Isolated Postchallenge Hyperglycemia and the Risk of Fatal Cardiovascular Disease in Older Women and Men

The Rancho Bernardo Study

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OBJECTIVE — To determine whether diabetes defined by isolated postchallenge hyperglycemia (IPH) (2-h postchallenge plasma glucose ≥11.1 mmol/l with fasting plasma glucose [FPG] <7.0 mmol/l) increases the risk of fatal cardiovascular disease (CVD) in older women and men.

RESEARCH DESIGN AND METHODS — In a prospective study, we followed 769 men and 1,089 women, aged 50–89 years, who had no history of diabetes or myocardial infarction and demonstrated no fasting hyperglycemia (i.e., FPG <7.0 mmol/l) when they underwent oral glucose tolerance testing at baseline in 1984–1987.

RESULTS — At baseline, 70% of 125 women and 48% of 133 men with previously undiagnosed diabetes had IPH. Over the next 7 years, women with IPH had a significantly increased risk of fatal CVD and heart disease compared with nondiabetic women. This increased risk was not observed in men with IPH. This association was independent of age, hypertension, central obesity, cigarette smoking, HDL cholesterol, and triglycerides (multiply adjusted hazard ratio and 95% CI: 2.6 and 1.4–4.7 for CVD; 2.9 and 1.3–6.4 for heart disease).

CONCLUSIONS — Diabetes defined by IPH alone is common in older adults and more than doubles the risk of fatal CVD and heart disease in older women. Because the prevalence of IPH increases with age, the use of fasting glucose alone for diabetes screening or diagnosis may fail to identify most older adults at high risk for CVD and should be reevaluated.

The prevalence of type 2 diabetes (or NIDDM) increases with age, and the disease is present in nearly one in five North Americans aged ≥65 years (1). Approximately half of the people who meet current diagnostic criteria for diabetes are not aware that they have diabetes (1,2). Two-thirds of these individuals have postchallenge hyperglycemia without fasting hyperglycemia. Because postchallenge glucose levels increase with age (~0.83 mmol/l per decade) in cross-sectional (3,4) and prospective (5) studies but fasting levels increase only 0.06–0.11 mmol/l per decade (6), isolated postchallenge hyperglycemia (IPH) becomes more common with age. This has led to debate about whether older adults who have only IPH have diabetes or clinically unimportant age-related changes in glucose homeostasis (3).

In addition, the clinical importance of IPH needs to be considered in terms of the revised test criteria for diabetes recently recommended by the American Diabetes Association (ADA) Expert Committee (7). The emphasis on fasting plasma glucose (FPG)—revised downward to ≥7.0 mmol/l—might be expected to cause clinicians to miss the diagnosis of diabetes in many older adults whose diabetes would not be detected except on an oral glucose tolerance test.

The clinical significance of IPH in elderly people would be supported if it predicted an excess of diabetes-specific complications, such as retinopathy; however, because these changes can take 15 or 20 years to develop, diabetes-specific changes may be absent in elderly individuals who succumb to other complications first. In Europe and North America, cardiovascular disease (CVD) is the most common cause of death in older adults and is a well-recognized, if less specific, complication of diabetes (8). We therefore reasoned that an excess of CVD in older adults with IPH would negate the concept that this altered homeostasis is part of normal aging, would challenge the rationale for an age-specific nomogram for the diagnosis of diabetes in old age (3), and would raise questions about the utility of the 1997 ADA revised criteria for diagnosis of diabetes in older adults.

In this study we report the relationship of IPH (postchallenge plasma glucose ≥11.1 mmol/l and FPG <7.0 mmol/l) to the 7-year risk of CVD and ischemic heart disease (IHD) in community-dwelling older men and women.

RESEARCH DESIGN AND METHODS

— Participants were members of the Rancho Bernardo cohort, a California community-based study of Caucasian adults of European ancestry. In 1984–1987, 82% of residents aged 50–85 years participated in a clinic visit that included a 75-g oral glucose tolerance test performed after a 12-h overnight fast. Fasting and 2-h postchallenge plasma glucose levels were measured in a diabetes research laboratory using a glucose oxidase assay. Lipids and lipoproteins were measured in a lipid research laboratory certified by the Centers for Disease Control. Cholesterol

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Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; ECG, electrocardiogram; FPG, fasting plasma glucose; IHD, ischemic heart disease; IPH, isolated postchallenge hyperglycemia; WHR, waist-to-hip ratio.

