Low HDL Cholesterol Is Associated With the Risk of Stroke in Elderly Diabetic Individuals

Changes in the risk for atherosclerotic diseases at various ages

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OBJECTIVE — To clarify the relationship between lipid levels and ischemic heart disease (IHD) and cerebrovascular disease (CVD) in diabetic individuals.

RESEARCH DESIGN AND METHODS — The Japan Cholesterol and Diabetes Mellitus Study is a prospective cohort study of 4,014 type 2 diabetic patients (1,936 women; mean ± SD age 67.4 ± 9.5 years). Lipid and glucose levels and other factors were investigated in relation to occurrence of IHD or CVD.

RESULTS — IHD and CVD occurred in 1.59 and 1.43% of participants, respectively, over a 2-year period. The relation of lower HDL or higher LDL cholesterol to occurrence of IHD in subjects <65 years old was significant. Lower HDL cholesterol was also significantly related to CVD in subjects ≥65 years old and especially in those >75 years old (n = 1,016; odds ratio 0.511 [95% CI 0.239–0.918]; $P < 0.05$). Stepwise multiple regression analysis with onset of CVD as a dependent variable showed the same result.

CONCLUSIONS — Lower HDL cholesterol is an important risk factor for not only IHD but also CVD, especially in diabetic elderly individuals.

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Type 2 diabetes, dyslipidemia, and aging are independent risk factors for cardiovascular diseases. Japanese individuals have lower rates of ischemic heart disease (IHD) and higher rates of cerebrovascular disease (CVD); however, diabetic individuals have an increased risk of IHD (1,2). Risk factors for IHD or CVD in elderly diabetic individuals are not fully known (3), and the Japan Cholesterol and Diabetes Mellitus Study was formulated to evaluate them (Umin Clinical Trials Registry, clinical trial reg. no. UMIN00000516; http://www.umin.ac.jp/ctr/index.htm).

RESEARCH DESIGN AND METHODS

— The Japan Cholesterol and Diabetes Mellitus Study is a single-center prospective cohort study comprised of 4,014 Japanese diabetic individuals on a consecutive outpatient basis recruited between September 2004 and March 2005 (1,936 women; mean ± SD age 67.4 ± 9.5 years [range 35–83 years]). Patients with previous IHD (myocardial infarction, unstable angina pectoris, angioplasty, or bypass grafting) or CVD (stroke) were excluded. Follow-up information was available for 98.2 and 92.3% of patients enrolled in the first and second years, respectively. Patients were divided into those aged <65 years, 65–74 years, and >75 years (n = 1,267, 1,731, and 1,016, respectively). The primary end points were onset of IHD or CVD. Plasma lipid, glucose, A1C, and other relevant levels were measured annually.

The study was approved by institutional review boards and by the safety-monitoring board. All events were confirmed by the organizing committee annually. The guidelines of the Japan Atherosclerosis Society (2002), stating that LDL cholesterol should be <120 mg/dl and HDL cholesterol >40 mg/dl in diabetic individuals, and the American Diabetes Association criteria for diagnosis of type 2 diabetes were used (4,5).

Results are presented as means ± SD. All statistical analyses were performed using JMP software (SAS Institute, Cary, NC). Incidences were analyzed in relation to risk factors. Univariate and multiple logistic regression analysis and stepwise analysis were used. Values of $P < 0.05$ were considered significant.

