Review Article

Dissecting the interaction between antiviral medication and diabetes mellitus

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) due to defects in insulin secretion, insulin action, or both. Infectious diseases caused by various viruses can impact human health. Studies have demonstrated that antiviral medications may be linked to the development of diabetes or the exacerbation of existing diabetes mellitus. This mini-review aims to summarize the current evidence on the effects of antiviral agents on blood glucose levels. Research has revealed that some antiviral drugs, such as Ribavirin, Remdesivir, Interferon-α, Lopinavir, Ritonavir, and Zidovudine, have the potential to increase the risk of developing diabetes mellitus or worsening preexisting diabetes. However, Raltegravir's impact on diabetes mellitus remains controversial. Therefore, it is suggested that blood glucose, insulin, glutamic acid decarboxylase, and islet cell autoantibody levels be measured before and during antiviral therapy.

Keywords: Diabetes Mellitus-Insulin-Antiviral Medication-Viral Infections

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin secretion, insulin resistance, or both (1, 2). In type 1 diabetes, the autoimmune destruction of pancreatic β-cells leads to absolute insulin deficiency, whereas type 2 diabetes arises from insulin resistance in peripheral tissues and progressive β-cell dysfunction. Other forms, such as gestational diabetes, also contribute to the global burden (3). The worldwide prevalence of diabetes has risen dramatically, affecting over 537 million adults (aged 20–79 years) in 2021, with projections exceeding 783 million by 2045 (4, 5). This increase is driven by aging populations, urbanization, sedentary lifestyles, and obesity, with low- and middle-income countries bearing the greatest burden (6).

Viruses are microscopic infectious agents that can replicate only inside the living cells of a host organism (7). Unlike bacteria, viruses are not considered fully alive because they lack the cellular machinery required for metabolism and reproduction on their own. Instead, they rely on infecting host cells to hijack their biochemical processes and produce new viral particles. Viruses consist of genetic material, either DNA or RNA, encased in a protein coat called a capsid, and some possess an additional lipid envelope derived from the host cell membrane (7).

Antiviral drugs are medications designed to treat viral infections by inhibiting viral replication without severely harming host cells. These drugs can minimize infection symptoms, shorten its duration, and help reduce virus transmission (8). Although antiviral medications are crucial for treating viral infections, they often come with side effects ranging from mild to severe. Based on clinical observations, some antiviral drugs have been suggested to affect diabetes (9). Evidence indicates that certain antivirals may be linked to altered blood sugar levels, either increasing the risk of hyperglycemia or worsening insulin resistance (10). This review aims to summarize data on the relationship between antiviral medications and diabetes, exploring the impact of antiviral drugs on blood glucose levels and management strategies for diabetic patients undergoing antiviral therapy.

Ribavirin

Ribavirin is an antiviral medication used to treat various viral infections. Acting as a guanosine analogue, it inhibits inosine monophosphate dehydrogenase, thereby reducing the GTP pool. Additionally, Ribavirin inhibits viral mRNA polymerase activity by binding to the nucleotide site, limiting viral replication and protein synthesis (11). This medication is effective against a diverse array of RNA and DNA viruses, including hepatitis C virus (HCV) and Lassa virus (LASV) (12).

Ribavirin can stimulate the immune system, leading to increased production of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), which may result in acute pancreatitis (13). While Ribavirin itself does not appear to have strong diabetogenic effects, its combination with interferon-alpha (IFN-α), a previous standard treatment for HCV, has been associated with disturbances in glucose metabolism, potentially increasing the risk of diabetes in susceptible individuals.

For example, after receiving a combination of Ribavirin and IFN-α for three months to treat chronic HCV, a 61-year-old man tested positive for glutamic acid decarboxylase and islet-cell autoantibodies. As a result, he developed type 1 diabetes mellitus and required daily insulin therapy (14). In another study, 189 non-diabetic individuals with chronic HCV infection were treated with IFN-α and Ribavirin from 2002 to 2005. Their blood glucose levels were consistently monitored before and after the treatment period. The results indicated that five patients developed type 1 diabetes mellitus (2.6%), three patients developed type 2 diabetes mellitus (1.6%), and one patient developed an unspecified form of diabetes mellitus (15).

