity of a viral infection both by increasing thrombosis risk and by promoting lung damage by enhancement of inflammatory responses.

Pulmonary, cardiovascular, and renal comorbidities as additional risk factors for severe infection

People with obesity, diabetes, or metabolic syndrome often present with structural and functional lung abnormalities. These include lower forced vital capacity and forced expiratory volume in one second, lower diffusion capacity and higher airway resistances, more frequent pulmonary fibrosis, hypertension and interstitial injury, and higher risk of hypoventilation-associated pneumonia.[182,183] Furthermore, macrovascular and microvascular complications including cardiovascular disease, stroke, and kidney disease are often already present in patients with metabolic diseases and can be aggravated and manifest overtly during stress and hypoxic conditions that are caused by many infections.

The role of drugs in protecting or promoting severe viral infections

Medications that are commonly used to treat metabolic diseases can have an effect on the course of viral infections. For example, among patients with type 2

diabetes and COVID-19, preadmission use of metformin, GLP-1RA, and SGLT2i were associated with higher mortality rates. Preadmission use of sulfonlyurea, thiazolidnedione or alpha-glucosidase inhibitors did not affect mortality.[82] Although the mechanisms involved in the potentially protective effects of these medications against severe SARS-CoV-2 infection remain largely unknown, it has been speculated that they might be anti-inflammatory, inhibit glycolysis that is often used by respiratory viruses, reduce oxidative stress, and improve endothelial function.[184,185] However, the epidemiological evidence might also be biased due to multiple confounding factors (eg, comorbidities such as the presence of cardiovascular disease, duration of diabetes, age, sex, and co-medication). Treatment initiation before or after an infection (at early or late stage) and treatment duration might play a role in the possible clinical benefit expected during a viral infection. For example, initiation of dapagliflozin treatment after SARS-CoV-2 infection in hospitalised patients with cardiometabolic risk factors did not provide statistically significant clinical benefit.[185] Similarly, metformin administration in people with overweight or obesity within 3 days of confirmed SARS-CoV-2 infection in a phase 3 clinical trial, did not prevent severe course of the disease.[186] However, in the same study, metformin reduced the incidence of post-COVID-19 condition by 42% over a 10-month follow-up period.[186] Other studies have suggested that statin use is associated with a reduction of all-cause mortality in COVID-19 and with protective effects against liver injury in HIV and HCV infections. Moreover, medications that are commonly used during infection, such as antibiotics, antivirals, immune-modulating drugs, and analgesics can further aggravate metabolic diseases and have severe side effects. For example, glucocorticoids such as dexamethasone that have been extensively used for COVID-19, can exacerbate hyperglycaemia or lead to new-onset diabetes.[187] Additionally, glucocorticoids are the leading cause of life-threatening hyperglycaemic hyperosmolar states among patients with diabetes. Furthermore, patients with obesity and metabolic syndrome often suffer from non-alcoholic steatohepatitis and are, therefore, more susceptible to drug-induced liver injury.[188]

Clinical relevance perspectives

The COVID-19 pandemic has led to extensive discussions about the necessary adjustments needed in the management of metabolic diseases during a pandemic. Detailed recommendations have been repeatedly published and primarily emphasise the need to maintain metabolic control at all times.[189] This maintenance is particularly important as during the COVID-19 pandemic, studies showed that people tended to lead a more sedentary lifestyle with unhealthier eating habits and often a restricted access to health care providers.[189] Importantly, the COVID-19 pandemic also made apparent the existence of a bidirectional relationship between metabolic and infectious diseases. Considering that epidemics and pandemics are expected to occur more frequently in the future,[4] it is now imperative to focus on better understanding the mechanisms involved in this bidirectional relationship, on developing effective prevention strategies for reducing the risk of development or progression of metabolic diseases after infection or conversely for reducing the risk of severe clinical course of an infection in patients with metabolic diseases and on optimising management and treatment of affected people. Specifically, the following areas are prominent knowledge gaps which need to be explored further.

Post-viral condition

The long term and long-lasting subtle effects of viral infections (even after virus clearance or loss of detection) on metabolism and their contribution to future metabolic disease development or aggravation, are under-investigated. This is both the case for viruses with high pathogenicity, and for viruses that are highly prevalent in the general population and associated with subclinical, uncomplicated disease courses (eg, herpesviruses or even SARS-CoV-2 with minimal clinical manifestations). Post-acute infection syndromes are observed in a considerable number of different viral infections but display a major overlap of symptoms and signs indicating the involvement of common pathophysiologic mechanisms.[39] However, in clinical settings, post-acute infection syndromes are still under-recognised and have ill-defined diagnostic criteria and no specified treatment strategies. Whether and by which mechanisms patients with metabolic diseases have an increased risk for post-viral sequelae, or conversely, whether and how post-infection sequelae induce or aggravate metabolic diseases, remains largely unknown. Implementation of clear diagnostic criteria, education of health-care providers, establishment of guidelines for adequate monitoring, and evaluation of different treatments are needed to improve management of post-viral conditions.