RESULTS

— Mean A1C, fasting plasma glucose, LDL cholesterol, triglyceride, HDL cholesterol, and systolic and diastolic blood pressure levels on registration were 7.53 ± 1.12%, 159.4 ± 52.7

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Table 1—*Adjusted multiple regression analyses of factors found to be significant by univariate regression analysis for IHD or CVD, as well as major atherogenic risk factors; total* n = *4,014*

	<65 years old (n = 1,276)		65–74 years old (n = 1,731)		≤75 years old (n = 1,016)	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
IHD						
Sex	1.469 (1.02–1.94)	0.02*	1.109 (1.02–1.74)	0.04*	0.829 (0.23–3.06)	0.78
Age	1.063 (0.96–1.20)	0.28	0.991 (0.86–1.15)	0.99	0.996 (0.83–1.17)	0.87
LDL cholesterol	1.225 (1.02–2.04)	0.04*	1.001 (0.72–1.25)	0.89	0.776 (0.43–1.40)	0.40
HDL cholesterol	0.659 (0.39–0.98)	0.04*	0.939 (0.68–1.25)	0.38	0.946 (0.58–1.29)	0.23
Triglycerides	1.356 (1.00–2.02)	0.05	0.731 (0.52–1.94)	0.18	0.881 (0.46–1.70)	0.71
A1C	1.179 (0.75–1.88)	0.27	1.082 (0.76–1.55)	0.67	1.274 (0.57–2.35)	0.44
SBP	0.702 (0.49–1.09)	0.15	1.082 (0.79–1.69)	0.15	1.051 (0.58–1.89)	0.87
DBP	1.020 (0.97–1.05)	0.28	1.088 (0.73–1.27)	0.24	1.998 (0.99–4.35)	0.08
CVD						
Sex	1.158 (0.68–2.17)	0.47	1.004 (0.79–1.69)	0.82	0.847 (0.45–1.52)	0.58
Age	1.006 (0.94–1.10)	0.88	0.982 (0.82–1.14)	0.39	1.139 (0.99–1.30)	0.06
LDL cholesterol	1.099 (0.98–1.23)	0.06	1.067 (0.76–1.44)	0.51	1.128 (0.64–1.59)	0.71
HDL cholesterol	0.888 (0.64–1.48)	0.09	0.758 (0.53–0.98)	0.04*	0.511 (0.24–0.92)	0.04*
Triglycerides	1.147 (0.68–2.04)	0.62	1.070 (0.69–1.67)	0.75	1.355 (0.75–2.56)	0.32
A1C	0.996 (0.64–1.28)	0.52	1.019 (0.75–1.74)	0.54	1.015 (0.60–1.72)	0.95
SBP	1.005 (0.67–1.33)	0.86	0.991 (0.94–1.13)	0.35	1.063 (0.62–1.57)	0.75
DBP	1.109 (0.61–2.13)	0.74	1.303 (0.81–2.09)	0.27	1.045 (0.68–1.5)	0.59

	IHD				CVD			
	<65 years old	65–74 years old	≤75 years old	Total	<65 years old	65–74 years old	≤75 years old	Total
HDL cholesterol (mg/dl)								
<44	2.31	2.49	1.68	2.14	1.13	1.99	2.62*	2.01
44–53	1.45	1.45	1.64	1.50	1.05	1.84	2.15*	1.64
54–63	1.25	1.41	0.98	1.23	1.44	0.80	0.88*	1.04
≥64	0.42	1.69	0.99	1.19	1.0	0.80	0.45*	0.72

Data were adjusted for sex. The ratio of male to female subjects is 1:1. *Statistically significant (P <0.05). DBP, diastolic blood pressure; SBP, systolic blood pressure.

mg/dl, 120.3 ± 32 mg/dl, 140.6 ± 108.3 mg/dl, 55.8 ± 18.0 mg/dl, 136.5 ± 17.1 mmHg, and 75.1 ± 11.1 mmHg, respectively. Insulin and oral agents for diabetes were prescribed for 19.9 and 70.5% of individuals, respectively. Dyslipidemia was seen in 79.1%, and antihyperlipidemic drugs were prescribed in 59.0%. Mean lipid and glucose metabolism levels did not change significantly over the 2-year study period.

In the first and second years, 83 and 69 vascular events occurred, respectively. IHD and CVD occurred in 0.80 and 0.71% of total patients per year. The relationship between IHD or CVD and background factors such as LDL cholesterol levels in each age-group was analyzed by univariate logistic regression.