Table 1—*Sex-specific cardiovascular risk factors in men and women with and without IPH at baseline: Rancho Bernardo Study, 1984–1987*

	Men		Women	
	Referent	IPH	Referent	IPH
n	705	64	999	90
Age (years)	69.6 ± 9.7	74.5 ± 7.8*	69.5 ± 9.2	74.5 ± 7.4*
BMI (kg/m²)	26.1 ± 3.3	25.8 ± 3.4	24.3 ± 3.6	25.4 ± 4.7†
WHR	0.914 ± 0.052	0.923 ± 0.058	0.793 ± 0.064	0.825 ± 0.059*
FPG (mmol/l)	5.46 ± 0.57	5.99 ± 0.70*	5.27 ± 0.58	5.81 ± 0.66*
Postchallenge plasma glucose (mmol/l)	6.64 ± 1.88	12.98 ± 1.70*	6.927 ± 1.76	13.07 ± 1.89*
Cholesterol (mmol/l)	11.76 ± 2.06	11.77 ± 2.21	12.62 ± 2.11	12.96 ± 2.53
LDL cholesterol (mmol/l)	7.47 ± 1.88	7.17 ± 1.71	7.54 ± 2.04	7.89 ± 2.27
HDL cholesterol (mmol/l)	3.01 ± 0.85	3.11 ± 0.99	3.88 ± 1.04	3.50 ± 1.04*
Triglycerides (log)	4.6 ± 0.5	4.7 ± 0.7	4.6 ± 0.5	4.8 ± 0.5*
Hypertension (%)	37.4	53.1†	38.7	55.6†
Alcohol use (at least one drink per week) (%)	75.9	71.8	68.0	58.9
Cigarette smoking (%)	11.1	9.4	15.2	11.1
Estrogen use (%)			30.4	28.9

Data are means ± SD unless otherwise indicated. The referent group was defined by FPG <7.0 mmol/l and postchallenge glucose <11.1 mmol/l; the IPH group was defined by FPG <7.0 mmol/l and postchallenge glucose ≥11.1 mmol/l. *$P < 0.01$ IPH; †$P < 0.05$ vs. referent group for same sex.

and triglycerides were measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott, Irving, TX), HDL cholesterol was measured by precipitation according to the protocol of the Lipid Research Clinics (9), and LDL cholesterol was calculated using the formula of Friedewald et al. (10). Systolic and diastolic blood pressure were measured in seated subjects according to the protocol of the Hypertension Detection and Follow-up Program (11); the mean of two blood pressures was recorded. Hypertension was defined as systolic blood pressure ≥160, diastolic blood pressure ≥90, or current use of antihypertensive medication. Height, weight, and waist and hip circumference were measured in subjects wearing light clothing and no shoes. BMI (weight/ height expressed in kilograms per meters squared) and waist-to-hip ratio (centimeters/centimeters) (WHR) were calculated as estimates of overall and central obesity, respectively. A 12-lead resting electrocardiogram (ECG) was obtained according to the Lipid Research Clinic's protocol and was coded by the Minnesota coding laboratory (12). Participants with Minnesota code 1.1 or a history of heart attack or severe chest pain lasting for more than 30 min (12) were considered to have had a myocardial infarction and were excluded from the present analysis.

A standard questionnaire was used to ask about a history of diabetes and weekly alcohol consumption and current cigarette smoking. Reported behaviors were indirectly validated by observing a significant positive correlation of reported alcohol intake with serum gamma glutamyl transferase and with HDL cholesterol levels, and of reported cigarette use with pulmonary function. Reported current medications were validated by a nurse, who examined pills and prescriptions brought to the clinic for that purpose.

All participants were followed for an average of 7 years; death certificates were obtained for all decedents. Underlying causes of death were coded by a certified nosologist according to the *International Classification of Diseases, Ninth Revision* (CVD death codes 400–438 and IHD death codes 410–414) (13). The diagnosis of CVD was validated by medical and interview records in 85% of a subset that represented 30% of all death certificates containing any mention of CVD. Statistical analyses were performed using SAS software (14). The Cox proportional hazards model was used to predict the independent contribution of IPH to CVD and IHD after adjusting for age and potential confounders. All probabilities are for two-tailed tests, with statistical significance defined as $P < 0.05$.

RESULTS — After exclusion of subjects with known diabetes or myocardial infarction (by history or resting ECG) at baseline evaluation in 1984–1987, there were 838 men and 1,124 women aged 50–89 years. In this group, 133 men and 125 women had newly diagnosed type 2 diabetes according to the 1997 diabetes classification (FPG ≥7.0 mmol/l and/or 2-h glucose ≥11.1 mmol/l). Among the 133 men with type 2 diabetes, 64 (48%) had IPH; among the 125 women with type 2 diabetes, 90 (72%) had IPH. The remaining 705 men and 999 women without diabetes according to either fasting or postchallenge glucose criteria serve as the referent groups for these analyses.

As shown in Table 1, both men and women with IPH were significantly older and had higher fasting and 2-h glucose levels and more hypertension than subjects without IPH. In women, but not men, IPH was also significantly and positively associated with BMI, WHR, and triglycerides and inversely associated with HDL cholesterol. Alcohol use, cigarette smoking, and estrogen use did not differ by IPH status. Results were similar in age-adjusted analyses (not shown).

