

# Metformin Might Inhibit Virus through Increasing Insulin Sensitivity

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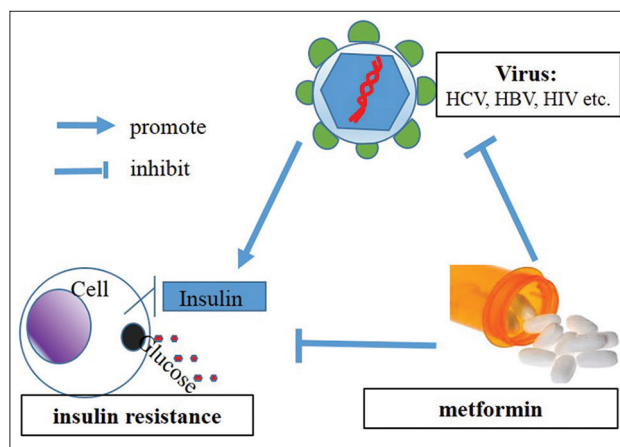
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To the Editor: Metformin is believed to be the most widely used medication for diabetes as well as the first-line medication for the treatment of type 2 diabetes, especially in patients who are overweight. Metformin is described as a magic medicine currently due to its broad range of potential benefits for polycystic ovary syndrome, cardiovascular disease, and various cancers and even prolonged lifespan. Recently, limited *in vitro* and *in vivo* research suggests that metformin may have inhibitory effect on virus, especially hepatitis C virus (HCV). Besides, it would be amazing if metformin possess antiviral function in hepatitis B virus (HBV), human immunodeficiency virus (HIV), etc., to benefits virus-infected patients from other aspects of mechanism.

Multiple potential action mechanisms of metformin have been proposed including inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase, inhibition of glucagon-induced elevation of cyclic adenosine monophosphate with reduced activation of protein kinase A, inhibition of mitochondrial glycerophosphate dehydrogenase,<sup>[1]</sup> as well as an effect on gut microbiota. It is supported by several experimental, clinical, and epidemiological data that insulin resistance (IR) is a pathological condition in which cells fail to respond normally to insulin. Virus infection has been demonstrated to have effects on glucose metabolism, leading to IR and, in predisposed individuals, type 2 diabetes. Metformin is an insulin-sensitizing agent. Although the mechanism of metformin inhibiting virus is unclear, it might regulate insulin sensitivity and benefit body antiviral function [Figure 1].

Epidemiological investigation showed that chronic HBV infection is associated with IR. In an *in vitro* study, a notably inhibitory effect on hepatitis B surface antigen (HBsAg) production, as well as a moderate inhibition in HBV replication and HBeAg expression, was observed by following metformin treatment. When administered in combination, metformin enhanced the inhibitory effects of interferon- $\alpha$ 2b on HBsAg expression and HBV replication and provided a complimentary role in HBsAg expression for lamivudine. This novel action of metformin derives partially from its inhibition on multiple HBV *cis*-acting elements.<sup>[2]</sup>

Epidemiological studies have indicated that HCV infection is related to IR and type 2 diabetes. Chronic HCV patients with



**Figure 1:** Although the mechanism of metformin inhibits virus is unclear, it might regulate insulin sensitivity and benefit body antiviral function.

IR and type 2 diabetes appear to have a decreased response to the standard pegylated-interferon-alpha and ribavirin antiviral therapy. Based on clinical observation, it is believed that IR is an independent predictor of the response to antiviral therapy in chronic hepatitis C patients treated with peg-interferon plus ribavirin and IR associated with nonresponse of chronic hepatitis C treatment. Sustained virological response decreases when insulin sensitivity is impaired, and it is referred that improving insulin sensitivity may be a useful adjunct to antiviral therapy in chronic hepatitis C patients. Clinical research demonstrated that sustained virological response was improved by adding metformin to the standard of care for patients with chronic hepatitis C genotype 1 and IR. Metformin improved IR in more than 50% of patients and increased virological response rate in 10% of patients with hepatitis

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C genotype 1 and homeostasis model assessment (HOMA) >2. Viral clearance was significantly higher in the metformin group at weeks 24 and 48, supporting the proposition of a better antiviral activity of peg interferon and ribavirin in patients receiving metformin.<sup>[3]</sup>

As IR plays a crucial role in hepatocarcinogenesis, improving IR may be an attractive approach to improve the prognosis of HCV cirrhosis. Nkontchou *et al.*<sup>[4]</sup> assessed the influence of metformin treatment on the prognosis of compensated HCV cirrhosis in patients undergoing type 2 diabetes. The results proved that among the patients with type 2 diabetes and HCV cirrhosis, compared with those who are not treated with metformin, the use of metformin is independently associated with reduced incidence of hepatocellular carcinoma and liver-related death/transplantation.

HIV-infected individuals have a higher risk of death that attributed to the increasing incidence of noncommunicable diseases, such as atherosclerotic cardiovascular diseases and diabetes mellitus. Hyperlipidemia and impaired glucose tolerance were commonly observed in HIV-infected patients. This is driven partly by the emergence of metabolic disorders, particularly dyslipidemia, IR, and lipodystrophy, in those achieving antiretroviral therapy. The HIV-lipodystrophy syndrome is associated with fat redistribution and metabolic abnormalities, including IR. HIV-infected youth with IR have lower mitochondrial respiration markers in comparison with youth without IR. Disordered mitochondrial respiration may be a potential mechanism for IR in this population. Coll *et al.*<sup>[5]</sup> investigated the effects of rosiglitazone or metformin on fasting and postprandial inflammatory and antioxidant variables in HIV-infected males with lipodystrophy. Before treatment, inflammatory variables remained unchanged, but there was a postprandial decrease in high-density lipoprotein cholesterol and paraoxonase (PON1) activity. Rosiglitazone and metformin reduced HOMA index similarly (−34% and −37%, respectively,  $P < 0.05$  for each). Both treatments increased fasting and postprandial PON1 activity and decreased postprandial monocyte chemoattractant protein 1 concentrations. This investigation may confer the protection effects of metformin against accelerated atherosclerosis in HIV-infected patients in association with lipodystrophy.

Metformin is one of the most popular antidiabetic drugs in the clinic. IR exists in virus infection patients, especially HCV, which had been broadly investigated. Adding metformin to pegylated-interferon-alpha and ribavirin therapy was reported to increase the response rate in chronic HCV patients. Besides, it has been suggested that this effect derives from an improved antiviral action of interferon.

The virus inhibitory function of metformin is still debatable. Therefore, more basic and clinical studies are needed to illuminate the underline mechanism as well as explore its application in real bedside world.

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### Conflicts of interest

There are no conflicts of interest.

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