New study reveals that herpesvirus infection may increase risk of developing diabetes

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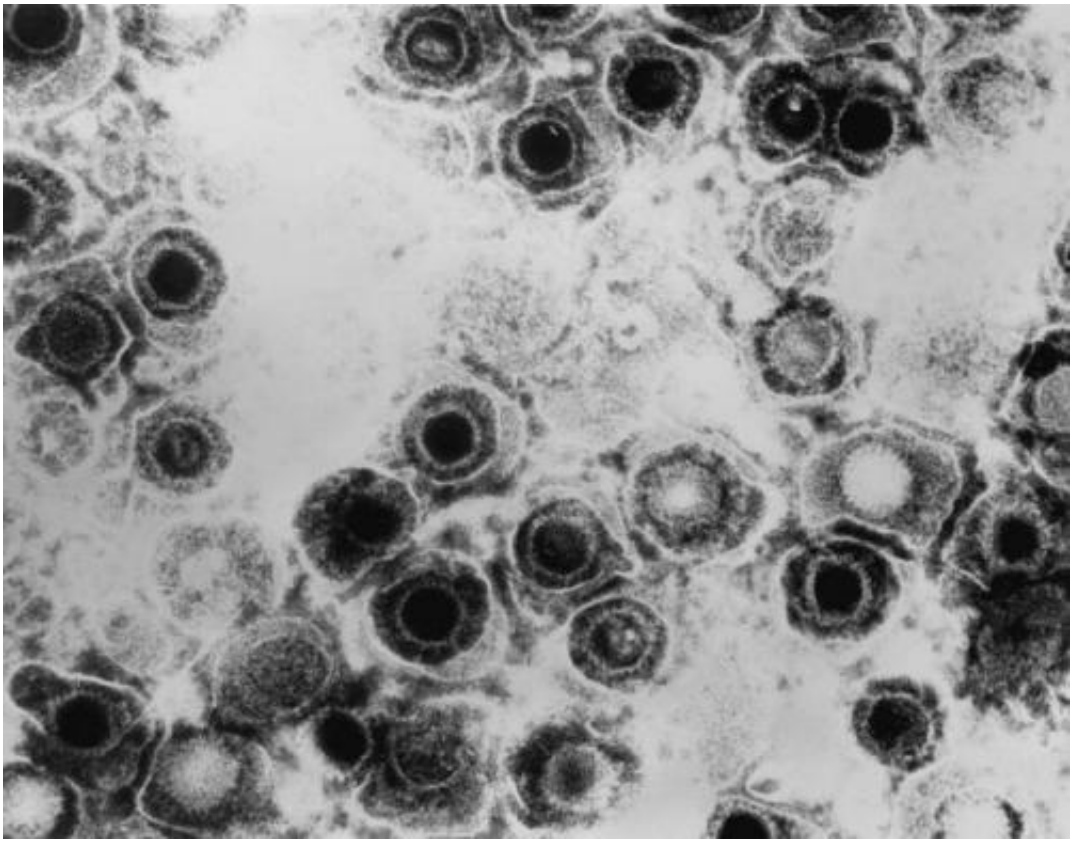

Herpes simplex virus. Credit: CDC

A new study published in *Diabetologia* (the journal of the European Association for the Study of Diabetes [EASD]) finds that two common herpesviruses may contribute to impaired glucose metabolism and an increase the risk of developing type 2 diabetes (T2D) among infected

individuals. The research was conducted by Dr. Tim Woelfle at Ludwig-Maximilians University and Helmholtz Munich, Germany, and colleagues.

Herpesviruses are one of the most prevalent viruses in humans, with eight types currently known: herpes simplex viruses (HSV) 1 and 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpesviruses (HHV) 6, 7 and 8. All of them cause lifelong latent infections in their hosts after an initial, usually mild or asymptomatic, primary infection.

T2D is one of the most widespread and important metabolic diseases, with an estimated 9.3% of the world's population having the condition as of 2019, exerting a high mortality burden primarily due to resultant cardiovascular disease. There are many known behavioral, environmental, and genetic risk factors for T2D, but until recently, viruses had only been proposed as playing a role in the development of type 1 diabetes, in which the pancreas stops producing enough insulin.

