Connecting the Dots: How Herpes Viruses Influence Type 2 Diabetes: Insights from Experimental Researches

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Dear Editor,

Many infections are recognized to play a role in type 1 diabetes but nothing is known about their impact on type 2 diabetes. Type 2 diabetes is a metabolic condition which is characterized by hyperglycemia brought on by inadequate or resistant insulin.[1]It is primarily a mild inflammatory chronic metabolic illness that shows clinical manifestations in a number of microvascular and macrovascular problems.[2]

It is a prevalent condition, and 2 of the biggest risk factors are old age and obesity. The recent study reveals that the risk may be increased by 2 herpes viruses, cytomegalovirus and herpes simplex virus. Adipocytokines, receptors, gene signaling pathways, and the immune system are just a few of the many bridging molecules that play a role in the pathophysiology of type 2 diabetes mellitus (T2DM). The study used reverse transcription-polymerase chain reaction (PCR) and in situ hybridization in pancreatic tissue from T2DM patients to discover the immediate early and late gene products of cytomegalovirus (CMV). Results have shown that viper-in (endoplasmic reticulum-associated interferon-induced viral inhibitory protein), which is directly induced by CMV through interaction with the CMV mitochondrial inhibitor of apoptosis (vMIA) protein, plays a role in lipid and glucose metabolism.[2] European researchers have found that adults who test positive for any virus are more likely to develop prediabetes in the next 7 years. Specifically, those infected with herpes simplex virus type 2 (HSV-2) were at higher risk than those without these infections, and those infected with cytomegalovirus (CMV).[3]

The current research examines the complex relationship between persistent viral infection and the onset of type 2 diabetes mellitus (T2DM), as well as the effects of antiviral therapy on T2DM outcomes. Important discoveries show that viral infection is linked to insulin resistance (IR) and type 2 diabetes (T2DM) via a number of ways, including alterations in adipocytokine profiles and insulin signaling pathways. Sustained virological response (SVR)-assisted viral eradication has the potential to decrease T2DM risk and IR incidence, with the degree of these effects dependent on lifestyle, clinical, genetic, and demographic factors.[4] Research indicates that SVR may enhance long-term results for T2DM patients by lowering their chances of acute coronary syndrome, ischemic stroke, and end-stage renal disease.T2DM risk factors are complicated by their interaction with non-alcoholic fatty liver disease (NAFLD), to which virally-induced steatosis contributes and associated steatosis affects glucose intolerance.[4]

A 48-year-old HIV-positive man from Nigeria highlights the complex connection between HIV, antiretroviral medication (ART), and metabolic issues via a different case study. Although the patient's unusual treatment options initially produced positive results, a prescription adjustment was necessary in 2005 due to a decline in health. Diabetes signs, such as hyperglycemia and altered lipid profiles, then became apparent. The conversation focuses on the rise in metabolic issues associated with HIV and antiretroviral therapy (ART), particularly highlighting the role protease inhibitors (PIs) play in promoting insulin resistance and dyslipidemia. This instance serves as an alarming instance of how crucial it is to keep an eye on and treat metabolic problems in HIV patients on antiretroviral therapy.[5]

Type 2 diabetes mellitus (T2DM) and viral infection are causally linked. Proteins including fetuin A and selenoprotein P are impacted by changes in glucose and lipid metabolism linked to insulin resistance and type 2 diabetes in chronic viral infections. Important signaling molecules including GSK3 and AMP-activated protein kinase (AMPK) are impacted by the virus, which impacts cellular reproduction and metabolism.[6,7] The virus inhibits AMPK, which results in decreased activity. When AMPK is restored, viral replication and fat accumulation are reduced. The function of GSK3β in the viral life cycle demonstrates that overexpression promotes replication while inhibition decreases it. Different metabolic pathways are impacted by the ways in which genotype-specific mechanisms contribute to the degradation of insulin receptor substrate (IRS-1).These findings provide prospective therapeutic options for controlling viral infections and related metabolic consequences by highlighting the intricate interactions between viral infection, metabolic dysregulation, and the development of type 2 diabetes.[6,7]

In an investigation, patients with type 2 diabetes mellitus (DM2) were examined for the presence of 4 chronic viral infections (Ebstein barr virus (EBR)), human papillomavirus (HPV), Cytomegalovirus (CMV), and Herpes simplex virus 1 (HSV-1). The scientists gathered samples from people with and without diabetes, and then they used tested-PCR to look for viral DNA. They discovered that patients with diabetes (71.1%) had higher viral DNA detection rates than individuals without diabetes (30%).[8]

Regular blood sugar levels were essential for those people, who were subjected to screening for 8 distinct herpes viruses, including HSVs 1 and 2, varicella-zoster virus, Epstein-Barr virus, and CMV. 46% of the patients exhibited antibodies that suggested a prior CMV infection. This shows that CMV is extremely common in the population under investigation. 11% of the participants tested positive for HSV-2, according to further investigation.[9] It was discovered that among those people, those who initially tested positive for HSV-2 were 59% more likely to develop prediabetes or diabetes compared to those who did not exhibit symptoms of a prior herpes infection. Furthermore, a 33% increased incidence of hyperglycemia or diabetes was seen in those infected with CMV.[9]

