Visceral Adiposity and Incident Coronary Heart Disease in Japanese-American Men

The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study

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OBJECTIVE — To identify risk factors for incident coronary heart disease (CHD).

RESEARCH DESIGN AND METHODS — A total of 175 Japanese-American men without CHD were followed for up to 10 years. Baseline variables were blood pressure, weight, BMI, fat areas by computed tomography, skinfold thicknesses, abdominal circumference, plasma insulin, C-peptide, cholesterol, LDL cholesterol, HDL cholesterol, HDL2 cholesterol, and HDL3 cholesterol, triglycerides, apoproteins A1 and B, and diagnosis of diabetes and hypertension. CHD was diagnosed by electrocardiogram and clinical events. Logistic regression was used to estimate odds ratio.

RESULTS — There were 50 incident cases of CHD. Using univariate logistic regression analysis, significant risk factors were intra-abdominal fat ($P = 0.0090$), fasting glucose ($P = 0.0002$), 2-h glucose ($P = 0.0008$), fasting HDL cholesterol ($P = 0.0086$), fasting HDL2 cholesterol ($P = 0.030$), fasting HDL3 cholesterol ($P = 0.018$), fasting triglycerides ($P = 0.013$), systolic ($P = 0.0007$) and diastolic blood pressure ($P = 0.0002$), and presence of diabetes ($P = 0.0023$). Multiple logistic regression models adjusted for BMI and age showed that intra-abdominal fat accounted for the effects of HDL cholesterol or triglycerides. In a multiple logistic regression model that included intra-abdominal fat, all systolic blood pressure and fasting glucose were significant. Substituting diastolic blood pressure for systolic blood pressure and 2-h glucose or diabetes status for fasting glucose produced similar results.

CONCLUSIONS — Visceral adiposity, blood pressure, and plasma glucose are important independent risk factors for incident CHD in this population of diabetic and nondiabetic Japanese-American men.

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Clustering of obesity, insulin resistance, hyperinsulinemia, dyslipidemia, glucose intolerance, and hypertension with coronary heart disease (CHD) is recognized as the insulin resistance syndrome (1,2). Furthermore, a central pattern of body fat distribution is now generally considered to be part of the syndrome (3–7). We have reported visceral adiposity to be associated with prevalent CHD (8) and incident type 2 diabetes (9) in Japanese Americans. In an examination of nonobese Japanese-American men, the amount of visceral fat was very strongly related to CHD risk factors (10). Although studies including many more participants have shown increased waist-to-hip ratio or subscapular skinfold thickness to be prospectively related to CHD (11–14), it has not yet been reported whether visceral adiposity increases the risk of incident CHD. The present report describes the relationship of intra-abdominal fat and other factors to incident CHD in a group of second-generation Japanese-American men followed over a 10-year period.

RESEARCH DESIGN AND METHODS

Study subjects

Details pertaining to recruitment and enrollment of subjects have been previously reported (15). The research protocol was reviewed and approved by the Human Subjects Review Committee at the University of Washington, and informed consent was obtained from each subject.

Subjects were classified after their initial visit as having or not having type 2 diabetes, based on information from subjects and their physicians and on results of a 75-g oral glucose tolerance test using World Health Organization criteria (16). CHD was diagnosed by clinical history (acute myocardial infarction, angina, coronary artery bypass graft, or coronary angioplasty) and from a resting 12-lead electrocardiogram (Minnesota Code items 1.1, 1.2, and 7.1) (17). Subjects who had CHD at baseline were not included in the prospective analysis. Sudden death by cardiac arrest during the follow-up period (ascertained from death certificates) was also considered diagnostic of CHD.

Of an original sample of 229 Japanese-American men, 175 men (mean age 61.2

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Abbreviations: CHD, coronary heart disease; ICR, incremental C-peptide response; IIR, incremental insulin response; PAI-1, plasminogen activator inhibitor-1.