The molecular mechanism by which the combination of Ribavirin and IFN-α leads to diabetes development is not completely understood. However, it has been suggested that this combination affects glucose metabolism by inducing insulin resistance (reducing cellular glucose uptake), impairing pancreatic β-cell function (interferon can trigger autoimmune damage), and increasing inflammatory cytokines, worsening metabolic dysfunction. Patients at higher risk for diabetes during Ribavirin therapy include those with pre-diabetes or metabolic syndrome, obesity or visceral adiposity, chronic HCV infection (HCV itself promotes insulin resistance), and concurrent interferon therapy.

Ritonavir

Ritonavir is a protease inhibitor used in the management of HIV/AIDS. It blocks the liver cytochrome P450-3A4 (CYP450-3A4) pathway, which is responsible for metabolizing other protease inhibitors. This inhibition

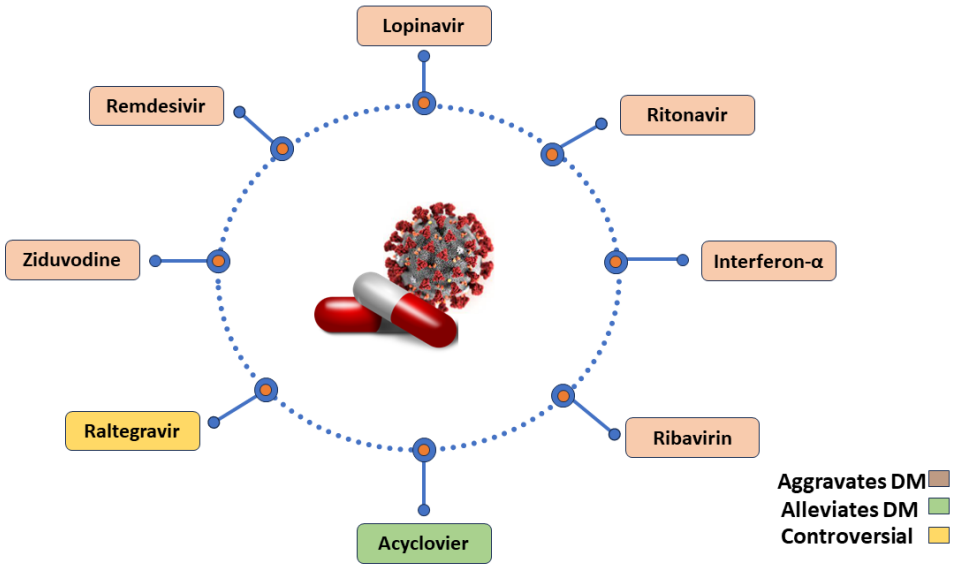

Figure 1. The effect of different antiviral drugs on diabetes development

reduces the breakdown of antiviral medications, thereby increasing serum drug concentrations (16, 17).

Ritonavir has been reported to be associated with metabolic disturbances, including insulin resistance and new-onset diabetes. It inhibits GLUT4-mediated glucose uptake in peripheral tissues (e.g., muscle, fat), thereby reducing insulin sensitivity. In healthy volunteers, a single 800 mg dose of Ritonavir decreased insulin sensitivity by 15% and non-oxidative glucose disposal by 30%. Additionally, Ritonavir decreases IRS-1 tyrosine phosphorylation and hinders the translocation of GLUT4 to the cell membrane (18, 19).

This finding was confirmed in a study by Vyas et al., which demonstrated that Ritonavir can induce peripheral insulin resistance in mice (20). Furthermore, Dejkhamron et al. evaluated the impact of lopinavir/ritonavir on 28 HIV-infected children. Their findings indicated that among the participants, the prevalence of insulin resistance was 42.9% (12/28), pre-diabetes mellitus was 10.7% (3/28), and hypertriglyceridemia was 75.0% (21/28) (21).

Lopinavir

Lopinavir is an antiretroviral protease inhibitor commonly used in HIV infection therapy, often in combination with Ritonavir as a booster (22). It affects HIV by binding to the catalytic site of HIV-1 aspartate protease, thereby inhibiting the cleavage of viral polyprotein precursors into mature, functional proteins essential for viral replication (23).

