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Review Article

Role of Metformin in Viral Diseases

Harshita Joshi, Gyanesh Singh*
Department of Bioengineering and Biosciences, Lovely Professional University, Punjab, India

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ABSTRACT

Metformin is a guanidine compound originally derived from *Galega officinalis*. It stops hepatic gluconeogenesis and initiates glucose uptake in skeletal muscles. Metformin is currently the preferred treatment provided to the patients of type-2 diabetes. Sufficient evidence is there to show that metformin is also an anti-aging drug, although, proper and accurate mechanism of metformin is yet to be explained. Metformin is a widely available anti-diabetic agent with an outstanding safety profile, and clinical and preclinical evidence indicate that through enhanced *ACE2* expression, metformin may provide cardiopulmonary defence in COVID-19 and also may help in the treatment of other viral diseases like HIV, hepatitis B and C, influenza and more.

Keywords: Metformin, Virus, Viral disease, COVID-19, Hepatitis, HIV

***Correspondence:** Gyanesh Singh, Department of Bioengineering and Biosciences, Lovely Professional University, Punjab, India, E-mail: harshitajoshi2514@gmail.com

INTRODUCTION

Viruses are microscopic parasites, usually much smaller than bacteria. Outside of a host organism, they lack the potential to prosper and replicate. Viruses primarily have a reputation for being the source of contagion. There is little denying the widespread occurrences of sickness and death has strengthened such a legacy for viruses. Although such viruses are definitely wise enemies of science and medical practitioners, some have been instrumental as research tools, encouraging the understanding of fundamental cellular processes such as protein synthesis mechanics and viruses themselves. Viruses are smallest disease causing agents often in the size range of 0.02 to 0.3 μm, although, some viruses can be as large as 1 μm. To make viruses, viral genome (RNA or DNA) is surrounded by a protein coat and often enzymes that are necessary to activate viral replication. Viruses can reproduce only inside relevant host mammalian, plant, or bacterial cells, and are referred to as obligatory intracellular parasites as such.

On the limits of what is called life, viruses teeter. They include, on the one hand, the key elements that make up all living organisms: Nucleic acids, DNA or RNA (only one or the other may have any given virus). Viruses, on the other hand lack the ability to read and act upon the information found within these nucleic acids individually. Viruses are not categorised according to the diseases they cause; instead, depending on whether the nucleic acid is single-or double-stranded, whether a viral shell is present and their mode of replication, they are divided into separate families. Single-stranded RNA viruses are further classified based on whether they have RNA that is positive or negative. Within the nucleus of host cells, DNA viruses prefer to replicate, while RNA viruses usually do so in the cytoplasm.in this article we will focus on the role of metformin in the treatment of various viral diseases. Metformin, specifically in patients who are overweight, is considered to be the most commonly prescribed diabetes drug as well as the first-line medication for the treatment of type 2 diabetes. Because of its wide variety of possible benefits for polycystic ovary syndrome, cardiovascular disease and multiple cancers and even extended lifespan, metformin is currently characterised as a miracle drug. Limited *in vitro* and *in vivo* experiments have recently suggested that metformin could have an inhibitory effect on Hepatitis C Virus (HCV) viruses. In addition, if metformin has an antivirus role in Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV), etc., it will be great to help patients afflicted with viruses from other facets of the mechanism.

LITERATURE REVIEW

Several alternative mechanisms of metformin action have been suggested, including mitochondrial respiratory chain (complex I) inhibition, AMP-activated protein kinase activation, glucagon-induced cyclic adenosine monophosphate elevation inhibition with reduced protein kinase A activation, mitochondrial glycerophosphate dehydrogenase inhibition, as well as an effect on gut microbial dehydrogenase. A variety of laboratory, scientific, and epidemiological evidence support the fact that insulin resistance is a pathological disease in which cells do not naturally respond to insulin. Infection with the virus has been found to impair the absorption of glucose, contributing to IR and type 2 diabetes in predisposed individuals. Metformin is an agent that sensitizes insulin while the metformin inhibiting virus mechanism remains unknown, insulin sensitivity may be regulated and the body's antivirus role may benefit treatment of metformin-controlled non-diabetic person's. Inflammation by improving the metabolism of glucose and by regulation of such intracellular immunometabolic control points as a protein kinase activated by adenosin 5 monophosphate, rapamycin and mammalian target, in combination with rapamycin modification of microbiota. Excessive inflammation, specifically, a cytokine storm, is associated with the case incidence and fatality of COVID-19. Metformin, a commonly used medication for the treatment of Type 2 Diabetes (T2D) and metabolic syndrome, has immunomodulatory action that inhibits the development of macrophage-based pro inflammatory cytokines and allows Neutrophil Extracellular Traps (NETs) to form. Metformin also prevents the development of pathogenic Th1 and Th17 cells from cytokines. Importantly, in preclinical animal models, therapy with metformin alleviates different lung injuries. Moreover, a recent proteomic analysis has shown that metformin can directly inhibit SARS-CoV-2 infection. In addition, observational clinical trials have revealed that therapy with metformin decreases COVID-19 T2D mortality. Therefore, for the treatment of patients with COVID-19 at risk of contracting serious illness, metformin has the ability to be repurposed (Chen X, *et al.*, 2019).