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

Table 1—*Baseline adipose variables by incident CHD status*

Baseline variable	Incident CHD status		*P* value	*P* value*
	CHD absent	CHD present		
n	125	50	—	—
Weight (kg)	69.8 ± 0.9	71.6 ± 1.2	0.25	0.24
BMI (kg/m^2)	25.4 ± 0.3	25.8 ± 0.4	0.37	0.34
Computed tomography fat area (cm^2)				
Total	417.1 ± 14.0	465.9 ± 20.8	0.063	0.052
Chest subcutaneous	92.7 ± 4.1	104.0 ± 5.6	0.13	0.14
Abdomen subcutaneous	129.3 ± 5.7	146.0 ± 7.9	0.11	0.068
Intra-abdominal	108.9 ± 4.7	133.0 ± 7.6	0.0075	0.016
Left thigh subcutaneous	43.1 ± 1.5	40.8 ± 2.1	0.39	0.72
Skinfold thickness (mm)				
Forearm	5.5 ± 0.2	5.8 ± 0.3	0.37	0.41
Biceps	6.6 ± 0.2	6.9 ± 0.4	0.52	0.69
Triceps	8.5 ± 0.3	8.6 ± 0.4	0.81	0.84
Subscapula	17.9 ± 0.5	20.5 ± 1.0	0.025	0.063
Chest	19.2 ± 0.7	20.9 ± 1.3	0.25	0.31
Abdomen	25.1 ± 0.9	26.9 ± 1.6	0.31	0.13
Thigh	10.4 ± 0.4	9.9 ± 0.6	0.50	0.69
Abdominal circumference (cm)	88.0 ± 0.7	90.2 ± 1.0	0.088	0.093

Data are means ± SEM. *Adjusted for baseline diabetes.

years) who did not have CHD at baseline were followed for up to 10 years. Of these 175 men, 54 had diabetes at baseline (mean age 61.6 years), and 121 men did not (mean age 61.0 years).

Measurements

At the subjects' initial visit, birth date, height (meters), and weight (kilograms) were recorded, and BMI was calculated (kilograms per meters squared). After an overnight 10-h fast, blood samples were withdrawn to measure plasma levels of glucose, insulin, C-peptide, cholesterol, triglycerides, HDL cholesterol, HDL2 cholesterol, HDL3 cholesterol, LDL cholesterol, and apoproteins A1 and B. A 75-g oral glucose load was then given and plasma samples at 30 min were assayed for insulin and C-peptide and at 120 min for glucose. β-Cell function was estimated by subtracting the insulin or C-peptide fasting value from the 30-min value to obtain the incremental insulin response (IIR) or incremental C-peptide response (ICR).

Biochemical measurements were performed as reported previously (8). Plasma glucose was measured by an automated hexokinase method (Department of Laboratory Medicine). Plasma insulin and C-peptide were measured by radioimmunoassay (Immunoassay Core, Diabetes Endocrinology Research Center). Lipid and lipoprotein measurements were performed according to modified procedures of the Lipid Research Clinics and apoproteins A1 and B by radioimmunoassays (Northwest Lipid Research Laboratory).

Blood pressure was measured in recumbent subjects by indirect auscultation and by a mercury sphygmomanometer read to the nearest 2 mmHg. Systolic pressure was determined by the first perception of sound and diastolic pressure by the disappearance of sound. Mean systolic and diastolic pressures were calculated from the second and third of three consecutive measurements. Hypertension was diagnosed if mean systolic pressure was ≥140 mmHg or mean diastolic pressure was ≥90 mmHg or if the subject was receiving antihypertensive medications.

Three computed tomography scans were done (chest at the level of the nipples, abdomen at the level of the umbilicus, and mid-thigh) to measure cross-sectional subcutaneous chest, abdomen, and left thigh and intra-abdominal fat areas (centimeters squared) (18,19). Total fat area was the sum of subcutaneous chest, subcutaneous abdomen, intra-abdominal, and two times subcutaneous left thigh fat areas. Skinfold thickness (millimeters) was measured (Lange calipers) on the left side of the body at seven anatomic sites (forearm, biceps, triceps, subscapula, chest, abdomen, anterior thigh) (19). Abdominal circumference was measured at the level of the umbilicus to the nearest tenth centimeter.

Statistical analysis

Statistical software packages SPSS and S-PLUS were used. Differences in values between subjects with CHD and those without were tested with the two-sample *t* test. Differences in percentages were tested using the χ^2 test. Where adjustment was made for baseline diabetes, analysis of covariance was used to assess significance of differences in means. Logistic regression was used to estimate the odds ratio for incident CHD in relation to an increase of 1 SD in baseline variables. All statistical tests were two-tailed.

RESULTS — Over the 10-year follow-up period, 50 men (28.6%) went on to develop CHD (6 were categorized on the basis of their death certificates). Of the 54 men with diabetes at baseline, 44.4% developed CHD, while of the 121 men without diabetes at baseline, only 21.5% developed CHD ($P = 0.0035$).

Of the baseline adipose measurements, only intra-abdominal fat was significantly greater in men who developed CHD and remained significant after adjusting for diabetes at baseline (Table 1). Baseline metabolic and blood pressure characteristics by incident CHD are shown in Table 2. Triglyceride levels were significantly higher, and levels of HDL cholesterol, HDL2 cholesterol, and HDL3 cholesterol were significantly lower in men who developed CHD. Fasting and 2-h plasma glucose and systolic and diastolic blood pressures were also significantly higher. All of these, except for HDL2 cholesterol and 2-h plasma glucose, remained significant after adjustment for diabetes at baseline. Prevalence of hypertension was 76.0% in those men who developed CHD, 55.2% in those who did not ($P = 0.017$).