Risk stratification

Advancements in precision medicine have led in many cases, to the identification of subgroups of patients with the same disease, but with different disease trajectories. In people with type 2 diabetes, five subgroups with differing disease progression and risk of diabetic complications have been identified.[190] However whether these sub-phenotypes are also associated with increased infection susceptibility and severity, development of post-acute infection syndromes, or risk of metabolic derangement during and after infection remains to be seen. Future endeavours may include identifying new subgroups of people with metabolic disease and at a greater risk of a complicated course during and after an infection, or conversely, people at a high risk of

Search strategy and selection criteria

We searched PubMed and Google Scholar, with no language restrictions, for articles published up to May, 2023. Search items included: "viral infections", "virus", "HIV", "HCV", "Enterovirus", "Coxsackievirus", "COVID-19", "Herpes", "CMV", "Influenza", "long COVID", "post-acute infection syndromes" "SARS-CoV-2", "diabetes", "metabolic syndrome", "obesity", "hyperglycaemia", "hyperglycemia", "NAFLD", "steatosis", and "microbiome". The reference lists of original articles, narrative reviews, clinical guidelines, systematic reviews, and meta-analyses were screened for relevant publications. The final reference list was selected on the basis of relevance to the topic of this Review.

developing a metabolic disease following a viral infection. For example, following SARS-CoV-2 infection, epidemiologic studies showed that the risk ratio for new onset diabetes depended on age, sex, socioeconomic factors, hospitalisation, pre-existing metabolic state, comorbidities, and the time since infection.[191,192] Since it would be almost impossible to screen all the affected population, we can use the information from such studies to prioritise monitoring of metabolic disease development or progression following infection in specific high-risk groups. The identification of high-risk groups can decrease the cost, time, and chance of failure in clinical studies. Such studies might focus on preventive measures or interventions to reduce the risk of development or progression of a metabolic disease after an infection. Conversely, they might focus on identifying management strategies to decrease the risk of severe infection in people with metabolic diseases.

Evaluation of treatments

There is limited information about the possible effects of lifestyle interventions or medications targeting metabolic diseases on infection susceptibility or severity. Most evidence so far has been derived from epidemiological studies that have important limitations due to confounding factors (eg, age, duration of metabolic disease, comorbidities, etc.). More randomised clinical trials, such as the ones performed for dapagliflozin and metformin in patients with SARS-CoV-2 infection[185,186] that will evaluate the effect of anti-diabetic, anti-obesity, and anti-hyperlipidaemic medications in infection susceptibility and severity are needed. Similarly, preclinical studies assessing the response to common infections in animal models of obesity, diabetes or NAFLD, and the effect of pharmacological and non-pharmacological interventions can provide important mechanistic insights. Conversely, preclinical and clinical studies should also focus on assessing the effect of vaccinations and anti-viral treatments on the trajectories of metabolic disease development and progression.

Conclusions

A considerable lack of information remains regarding the mechanisms governing the bidirectional relationship between metabolic diseases and viral infectious diseases. This includes information related to virus type or metabolic sub-phenotypes, the acute versus long-term effects of infections on metabolic health, and the best preventive or therapeutic measures to reduce either the risk of metabolic disease development and aggravation, or the risk of severe infection in people with metabolic diseases. A large cause for these knowledge deficits could be the limited scientific awareness on the interactions between viruses and metabolic disease. The COVID-19 pandemic led to increased public awareness both about preventive measures against the spread of infectious diseases and about the presence of clinically vulnerable people who are at high risk for severe or even life-threatening complications. Furthemore, the COVID-19 pandemic increased multidisciplinary discussions and research efforts from scientists with complementary expertise, such as from infectiologists, diabetologists, endocrinologists, immunologists, and cardiologists. Going forward, it will be important to train a new generation of scientists, clinicians, and health-care personnel with a combined knowledge in both the fields of metabolic and infectious diseases. This training will further understanding of complex cross-specialty scientific questions in a timely manner, increase health-care providers and public awareness, and lead to more effective preventive and treatment strategies aiming to improve overall health, while simultaneously preparing us for future pandemics.

Contributors

NP wrote several sections of the Review and all other authors wrote smaller sections. NP and MG prepared the tables and figures. All authors reviewed successive drafts of the Review, approved the final submitted version, and had final responsibility for the decision to submit for publication.

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