COVID-19

Presently, Coronavirus Disease 2019 (COVID-19), caused by infection with SARS-CoV-2 has become a global disease. To date, no appropriate cure for acute lung injury has been identified. Triggered by viral infections metformin is a commercially licensed medication that is anti-diabetes medicine. In recent years,

metformin has been shown to that has not only immunomodulatory and antiviral functions, but also immunomodulatory and antiviral activities. It prevents different acute respiratory accidents in animal models. 332 protein interactions have been identified in a recent study between SARS-CoV-2 proteins and human-affinity proteins Analysis of purificationmass spectrometry (Gomez RM, *et al*. 2009).

The study has been finished and metformin was found to be capable of targeting the relationships between viral proteins and host factors, such as Nsp7 and Nsp7 viral proteins Human *NDUFA2, Orf9c* viral protein, and human *NDUFAF1* viral protein or *NDUFB9*, which has antiviral activity thus, Metformin has also been reported to have antiviral acts. In other viral diseases, by way of AMPK activation (Acosta SR, *et al*., 2017; Cheng F, *et al*., 2016; Xie W, *et al*., 2015; Honda M, *et al*., 2016). Such results mean that metformin may be used for SARS-CoV-2 infection as a possible therapeutic agent and other viral infections, especially when combined with other infections, agents with antiviral medications. In addition, SARS-CoV-22 can also be blocked by metformin. Infection by interfering with its ACE2 activity *via* The AMPK activation. Phosphorylates from AMPK, ACE2 Ser680. It enhances the expression of ACE2 in human endothelial cells and by boosting its stability. Metformin also improves the ACE2 phosphorylation and expression (Zhang J, *et al*., 2018). It is assumed phosphorylation can contribute to conformative and functional changes in the ACE2 receptor and reducing the binding of the receptor SARS-CoV-2 (Sharma S, *et al*., 2020). By binding to ACE2, the entry of SARSCoV-2 into cells down regulates its expression; it contributes to a renin-angiotensin-aldosterone deficit and method (RAS) of proinflammatory and prophibrotic promotion Repercussions. The RAS mismatch is likely to be averted by way of ACE2 expression upregulation by metformin (Sliva AC, *et al*., 2013). Accordingly, metformin would not only prohibit SARS-CoV-2 from entering, it would also prevent SARS-CoV-2 from entering. Its deleterious effects are also minimized.