By using univariate logistic regression analysis, the risk of developing CHD was increased significantly for the following variables (the value of a 1 SD increase in the variable, odds ratio for a 1 SD increase in the variable, 95% CI, and *P* value are shown): intra-abdominal fat (53.8, 1.57, 1.11–2.23, $P = 0.0090$); fasting (2.74, 1.91, 1.36–2.68, $P = 0.0002$) and 2-h glucose (6.07, 1.73, 1.25–2.40, $P = 0.0008$); fasting HDL (0.34, 0.60, 0.41–0.88, $P = 0.0086$), HDL2 (0.21, 0.65, 0.44–0.97, $P = 0.030$), and HDL3 cholesterol (0.18, 0.65, 0.46–0.94, $P = 0.018$); fasting triglycerides (2.37, 1.56, 1.09–2.23, $P = 0.013$); and systolic (18.4, 1.83, 1.28–2.60, $P = 0.0007$) and diastolic blood pressure (9.6, 2.05, 1.40–3.01, $P = 0.0002$). These results remained significant after adjusting for age and BMI. The odds ratio for development of CHD by presence

versus absence of diabetes at baseline was 1.71 (1.20–2.43; $P = 0.0023$).

To further test the hypothesis that intra-abdominal fat was an independent predictor of CHD risk, several multiple logistic regression models that included potential confounding variables were examined. All models included adjustments for BMI and age. Models that included both intra-abdominal fat and HDL cholesterol or triglycerides demonstrated that whereas intra-abdominal fat was still significantly related to CHD risk, HDL cholesterol or triglycerides no longer were. In a model where intra-abdominal fat, systolic blood pressure, and fasting glucose were all included, each retained a significant association with CHD with odds ratios (95% CI; *P* value) of 1.60 (1.00–2.58; $P = 0.047$), 1.80 (1.20–2.71; $P = 0.0039$), and 1.69 (1.18–2.43; $P = 0.0036$), respectively. Substituting diastolic blood pressure for systolic blood pressure and 2-h glucose or diabetes status for fasting glucose produced similar results. However, 2-h glucose was no longer significantly associated with the development of CHD when diabetes at baseline was in the model, whereas fasting glucose remained significant. Fasting insulin and fasting C-peptide levels were not significant, even when IIR and ICR were in the model to correct for deficient β-cell secretion of these peptides.

Table 2—*Baseline metabolic and blood pressure variables by incident CHD status*

Baseline variable	Incident CHD status: CHD absent	Incident CHD status: CHD present	*P* value	*P* value*
n	125	50	—	—
Insulin (pmol/l)				
Fasting	69.5 ± 3.3	81.3 ± 7.7	0.16	0.35
Increment at 30 min	319.9 ± 25.9	268.7 ± 27.2	0.18	0.84
C-peptide (nmol/l)				
Fasting	0.90 ± 0.03	1.01 ± 0.06	0.11	0.22
Increment at 30 min	0.83 ± 0.04	0.76 ± 0.08	0.42	0.42
Glucose (mmol/l)				
Fasting	6.41 ± 0.17	8.33 ± 0.54	0.0012	0.0037
2-h	10.12 ± 0.46	13.68 ± 1.06	0.0029	0.086
Lipids (mmol/l)				
Cholesterol	6.05 ± 0.10	6.22 ± 0.17	0.37	0.25
LDL cholesterol	3.94 ± 0.09	3.98 ± 0.15	0.83	0.65
HDL cholesterol	1.36 ± 0.03	1.21 ± 0.04	0.0073	0.022
HDL2 cholesterol	0.30 ± 0.02	0.22 ± 0.03	0.028	0.077
HDL3 cholesterol	1.07 ± 0.02	0.99 ± 0.02	0.016	0.033
Triglycerides	1.60 ± 0.07	2.07 ± 0.19	0.028	0.014
Apoprotein A1 (mg/dl)	148.6 ± 2.2	141.0 ± 3.0	0.054	0.087
Apoprotein B (mg/dl)	126.9 ± 2.6	133.4 ± 4.4	0.19	0.14
Systolic blood pressure (mmHg)	135.1 ± 1.5	145.1 ± 2.8	0.0003	0.0017
Diastolic blood pressure (mmHg)	78.4 ± 0.8	84.8 ± 1.4	0.0001	0.0001

Data are means ± SEM. *Adjusted for baseline diabetes.