Sex, age, LDL cholesterol, HDL cholesterol, and triglyceride were significantly related to IDH in patients aged <65 years. Age, sex, history of hypertension, and antihypertensive drugs were related in patients aged between 65 and 74 years, and sex and systolic and diastolic blood pressure were related in patients aged > 75 years. CVD and LDL cholesterol were related in patients aged <65 years, and HDL cholesterol and systolic blood pressure were related in patients aged >75 years.

We performed multiple regression analysis with factors found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors (A1C, etc.) in three age-groups (Table 1). LDL and HDL cholesterol were associated with IHD in patients aged < 65 years but not in other age-groups. Sex was associated with IHD in individuals aged <74 years. HDL cholesterol was also associated with CVD in individuals between aged between 65 and 74 years and >75 years.

Stepwise multiple regression analysis was performed using factors that were found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors. HDL and LDL cholesterol were associated with IHD in individuals aged <65 years (HDL cholesterol odds ratio 0.79 [95% CI 0.58–0.96; P = 0.04] and LDL cholesterol 0.60 [0.33–0.99; P = 0.04]). HDL cholesterol was associated with CVD in individuals aged between 65 and 74 years and ≥75 years (65–74 years 0.73 [0.56–0.94; P = 0.04] and ≥75 years 0.60 [0.35–0.91; P = 0.01]).

The relation of age or HDL cholesterol to IHD and CVD was evaluated in quartile categories. HDL cholesterol levels were inversely correlated with IHD in individuals aged <65 years (hazards ratio 0.633 [95% CI 0.428–0.975]) but not in other groups. The relationship between CVD and HDL cholesterol was prominent in those aged >75years but not in other age-groups (Table 1). There were no sex-related differences in the relationship of HDL cholesterol with CVD. There was no relationship between LDL, triglyceride, fasting blood glucose, or A1C and the frequency of CVD.

CONCLUSIONS — This study represents one of the largest-scale attempts to examine IHD and CVD in middle-aged and elderly diabetic individuals. In the U.S., evidence suggests that middle-aged diabetic individuals have an IHD risk similar to that for individuals with myocardial infarction (6). However, this risk may not exist in elderly diabetic individuals. Many guidelines to prevent atherothrombotic diseases recommend strict control of LDL cholesterol in diabetic patients but the same guideline for HDL cholesterol control (40 mg/dl) as that used for nondiabetic subjects (4–7).

A novel finding was that type 2 diabetic elderly individuals had frequent CVD, and incidence rates were associated with HDL cholesterol. Few data were available for the relationship among elderly, type 2 diabetes, and CVD (8,9).

There have been three large-scale clinical studies of statins that included participants aged up to 75 years (10–12). Although they reported that statins exerted effects on IHD (including in diabetic individuals), effects were not pronounced. (Prosper reported that statins induced a 16% decrease in IHD without any effects on CVD.) The data suggest that because LDL cholesterol decreased, simple LDL cholesterol control may not prevent IHD or CVD in elderly individuals. Our study shows the importance of HDL cholesterol in CVD in elderly diabetic individuals and in IHD in middle-aged diabetic individuals. If HDL cholesterol is well controlled in elderly diabetic patients, then CVD and IHD might be decreased to the levels found in middle-aged cohorts. Patients prescribed statins whose HDL cholesterol was <40 mg/dl showed the same risk (data not shown). Although medicated patients may be more conscious of diseases, HDL cholesterol is a strong risk factor and masks the effects of statins.

In conclusion, HDL and LDL cholesterol were risk factors for IHD in diabetic patients aged <65 years. In addition, HDL cholesterol was a risk factor for CVD in elderly diabetic subjects, especially those aged >75 years. HDL cholesterol may help prevent CVD in elderly diabetic subjects. Risk factors for IHD and CVD appear to change with advancing age.

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