Lopinavir has been associated with metabolic disturbances, including potential effects on glucose metabolism and diabetes development. It upregulates protein tyrosine phosphatase 1B (PTP1B), leading to the inactivation of the insulin receptor. Additionally, it can induce phosphorylation of IRS-1 in the insulin signaling pathway, ultimately causing insulin resistance (24, 25).

In a study conducted by Noor et al., which included 30 HIV-seronegative healthy adults, the effects of Lopinavir, Ritonavir, and Atazanavir on insulin-stimulated glucose disposal were investigated by monitoring blood sugar and insulin levels. The study found that the administration of Atazanavir to healthy individuals over a 5-day period did not affect insulin sensitivity. However, Lopinavir and Ritonavir were linked to the development of insulin resistance in the participants (26).

In HIV-negative men, four weeks of Lopinavir and Ritonavir did not significantly alter fasting glucose or insulin-mediated glucose disposal but did worsen glucose tolerance during oral glucose tolerance tests (OGTT) (27). Furthermore, the combination of Lopinavir and Ritonavir increased triglycerides, very low-density lipoprotein (VLDL) cholesterol, and free fatty acids, all of which are associated with insulin resistance in healthy volunteers (28).

Remdesivir

Remdesivir is administered to manage coronavirus disease 2019 (COVID-19) in hospitalized patients and individuals at high risk of progressing to hospitalization or mortality. Its mechanism of action involves the inhibition of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), a key enzyme necessary for viral replication and the production of circulating virions in the body (29).

Remdesivir functions as a prodrug that enters cells and undergoes metabolism to form the active compound, remdesivir triphosphate (RDV-TP). RDV-TP competes with adenosine triphosphate (ATP) for integration into developing SARS-CoV-2 viral RNA, leading to delayed chain termination and interference with viral replication (30).

Rachel et al. demonstrated a significant increase in random blood sugar levels in COVID-19 patients who received antiviral drugs such as Lopinavir and Ritonavir (31). Kim et al. studied 931 hospitalized patients diagnosed with COVID-19 who received Remdesivir as part of their treatment regimen. The findings indicated that 6.3% of patients who received Remdesivir experienced hyperglycemic adverse events, with hyperglycemic complications being more common in patients older than 65 years (32). In another study, Remdesivir was associated with hyperglycemia in 32 COVID-19 patients (33).

Acyclovir

Acyclovir is a widely used antiviral medication for herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. Recently, it has been investigated for its potential effects on diabetes development. Emerging research suggests that Acyclovir may influence glucose metabolism, though findings are mixed—some studies indicate beneficial effects on insulin resistance, while others highlight potential risks in diabetic patients (34).

Recent preclinical studies demonstrate that Acyclovir may improve insulin sensitivity in diabetic models. It activates pyruvate kinase M1 (PKM1), which stimulates the AMPK/SIRT1 signaling pathway—a key regulator of glucose metabolism and insulin sensitivity. This activation leads to reduced oxidative stress, lower blood lipid levels, and improved glucose uptake in liver cells (35). In diabetic mice, Acyclovir treatment significantly lowered blood glucose levels and improved insulin resistance, suggesting potential as a repurposed antidiabetic drug (35).

Despite its potential benefits, Acyclovir use in diabetic individuals carries specific risks, particularly related to kidney function. Diabetic patients, especially the elderly, are at higher risk of acute kidney injury (AKI) due to Acyclovir-induced renal tubular crystal deposition. A

case study reported severe AKI and neurotoxicity in an elderly diabetic patient receiving Valacyclovir (an Acyclovir prodrug) (36).

Taken together, Acyclovir exhibits dual implications in diabetes. Further clinical trials are needed to validate its antidiabetic potential and optimize dosing strategies for diabetic populations. For now, clinicians should weigh its benefits and risks, particularly in elderly or renally compromised patients.

Interferon Alpha (IFN-α)

Interferon alpha (IFN-α) is an immune-regulating signaling protein with antiviral and antiproliferative properties. It is a type I interferon produced by cells in response to viral infections and serves as a key component of the innate immune response. IFN-α has been extensively used to treat viral hepatitis, including hepatitis C, where it is often administered in combination with Ribavirin and protease inhibitors (37).