The possible link between cytomegalovirus (CMV) infection and the risk of type 2 diabetes was revealed by 2 different investigations. Anti-CMV IgG antibodies were found to be much more common in diabetic patients (97.6%) than in non-diabetic controls (86.7%) in a study involving 113 hemodialysis patients in San Antonio, Texas. This finding suggests a strong correlation between CMV exposure and diabetes. Subsequent study within this cohort supported the link, showing a relationship between diabetes, CMV seropositivity, and higher vascular problems, as well as up to a 12-fold increased risk of type 2 diabetes among those who had previously been exposed to CMV.[10] In a comparable manner, HSV2 and CMV seropositivity was linked to an increased risk of (pre)diabetes and elevated baseline HbA1c values in the KORA cohort research investigating the function of herpes viruses in the development of diabetes. This suggests that these viruses may have a role in impaired glucose metabolism.[11] A further study on Iraqi patients revealed that type 2 diabetics had 3.4 times greater odds of being CMV IgG seropositive, highlighting the possibility of CMV infection acting as a stand-alone risk factor for the development of diabetes.[12]

More patients with diabetes were found in the HSV-1 IgG seropositive group than the HSV-1 IgG seronegative group (16.1 vs11.4%), the adjusted odds ratio of type 2 diabetes was 1.5 for HSV-1 infection, which indicated an association of HSV-1 infection with type 2 diabetes.[13] Chronic inflammation is involved closely and early on in the pathogenesis of type 2 diabetes.HSV-1 infection can cause the pancreas multiple small foci of hemorrhagic necrosis in humans and could induce the production of cytokines and inflammation response.The inflammation related with abnormal function of cells after HSV-1 infection might be helpful to elucidate the association of HSV-1 infection with type 2 diabetes In summary, the association of HSV-1 infection with type 2 diabetes further supported the notion that inflammation and virus infection might be the risk of development of type 2 diabetes.[13]

The relationship between HSV2 and CMV serostatus and the occurrence of (pre)diabetes suggests that these herpesviruses might play a role in the development of impaired glucose metabolism. These studies emphasize the connection between the viruses and (pre-) diabetes and underscore the importance of conducting more research to assess methods of preventing viral infections in public health. This could potentially involve the creation of successful vaccines targeting herpes viruses.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Author Contributions

Ushna Zameer: Conceptualization; Supervision. **Eisha Saqib:** Investigation; Writing – original draft. **Muhammad Salman Munshi:** Methodology; Writing – original draft. **Samia Rohail:** Investigation; Writing – review & editing.

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Availability of Data and Materials

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REFERENCES

1. Karim S, Mirza Z, Kamal M, et al. An association of virus infection with type 2 diabetes and Alzheimer's disease. *CNS Neurol Disord Drug Targets*. 2014;13:429-439.
2. Yoo SG, Han KD, Lee KH, La Y, Kwon DE, Han SH. Impact of Cytomegalovirus disease on new-onset type 2 diabetes mellitus: population-based matched case-control cohort study. *Diabetes Metab J*. 2019;43:815.
3. Could herpes viruses help drive type 2 diabetes? [Internet]. Brighamandwomens.org. Accessed March 2, 2024. https://healthlibrary.brighamandwomens.org/Library/DiseasesConditions/Pediatric/HighRiskPregnancy/6,1657300711
4. Vanni E, Bugianesi E, Saracco G. Treatment of type 2 diabetes mellitus by viral eradication in chronic hepatitis C: Myth or reality? *Dig Liver Dis*. 2016;48:105-111. doi:10.1016/j.dld.2015.10.016
5. Bakari A, Sani-Bello F, Shehu MS, Mai A, Aliyu I, Lawal I. Anti-retroviral therapy induced diabetes in a Nigerian. *Afr Health Sci*. 2007;7:133-135. doi:10.5555/AFHS.2007.7.3.133
6. Rajsfus BF, Mohana-Borges R, Allonso D. Diabetogenic viruses: linking viruses to diabetes mellitus. *Heliyon*. 2023;9:e15021. doi:10.1016/j.heliyon.2023.e15021
7. Toniolo A, Cassani G, Puggioni A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. *Rev Med Microbiol*. 2019;30:1–17.
8. Dworzański J, Drop B, Kliszczewska E, Strycharz-Dudziak M, Polz-Dacewicz M. Prevalence of Epstein-Barr virus, human papillomavirus, cytomegalovirus and herpes simplex virus type 1 in patients with diabetes mellitus type 2 in south-eastern Poland. *PLoS One*. 2019;14:e0222607.
9. Akash S, Azad MAK, Mukerjee N, Bibi S. Re-emergence of herpes simplex virus type-1 and type-2 manifestations in type 2 diabetes patients: its current status, genomic characteristics, diagnosis, treatment, and future outlook. *Int J Surg*. 2023;109:96–98.
10. Roberts BW, Cech I. Association of type 2 diabetes mellitus and seroprevalence for Cytomegalovirus. *South Med J*. 2005;98:686-692.
11. Woelfle T, Linkohr B, Waterboer T, et al. Health impact of seven herpesviruses on (pre)diabetes incidence and HbA1c: results from the KORA cohort. *Diabetologia*. 2022;65:1328-1338.
12. Hasan HM, Salloom DF. Human Cytomegalovirus infection as a risk factor for type 2 diabetes mellitus development in a sample of Iraqi patients. *Med-Leg Update*. 2021;21:639–644. doi:10.37506/mlu.v21i2.2754
13. Sun Y, Pei W, Wu Y, Yang Y. An association of herpes simplex virus type 1 infection with type 2 diabetes. *Diabetes Care*. 2005;28:435-436.