

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

YUHUA SUN, PHD  
WEIDONG PEI, PHD

YONGJIAN WU, MD  
YUEJIN YANG, MD

**A**lthough 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,  $\beta$ -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  $\geq 7.0$  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  $-80^{\circ}\text{C}$  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  $\chi^2$  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  $\beta$ -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

From the Cardiovascular Institute, Fu Wai Heart Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China.

Address correspondence and reprint requests to Yuejin Yang, MD, Cardiovascular Institute, Fu Wai Heart Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beilishilu 167, Beijing 100037, China. E-mail: sunyh0903@yahoo.com.

Received for publication 16 September 2004 and accepted in revised form 5 November 2004.

**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.

© 2005 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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 seropositivity	95 (46.1)	494 (36.3)	0.007
BMI (kg/m <sup>2</sup> )	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 pneumoniae*, cytomegalovirus, or HSV-2 (data not shown), is independently associated with 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.

References

1. Taylor R: Causation of type 2 diabetes: the Gordian knot unravels. *N Engl J Med* 350: 639–641, 2004
2. Jun HS, Yoon JW: A new look at viruses in type 1 diabetes. *Diabetes Metab Res Rev* 19:8–31, 2003
3. Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, Szklo M, Thomas DL: Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 38:50–56, 2003
4. Lecube A, Hernandez C, Genesca J, Esteban JI, Jardi R, Simo R: High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care* 27:1171–1175, 2004
5. Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Manttari M: Infections, inflammation, and the risk of coronary heart disease. *Circulation* 101:252–257, 2000
6. Zhu J, Nieto FJ, Horne BD, Anderson JL, Muhlestein JB, Epstein SE: Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation* 103:45–51, 2001
7. Luscher TF, Creager MA, Beckman JA, Cosentino F: Diabetes and vascular disease. Pathophysiology, clinical consequences, and medical therapy: part II. *Circulation* 108:1655–1661, 2003
8. Expert Panel on Detection, Evaluation,

and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001

9. American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1):S5–S10, 2004
10. Pickup JC: Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 27:813–823, 2004
11. Helmersson J, Vessby B, Larsson A, Basu S: Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. *Circulation* 109:1729–1734, 2004
12. Christen U, Darwiche R, Thomas HE, Wolfe T, Rodrigo E, Chervonsky A, Flavell RA, von Herrath MG: Virally induced inflammation triggers fratricide of Fasligand-expressing β-cells. *Diabetes* 53: 591–596, 2004
13. Berkowitz C, Moyal M, Rosen-Wolff A, Darai G, Becker Y: Herpes simplex virus type 1 (HSV-1) UL56 gene is involved in viral intraperitoneal pathogenicity to immunocompetent mice. *Arch Virol* 134: 73–83, 1994
14. Shintaku M, Umehara Y, Iwaisako K, Tahara M, Adachi Y: Herpes simplex pancreatitis. *Arch Pathol Lab Med* 127:231–234, 2003
15. Epstein SE: The multiple mechanisms by which infection may contribute to atherosclerosis development and course. *Circ Res* 90:2–4, 2002
16. Muhstein JB, Anderson JL: Infectious serology and atherosclerosis: how burdensome is the risk? *Circulation* 107:220–222, 2003
17. Lund K, Ziola B: Synthesis of mitochondrial macromolecules in herpes simplex type 1 virus infected Vero cells. *Biochem Cell Biol* 64:1303–1309, 1986
18. Murata T, Goshima F, Daikoku T, Inagaki-Ohara K, Takakuwa H, Kato K, Nishiyama Y: Mitochondrial distribution and function in herpes simplex virus-infected cells. *J Gen Virol* 81:401–406, 2000
19. Ashley-Morrow R, Nollkamper J, Robinson NJ, Bishop N, Smith J: Performance of focus ELISA tests for herpes simplex virus type 1 (HSV-1) and HSV-2 antibodies among women in ten diverse geographical locations. *Clin Microbiol Infect* 10:530–536, 2004

Downloaded from http://diabetesjournals.org/care/article-pdf/28/2/435/665954/28c020500435.pdf by guest on 13 October 2024