Hepatitis B

One of the leading infections of the Hepatitis B Virus (HBV) is worldwide origins of chronic liver disease and the success of commercially available Chronic Hepatitis therapies B (CHB) is still not satisfactory (Dienstag JL, 2008). Authorized by the Interferon (IFNs) and nucleo (t) ide therapy In reducing HBV viremia, analogues (NAs) are effective; Monotherapy and its mixture, however, are fewer efficient against loss of HBV surface antigen (HBsAg), a reliable A desirable long-term prognosis predictor (Stein LL and Loomba R, 2009; J Hepato, 2012). Present drug regimens result in a reduction of HBsAg of less than after a 12 month span, 7 percent of HBeAg-positive patients IFN therapy and 3 percent, respectively, of NAs. The persistent rate of loss of HBsAg is considerably lower in Patients of HBeAg-negative (J Hepato, 2012). HBsAg is not only important for the production of HBV virions. It can also suppress host immune entry and hepatocyte entry, reactions to HBV (Patient R, *et al*., 2009; Brouw ML, *et al*. 2009). Animal experiments have proposed that the decline in clevudine antigenemia has led to the partial restoration of host immune responses and strengthened. The effects of therapeutic vaccinations (Menne S, *et al*., 2002) HBsAg antigenaemia are therefore now known as a novel antiviral target care. Metformin is an antihyperglycaemic agent and is commonly used and behaves preferentially in hepatocytes due to the elevated intracellular absorption *via* the organic liver-enriched mediator transporter cation 1 (American diabetes association, 2011; Viollet B, *et al*., 2012; Graham GG, *et al*., 2011). Apart from traditional use, metformin is meant for the treatment of type 2 diabetes mellitus. It is used in the treatment of cancer and illustrates multifaceted defense against numerous liver diseases, including liver damage, disease with non-alcoholic fatty liver, infection with hepatitis C virus, fibrosis of the liver and hepatocellular carcinoma in recent years human or livestock research (Viollet B, *et al*., 2012; Bergheim I, *et al*., 2006; Mazza A, *et al*., 2012; Lim JY, *et al*., 2012; Donadon V, *et al*., 2010; Chen HP, *et al*., 2013). It is hypothesized to be a negative regulator for HBV genome transcription, provided the co-ordinated regulation of genomic transcription of liver metabolism and HBV. Two metabolic regulators demonstrated the potential to inhibit HBV (Yishay BI, *et al*., 2011; Wakui Y, *et al*., 2010; Bader T and Korba T, 2010) transcription and gene expression. Therefore, we conducted this research to examine the impact of metformin on speech of HBsAg and replication of HBV and to assess a possible synergistic effect with *in vitro* IFN and NAs. Metformin has been found to be capable of substantially reducing the development of HBsAg and moderately Reduces replication of HBV and expression of HBeAg by Control over transcription. Metformin could, critically, work in its antiviral form, synergistically with LMV and IFN-a2b Repercussions. Actually, IFNs and NAs are used for the care of Infection of chronic HBV. Neither of them, though, nor their mixture essentially decreases the expression of HBV genes. Treatment with NAs could also be involved with a potential HBsAgg hepatocyte retention (Lau GK, *et al*., 2005; Marcellin P, *et al*., 2004; Zoulim F, 2012; Iser DM, *et al*., 2010; Warner N and Locarnini S, 2008). Therefore, the combination, based on our findings, with metformin could lead to HBV DNA synthesis suppression and the processing of proteins same day at the same time.

The results showed that metformin was capable of the transcriptional activities of HBV promoters are downregulated, giving a mechanistic explanation of this latest Effect. The great benefit of metformin over other medicines is its (Chong CR and Sullivan DJ, 2007; Graham GG, *et al*. 2011) described pharmacokinetics. Metformin has selective distribution in hepatocytes in contrast with rosiglitazone and simvastatin (Viollet B, *et al*., 2012; Wakui Y, *et al*., 2010). This makes it more relevant, for the treatment of HBV infection and valuable, considering the different actions of metformin as a modulator. Nonetheless, In order to assess its potential use as an anti-HBV, hepatic metabolism, *in vivo* tests and clinical confirmation are required on drugs.

Human Immunodeficiency Virus (HIV)

HIV (human immunodeficiency virus) is a virus that destroys cells that render a person more resistant to other infections and diseases by helping the body combat infection. It is transmitted by touching a person with HIV with certain body fluids, most commonly during unprotected sex (sex without a condom or HIV medication to prevent or treat HIV), or by sharing injection drug equipment. HIV will lead to the disease AIDS (Acquired Immunodeficiency Syndrome) if left untreated. The Human Immunodeficiency Virus (HIV) attacks the immune system and weakens the defense of people against many kinds of cancer and infections. Infected individuals eventually become immune deficient as the virus destroys and impairs the function of immune cells. Usually, immune function is assessed by the cell count of CD4.

Immunodeficiency results in increased vulnerability to a wide variety of viruses, tumors and other diseases that can be fought off by people with healthy immune systems. Depending on the person, the most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS), which can take several years to develop if not treated. The existence of such tumors, diseases or other significant long-term clinical manifestations describes AIDS.

HIV-infected people have a higher risk of death, which is attributed to the growing prevalence of non-communicable diseases, such as Such as coronary atherosclerotic disorders and diabetes mellitus. Commonly, hyperlipidemia and impaired tolerance to glucose were observed in patients infected by HIV. This is in part driven by the Apparition of metabolic disorders, especially dyslipidemia, IR, and lipodystrophy in antiretroviral therapy patients. The Fat redistribution is associated with HIV-lipodystrophy syndrome metabolic, including IR, and metabolic disorders. Infected by HIV Young people with IR have lower markers of mitochondrial respiration in youth comparison without IR.