Over the next 7 years, there were 70 CVD deaths and 36 IHD deaths among men and 57 CVD deaths and 32 IHD deaths among women; 6 CVD deaths and 3 IHD deaths were in men with IPH, and 15 CVD deaths and 9 IHD deaths were in women with IPH. The 7-year age adjusted CVD and IHD mortality rates were 9.4 and 4.9 in men from the referent group and 6.5 and 3.1 in men with IPH. In women, the 7-year age-adjusted CVD and IHD mortality rates were 4.7 and 2.4 in the referent group and 10.5 ($P < 0.05$ vs. referent) and 4.7 ($P < 0.01$ vs. referent) in those with IPH. In the age-adjusted Cox proportional hazards models, shown in Table 2, IPH was not associated with CVD or IHD death in men

Table 2—*IPH and the risk of CVD or IHD mortality in men and women (Cox proportional hazards results): Rancho Bernardo Study, 7-year follow-up (from 1984–1987 to 1992)*

	CVD mortality				IHD mortality			
	Men		Women		Men		Women	
IPH	RH (95% CI)	*P*	RH (95% CI)	*P*	RH (95% CI)	*P*	RH (95% CI)	*P*
Age-adjusted	0.7 (0.3–1.6)	NS	2.6 (1.5–4.8)	0.001	0.7 (0.2–2.3)	NS	3.2 (1.5–7.0)	0.003
Multiply adjusted	0.7 (0.3–1.6)	NS	2.6 (1.4–4.7)	0.005	0.6 (0.2–2.0)	NS	2.9 (1.3–6.4)	0.01

See Table 1 for definitions of referent and IPH groups. "Multiply adjusted" indicates adjustment for age, WHR, triglycerides, HDL cholesterol, hypertension, and current smoking. RH, relative hazards of IPH versus referent group.

(hazard ratios, 0.7; $P > 0.05$) but was associated with CVD and IHD mortality in women (hazard ratios, 2.6 and 3.2, respectively; $P < 0.001$ and 0.003).

Although more metabolic abnormalities were found in women with IPH than in men with IPH (Table 1), risk ratios were not materially changed in Cox models adjusted for age, WHR, triglycerides, HDL cholesterol, hypertension, and cigarette smoking, and again, IPH predicted both fatal CVD and IHD in women but not men (Table 2). When BMI replaced WHR in these models, it was not associated with CVD or IHD death in men or women. Men and women with IPH had higher fasting glucose levels than men and women without IPH. When fasting glucose was added to these models, it did not materially change the results; fasting glucose was independently and directly associated with CVD deaths in women ($P = 0.04$). Redefining IPH by the 1985 World Health Organization's criteria (15) (FPG <7.8 mmol/l) yielded an additional 10 men and 8 women with IPH; the absent association of IPH with fatal CVD in men and its strong association in women persisted in analyses based on this redefinition of IPH (data not shown). Using the 1985 criteria for impaired glucose tolerance (FPG <7.8 mmol/l and 2-h postchallenge glucose 7.8–11.1 mmol/l), we found no association between impaired glucose tolerance and CVD or IHD in men or women (A.F., E.B.C., unpublished observations).

CONCLUSIONS — In this cohort of community-dwelling older men and women, diabetes based on IPH alone was a strong independent predictor of CVD and IHD in women but not in men; these results are compatible with women's greater risk of CVD associated with diabetes, as reported in many other studies (8). This difference persisted in analyses adjusting for all the measured risk factors, including those that differed by sex (obesity, HDL cholesterol, and triglycerides). It is possible that more high-risk men with IPH-defined diabetes had already died, but this seems unlikely because the CVD death rates in diabetic men and women in this cohort were very similar (16). The sex difference was not explained by a different glycemia-CVD threshold, because impaired glucose tolerance did not predict CVD or IHD in either sex in this cohort (A.F., E.B.C., unpublished observations). Most likely, the absence of the glycemia-CHD effect in men was an artifact of the smaller number of men with IPH than women with IPH.

Whatever the mechanism for the different findings between men and women with IPH, these results strongly suggest that diabetes diagnosed by IPH is not a benign phenomenon in women, and they cast doubt on the use of age-specific nomograms to define diabetes or normoglycemia in the elderly. These results also have implications for the use of fasting hyperglycemia as an acceptable screening test for diabetes in older adults. Fully 72% of women with previously undiagnosed diabetes had IPH, a diagnosis that would have been missed had only tests of fasting glucose been used.

There were three reasons in the ADA's revised guidelines for the focus on fasting glycemia in the screening and diagnosis of diabetes: *1*) patients and physicians do not like the glucose tolerance test, and therefore it is not used; 2) in the studies cited, the fasting glucose level that correlated most closely with a postchallenge level of 11.1 mmol/l was 7.0 mmol/l; and *3*) these levels of fasting glucose and postchallenge glucose were equally good predictors of diabetes-specific adverse outcomes such as retinopathy. The Expert Committee's recommendation, however, was based on studies that did not include subjects >75 years of age (7). As our study suggests, the public health impact may be different in elderly people—particularly in women, who tend to have higher postchallenge glucose levels (4) and longer life expectancy (17) than men, and who lose most of their protection against IHD when they develop diabetes (16).

We recommend that other investigators determine both the prevalence of IPH in older adults with previously undiagnosed diabetes and its subsequent association with CVD risk in men and women.

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