CONCLUSIONS — Because of the opportunity to follow a group of 175 Japanese-American men who did not have CHD at baseline, we now have identified the significant relationships of intra-abdominal fat and a number of other presumptive risk variables to incident CHD over a 10-year follow-up period.

Although this study does not explain the pathogenic relationship of visceral adiposity to CHD in Japanese-American men, it is likely that it is due to the various abnormalities that are now known to be associated with the insulin resistance syndrome. These include diabetes, hypertension, smaller and denser LDL particles, lower plasma levels of HDL cholesterol, higher plasma levels of triglycerides, plasminogen activator inhibitor-1 (PAI-1), and fibrinogen, and insulin resistance, but not plasma levels of total or LDL cholesterol (1–7,10,20–33). Unfortunately, when the baseline studies were begun in this cohort in 1983, LDL size and density and plasma levels of fibrinogen and of PAI-1 were not being measured.

Notably, fasting plasma levels of insulin or C-peptide were not significant risk factors in this population. Several longitudinal studies (e.g., the Helsinki Policemen Study [34], the Busselton Study [35], the Paris Prospective Study [36], and the British Regional Heart Study [37]) have shown an association of plasma levels of insulin with development of CHD. In part, this may be due to the much larger study samples in these studies, ranging from 1,059 in the Helsinki Study to 7,534 in the Paris Study. The Caerphilly Prospective Study involving 2,512 men, however, did not find fasting insulin concentration to be an independent risk factor for CHD (38).

However, it should be noted that fasting plasma levels of insulin or C-peptide are imperfect surrogate measures for insulin resistance, especially among individuals who have either impaired glucose tolerance or diabetes (39), in part because abnormal β-cell function may confound the association of fasting plasma levels of insulin or C-peptide with disease (40). We addressed this possibility by including in some of the statistical models variables that assess insulin or C-peptide secretion (IIR or ICR), yet fasting insulin and C-peptide remained nonsignificant. Nonetheless, in another study using as a measurement of insulin resistance the insulin suppression test and measurements of steady-state plasma glucose to estimate insulin-mediated glucose disposal, a significant relationship was obtained between insulin resistance and development of cardiovascular disease (41). Thus it is possible that the relationship of incident CHD with visceral adiposity and the absence of a relationship with fasting insulin or C-peptide may be due to the measurement of intra-abdominal fat being a more reliable indicator of insulin resistance than are fasting plasma levels of insulin or C-peptide.

The relationship of glycemia to the risk of CHD is of interest. Several studies have suggested an increased risk of CHD with increasing severity of glucose intolerance. The Whitehall Study showed at the 15-year follow-up that the relative risk of CHD was 1.2 for glucose-intolerant participants, 2.2 in those previously known to be diabetic, and 2.6 in newly diagnosed diabetic individuals, compared with participants who were nondiabetic and normoglycemic (42,43). The Paris Prospective Study showed increased relative risk of CHD mortality with hyperglycemia, 1.9 for men with impaired glucose tolerance, 2.1 for men with newly diagnosed diabetes, and 3.0 for men with previously diagnosed diabetes (43). Similar results were reported in the Framingham Study (44). Post–challenge glucose levels were associated with CHD among Japanese-American men in Honolulu (45). More recently, the U.K. Prospective Diabetes Study showed a

borderline significant relationship between myocardial infarction and glycemia among diabetic subjects (46).

There are a number of potential mechanisms whereby plasma glucose levels may influence risk of CHD, including biochemical, physiological, and cellular changes that occur in the blood and the arterial wall. Increased oxidative stress may be an important link between plasma glucose levels and CHD (47,48). Advanced glycosylated end products may generate oxygen-free radicals. These end products have been hypothesized to activate macrophage chemotaxis, induce macrophage release of cytokines, inactivate nitric oxide, increase leukocyte adhesion to the endothelium, and increase platelet aggregation, resulting in macrophage infiltration at the site of atherosclerotic plaques and in increased vulnerability of plaques to thrombosis (49–52). PAI-1 is localized in coronary arterial lesions to a greater extent in subjects with diabetes than in nondiabetic subjects, and this could lead to decreased fibrinolysis (53). Hyperglycemia results in endothelial dysfunction characterized by enhanced vasoconstriction and impaired vasodilation because of both decreased nitric oxide availability and increased endothelin production (54–56). Myocardial blood flow has been demonstrated to be lower in patients who have type 2 diabetes and to decrease when plasma levels of glucose are raised (57,58).

In conclusion, visceral adiposity is a significant prospective risk factor for incident CHD among Japanese-American men. The mechanisms responsible for this remain to be elucidated, however. It is also of interest that the plasma level of glucose was a significant predictor of CHD independent of diabetes. This latest finding has possible implications for the prevention or delay of CHD through improved glycemic control in patients with diabetes.

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