In non-obese diabetic (NOD) mice, IFN-α is upregulated in pancreatic lymph nodes early in life (3–4 weeks), initiating autoimmune diabetes. Blocking IFN-α receptor signaling delays diabetes onset and reduces incidence by promoting immune tolerance, including increased production of IL-4 and IL-10 (38). Additionally, IFN-α triggers apoptosis of pancreatic beta cells through activation of the NF-κB pathway. The resulting apoptotic material stimulates an autoimmune reaction against beta cells (39).

Fabris et al. reported 31 cases of type 1 diabetes associated with IFN-α treatment in patients with chronic hepatitis C infection. Their study revealed a 3–7% increase in islet cell and glutamic acid decarboxylase autoantibody levels in individuals who underwent IFN-α therapy (40). However, Piquer et al. evaluated 277 non-diabetic patients who received IFN-α for 24 weeks following hepatitis C virus infection and found that beta-cell autoimmunity markers—such as islet cell, glutamic acid decarboxylase, and anti-islet antigen 2 autoantibodies—were not significantly associated with IFN-α therapy (41).

Tanaka et al. documented a case in which a 51-year-old man developed type 1 diabetes after receiving IFN-α treatment for 24 weeks (42).

Raltegravir

Raltegravir is the first integrase inhibitor approved for clinical use in treating HIV-1 infection (43). It targets the viral enzyme integrase, which catalyzes the integration of viral DNA into the host chromosome (43). Raltegravir has been studied for its potential impact on glucose metabolism and diabetes risk. The evidence presents mixed findings, with most studies suggesting no significant association between Raltegravir and diabetes development, though some conflicting data exist. A 96-week randomized trial found that insulin resistance (measured by HOMA-IR) increased following Raltegravir use in a prospective open-label randomized study (44). However, a review of 10 studies involving 62,400 participants found no significant difference in diabetes incidence among patients receiving integrase strand transfer inhibitors, including Raltegravir (45).

Zidovudine (AZT)

Zidovudine, also known as azidothymidine (AZT), is a synthetic nucleoside thymidine analogue categorized as a nucleoside reverse transcriptase inhibitor (NRTI). It interferes with HIV-1 reverse transcriptase, preventing the synthesis of DNA from viral RNA (46).

Zidovudine has been associated with the development of diabetes mellitus in people living with HIV. A case study described a Chinese man who developed diabetes mellitus (glucose level of 31.8 mmol/L, HbA1c 8.5%) while on Zidovudine. After discontinuing Zidovudine and switching to another antiretroviral, his hyperglycemia improved, and he no longer required diabetic medications, suggesting a direct link between Zidovudine and reversible diabetes (47).

A clinical trial found that a regimen containing Zidovudine/Lamivudine contributed to insulin resistance within just three months of starting therapy. Patients experienced a 25% decrease in insulin-mediated glucose disposal and a 22% increase in fasting lipolysis, independent of changes in body composition (48).

A large South African cohort study involving 56,298 patients found that Zidovudine exposure was associated with an increased risk of incident diabetes (HR 1.27, 95% CI: 1.10–1.46), along with Stavudine and Efavirenz (49). Similarly, another study conducted in British Columbia, Canada, involving older HIV patients (≥50 years), concluded that prolonged exposure to older nucleoside reverse transcriptase inhibitors, such as Zidovudine and Stavudine, significantly increased diabetes risk (50).

This study examined the relationship between various antiviral medications and diabetes mellitus in patients undergoing antiviral therapy. The data suggest that the relationship between antiviral drugs and diabetes development is complex. While some antiviral drugs contribute to diabetes development—particularly in HIV therapy—others may offer new strategies for preventing or treating type 1 diabetes by targeting viral triggers. Further research is needed to optimize antiviral therapies, minimize metabolic side effects, and explore vaccines against diabetes-associated viruses. This dual role highlights the importance of personalized medicine in managing both viral infections and diabetes risk.

Conflict of Interest

The authors have nothing to declare.

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