Mitochondrial disorganization in this population, respiration can be a possible mechanism for IR (Coll B, *et al*., 2006). The effects of rosiglitazone or metformin have been studied on inflammatory and antioxidant factors for fasting and postprandial lipodystrophy in HIV-infected males. Before counselling, it remained unchanged for inflammatory variables, but there was a postprandial decrease in cholesterol in high-density lipoprotein and the activity of paraoxonase (PON1). Similarly, the HOMA index decreased (-34 percent and -37 percent respectively, for each, P <0.05). Both therapies improved fasting and postprandial activity of PON1 and reduction in postprandial monocytes protein-1 chemoattractant concentrations. This investigation could be subject to provide the protective effects of metformin against accelerated acceleration in association with HIV-infected patients, atherosclerosis through lipodystrophy.

Dengue virus

Dengue is the most common viral infection transmitted by arthropods and the number of recorded cases is growing in the Americans, even in Europe and the Western Pacifc (Murray, *et al*., 2013). It is caused by four serotypes of antigenically distinct The Flavivirus family of dengue viruses (DENV-1, DENV-2, DENV-3 and DENV-4), all of which are dengue viruses. Transmitted by mosquitoes from *Aedes aegypti* and *Aedes albopictus* (Simmons, *et al*., 2013). Estimated dengue infections of 390 million they occur each year worldwide, including 96 million with clinical symptoms. It is expected that Asia will have the highest strain of 273 million infections per year. Provided the pathogenesis of dengue, a complex interlinked mechanism is there are humoral and cell immune systems, inflammatory cytokines and chemical mediators (Martina, *et al*., 2009; Bhatt S, *et al*., 2013) including the possible risk of serious dengue manifestations among diabetic patients with metformin may be decreased because of immunomodulatory and anti-infammatory properties, care.

DISCUSSION

Against this backdrop of the rising incidence of dengue globally, the burden of noncommunicable diseases is increasing as well. Diabetes Mellitus (DM) is one of the most significant and prevalent in this group. According to the To the WHO, DM currently affects

347 million people worldwide and is estimated to be the seventh leading cause of death by 2030 (Danaei, *et al*., 2011). Metformin, which is part of all Oral Hypoglycemic Agents (OHAs) used to treat DM, is the most frequently prescribed and widely used ingredient is the biguanide family. Reduction of blood glucose by the action of metformin by suppressing gluconeogenesis 5 is achieved by Increasing sensitivity of peripheral tissue to Insulin (Mclntyre, *et al*., 1991) In addition, it has also been shown that metformin has multiple pleiotropic actions, including Anti-infamic 8 (Isoda, *et al*., 2006) immunomodulating, cardioprotective and vasculo-protective actions-anti-cancer, the growth of micro-organisms is reduced and limited. Metformin's awesome journey from herbal roots to the prestigious therapeutic agent was turbulent. They were found, forgotten, rediscovered, repurposed rejected, saved, rescued, exonerated and may have more secrets to share. Among pharmacotherapies, metformin is uncommon because it does not appear to have a single mechanistic goal: It counters insulin resistance and affects metabolic, vascular and vascular effects *via* various effects, other physiological functions that they are modest individually, but substantial collectively.

CONCLUSION

Metformin, the glucose-lowering market leader, T2DM control agents have a dynamic mechanism of multiple pathways are involved, some of which lead to anti-inflammatory activity that can help to reduce the risk of severe COVID-19 above the glucose regulation effects. Any preliminary information data from retrospective studies confirmed that there was a decrease in death rates among metformin users compared with those among non-users COVID-19 hospitalized T2DM patients. Caution is, however, required when interpreting these observational findings, since only RCTs are able to provide conclusive conclusions. Nonetheless, there are no negative signs of protection at least, so there is no Reason for stopping metformin therapy during infection with COVID-19 hypoxia and/or hypoxia, except in cases of extreme gastrointestinal symptoms or failure of multiple organs. Metformin is been used in various field. Metformin has shown really great results in the treatment of HBV infection, HIV, and dengue by affecting multiple pathways, supressing HBsAg production. To add metformin to treatment with pegylated interferon-alpha and ribavirin has been documented, increasing the response rate in patients with chronic HCV. In addition, it has this effect which was suggested to be derived from an improved antiviral interferon action. Metformin's virus-inhibitory function is still debatable. More basic and clinical studies are therefore needed to illuminate the as well as exploring its application in real terms, the emphasis mechanism world of bedside.

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