An Association of Herpes Simplex Virus Type 1 Infection With Type 2 Diabetes

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Although the primary cause of type 2 diabetes is unknown, two breakthroughs have been made regarding its development (1). First, insulin resistance in muscle is the earliest detectable defect in people in whom type 2 diabetes will later develop. Second, β-cell function has to be abnormal before hyperglycemia develops. One of the risk factors for diabetes development might be virus infection (2). Preexisting hepatitis C virus infection may increase the risk for type 2 diabetes (3,4).

Herpes simplex virus type 1 (HSV-1) has been recognized as a potential pathogen of cardiovascular diseases. The presence of antibodies to HSV-1 is reported to be associated with an increase in the risk of incident myocardial infarction and coronary heart death (5,6). Type 2 diabetes is a major risk factor for cardiovascular morbidity and mortality (7) and is recorded as a coronary artery disease risk equivalent (8). In this study, we attempted to investigate the potential relationship between HSV-1 infection and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— All subjects were consecutive inpatients at Beijing Fu Wai Heart Hospital. Diabetes was diagnosed as follows (9): patients who had overnight fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or were taking antidiabetic medication. Patients not meeting these criteria were not considered to have diabetes. Subjects taking insulin alone (type 1 diabetes) were excluded from the analyses, ensuring that all patients with the diagnosis of diabetes had type 2 diabetes. The local ethics committee approved the study, and informed consent was obtained from all patients. The following potential risk factors for diabetes were analyzed in this study: age, cigarette smoking, physical inactivity, BMI, hypertension, dyslipidemia, coronary artery disease, and immunoglobulin G (IgG) seropositive status to HSV-1.

Serum samples were collected and frozen at −80°C until analysis. Each serum sample was tested for specific anti–HSV-1 IgG antibody by enzyme-linked immunosorbent assay with a commercially available kit (Virus Institute, Chinese Academy of Prevention Medical Sciences, Beijing, China). Cellular filtrates obtained by ultrasonic destruction of Vero cells infected with the standard HSV-1 strain were used as the specific HSV-1–coated antigen to detect the specific HSV-1 IgG. Presence or absence of anti–HSV-1 IgG was determined by comparing the absorbency value of the sample to a cutoff value. This cutoff value was calculated from the negative and positive control absorbency value according to the manufacturer's protocol. IgG seropositivity to HSV-1 indicated prior infection of HSV-1.

In univariate analysis, an independent two-sample t test was used for the normally distributed continuous variables and χ^2 test was used to compare categorical variables. In multivariate analysis, binary logistic regression was used to control the potential confounding factors and to calculate the adjusted odds ratio with its associated 95% CI. Values of $P < 0.05$ were considered to indicate statistical significance.

RESULTS

— Among 1,566 subjects, 206 (13.2%) had type 2 diabetes and 1,360 were nondiabetic control subjects. In patients aged >65 years, hypertension and coronary artery disease were more frequently found in the patients with diabetes than control subjects (all $P < 0.05$). The prevalence of HSV-1 infection was significantly higher in the diabetic than control group (46.1 vs. 36.3%, $P = 0.007$), as shown in Table 1. More patients with diabetes were found in the HSV-1 IgG seropositive group than the HSV-1 IgG seronegative group (16.1 vs. 11.4%, $P = 0.007$). After adjustment for confounding factors, the adjusted odds ratio of type 2 diabetes was 1.5 (1.1–2.0, $P = 0.01$) for HSV-1 infection, which indicated an association of HSV-1 infection with type 2 diabetes. The adjusted covariates included age, male sex, smoking, physical inactivity, BMI, dyslipidemia, hypertension, and coronary artery disease.

CONCLUSIONS

— A significant association of HSV-1 infection with type 2 diabetes was found in the present study. All subjects were hepatitis C virus antibody seronegative, so the confounding relationship between hepatitis C virus infection and type 2 diabetes can be excluded.

Chronic inflammation is involved closely and early on in the pathogenesis of type 2 diabetes (10,11). Viral infection of the pancreas, but not islets, can lead to induction of Fas on β-cells, which renders them susceptible to Fas/Fas-ligand–mediated apoptosis and resulting in a significant degree of clinically manifest diabetes (12). HSV-1 DNA might reside in surviving HSV-1–infected mice in a "latent" state in pancreas (13). HSV-1 infection can cause the pancreas multiple small foci of hemorrhagic necrosis in humans (14) and could induce the production of cytokines and inflammation response

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Abbreviations: HSV-1, herpes simplex virus type 1; IgG, immunoglobulin G.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic characteristics of the study subjects*

	Diabetic subjects	Control subjects	*P*
n	206	1360	
Sex (male)	158 (76.7)	1,111 (81.7)	0.089
Age (years)			
∼34	0 (0)	21 (1.5)	0.098
∼35	9 (4.4)	146 (12.1)	0.003
∼45	57 (27.7)	391 (28.8)	0.749
∼55	70 (34.0)	462 (34.0)	0.998
∼65	70 (34.0)	322 (23.7)	0.001
Smoking	121 (58.7)	834 (61.3)	0.478
Hypertension	117 (56.8)	553 (40.7)	0.000
Dyslipidemia	76 (36.9)	417 (30.7)	0.073
Coronary artery disease	185 (89.8)	1092 (80.3)	0.001
Physical inactivity	153 (74.3)	1016 (74.7)	0.894
HSV-1 IgG seroposivitity	95 (46.1)	494 (36.3)	0.007
BMI (kg/m^2)	25.7 ± 3.1	25.4 ± 3.1	0.229

Data are means ± SD or *n* (%).

(15,16). Additionally, levels of cellular ATP and lactate and mitochondrial membrane potential are decreased at the late stage of infection with HSV (17). Synthesis of mitochondrial proteins and phospholipid synthesis in mitochondria in HSV-1–infected cells progressively decreases (18), which could be associated with dysregulation of intramyocellular fatty acid metabolism and insulin resistance. The inflammation related with abnormal function of β-cells and mitochondrial dysfunction after HSV-1 infection might be helpful to elucidate the association of HSV-1 infection with type 2 diabetes observed in this study.

This finding is not consistent with the assumption that diabetes leads to HSV-1 infection, because among several pathogens thought to be involved in the pathogenesis of cardiovascular diseases, only HSV-1 infection, i.e., not *Chlamydia* pneumonia, cytomegalovirus, or HSV-2 (data not shown), is independently associated type 2 diabetes (present study). However, a new type-specific enzyme-linked immunosorbent assay, based on recombinant gG-1, with a better specificity is warranted to further discriminate between HSV-1 and HSV-2 IgG (19). A prospective study is needed to demonstrate that HSV-1 infection associate with the subsequent development of 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.

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