An individual may be diagnosed as having prediabetes when they exhibit impaired fasting glucose (IFG) or an impaired glucose tolerance (IGT). Previous studies have found that incidence rate of T2D is much higher in people with prediabetes (7.6% per person-year) than among individuals with normal glucose tolerance (0.6% per person-year)

The research was based on health data for 1,967 subjects in the KORA (Cooperative Health Research in the Augsburg Region) population-based health research platform in the south of Germany. Participants underwent detailed health examinations at baseline (2006-2008) and at follow-up (2013-2014), which included testing for the presence of human herpesviruses, oral glucose tolerance tests (OGTT), and measurement of glycated hemoglobin (HbA_{1c}) (a measure of blood sugar control over the previous 3 months).

The study group had a median age of 54 years at baseline; 962 (49%) were men and 999 (51%) were women. Incidence analysis for the development of (pre)diabetes used the data for those 1257 participants with normal glucose tolerance at baseline (median age 49 years, 42% male and 58% female [528 and 729 individuals, respectively]).

Participants with no prior diagnosis of T2D underwent a standard OGTT with diabetes status assigned using thresholds recommended by the American Diabetes Association. Further analyses of blood samples were performed to detect the presence of antibodies to 7 of the 8 known human herpesviruses which would indicate the presence of both primary and latent infections. The following variables known to be associated with diabetes risk were also assessed at baseline: sex, age, BMI, years of education, ever-smoking status (yes/no), leisure time physical activity (active/inactive), parental diabetes (yes/no), and hypertension (yes/no, defined as blood pressure higher than 140/90mmHg).

The prevalence of prediabetes (IFG and IGT) was 27.5% at baseline and 36.2% at follow-up, while T2D was present in 8.5% of participants at baseline and 14.6% at follow-up. Out of the 1257 volunteers with normal glucose tolerance at baseline, 364 went on to develop prediabetes and 17 developed T2D during the mean follow-up period of 6.5 years. The authors found that age, BMI, smoking, and years of education were all associated with an individual's risk of developing both prediabetes and T2D.

Blood testing at the beginning of the study found that EBV was the most prevalent herpesvirus, with 98% of the sample group being seropositive, followed by HSV1 (88%), HHV7 (85%), VZV (79%), CMV (46%), HHV6 (39%) and HSV2 (11%). Participants were seropositive for an average of 4.4 herpesviruses at baseline and 4.7 at follow-up. Around one third (34%) tested positive for more viruses at the end of the follow-up period, 54% had the same number, and only 12% were positive for

fewer viruses than at the start. While herpesviruses are persistent in their hosts, they may not always be detected by antibodies in blood. Infection usually occurs in early childhood but can take place in later life, so while the observed seroconversions may be new cases, they are more likely to be due to the immune response to a previously undetected virus. Similarly, a person who loses seropositivity cannot be considered free of the virus and is much more likely to be in an undetectable latency state.

Of the seven herpesviruses examined, HSV2 and CMV were associated with incidence of (pre)diabetes among individuals with normal glucose tolerance at baseline that were independent of other risk factors. Individuals with HSV2 were 59% more likely to develop (pre)diabetes than those who were seronegative, while CMV infection was associated with a 33% increased (pre)diabetes incidence.

The study found that both HSV2 and CMV consistently and complementarily contributed to the development of (pre)diabetes, even after accounting for sex, age, BMI, education, smoking, physical activity, parental diabetes, hypertension, lipid levels, insulin resistance and fasting glucose. HSV2 was also found to be associated with HbA_{1c} levels, independent of other confounders and the prevalence of (pre)diabetes itself.

The authors say, "Our study suggested that while (pre)diabetes incidence was primarily explained by age, BMI, cholesterol and fasting glucose, both HSV2 and CMV added additional complementary risk information, despite high viral prevalence and co-occurrence."

The mechanisms by which these viruses could contribute to the development of (pre)diabetes remain to be discovered. Both HSV2 and CMV cause chronic infections that could modulate the immune system by stimulating or suppressing its activity, which in turn can influence the function of the endocrine (hormonal) system. Previous research has

established that there are as-yet unknown causes of T2D besides those involving the development of metabolic syndrome.

The authors conclude, "These results highlight the link between viruses and (pre)diabetes, and the need for more research evaluating public health viral prevention strategies, possibly including the development of effective vaccines against herpesviruses."

More information: Tim Woelfle et al, Health impact of seven herpesviruses on (pre)diabetes incidence and HbA1c: results from the KORA cohort, *Diabetologia* (2022). DOI: 10.1007/s00125-022-05704-7

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