# Postchallenge Glucose Concentration and Coronary Heart Disease in Men of Japanese Ancestry

## Honolulu Heart Program

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**SUMMARY**

**Since 1965, the Honolulu Heart Program has followed 8006 men of Japanese ancestry, aged 45–70 yr at study entry, for the development of cardiovascular disease. To investigate the role of glucose concentration 1 h after a 50-g challenge on the risk of fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI), 6394 nondiabetic men were followed for 12 yr for the first development of CHD. The rate of fatal CHD increased linearly with amount of glucose. Men in the fourth quintile of postchallenge glucose (157–189 mg/dl) had twice the age-adjusted risk of fatal CHD of those in the lowest quintile ($P < .05$). Relative risk increased to threefold among those in the top quintile and remained statistically significant after adjustment for other risk factors including body mass, total cholesterol, hypertension, left ventricular hypertrophy, and hematocrit ($P < .001$). When glucose was considered as a linear term in the proportional hazards model, a highly significant relation was noted with fatal CHD alone and when combined with nonfatal MI ($P < .001$). We conclude that a continuously increasing risk gradient exists between postchallenge glucose and subsequent CHD that is independent of other known risk factors. *Diabetes* 36:689–92, 1987**

Coronary heart disease (CHD) is much more common among subjects with diabetes mellitus than among nondiabetic individuals (1). Among nondiabetics, however, the relationship of elevated concentration of glucose to the incidence of CHD is controversial. Although some studies suggest a nonlinear association of glucose to heart disease, few studies have had enough events to adequately address this question.

The Whitehall study demonstrated an apparent nonlinear relationship between glucose and heart disease, with a twofold increase of CHD occurring in men above the 95th percentile of postchallenge glucose compared with those in the lowest quintile (2). The Bedford survey reported that elevated postchallenge glucose (120–199 mg/dl) was predictive of cardiovascular mortality only among women (3). More recently, Barrett-Connor et al. (4) have shown that fasting blood glucose is linearly related to the risk of CHD in men, with an apparent threshold effect in women. In a comprehensive review of earlier studies, the International Collaborative Group (5) failed to find a clear role for glucose in the etiology of CHD.

This report examines the nature of the relationship between 1-h blood glucose concentration after a 50-g challenge and the 12-yr incidence of fatal CHD and nonfatal myocardial infarction (MI) in 6394 men of Japanese ancestry in the Honolulu Heart Program.

### MATERIALS AND METHODS

Since 1965, the Honolulu Heart Program has followed 8006 men, aged 45–70 yr at study entry, of Japanese ancestry living on the island of Oahu for the development of cardiovascular disease. As part of a baseline physical examination, determination of several cardiovascular risk factors was made. In addition, initial screening identified prevalent cases of CHD and 601 cases of diabetes with clinical history (physician diagnosed or receiving insulin or oral hypoglycemic agents). These individuals were excluded in this report. There were 669 subjects receiving antihypertensive medication who were also excluded due to the potential effects of such treatment on glucose tolerance. This left 6394 men in the analyses.

Fatal CHD was defined according to the following standardized criteria: *1*) any death in which autopsy findings, in conjunction with a consistent clinical history, showed the

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TABLE 1
Distribution of 1-h serum glucose 50-g postchallenge in three studies

| | Glucose concentration (mg/dl) | | | |
|---|---|---|---|---|
| | >160 | >180 | >200 | >220 |
| Honolulu Heart Study | 38 | 26 | 16 | 10 |
| Puerto Rico Heart Health Program* | 38 | 23 | 13 | 8 |
| Health Examination Survey† | 18 | 10 | 5 | 3 |

Values are percentage above specified glucose concentration.
*Ref. 12; †ref. 13.

immediate or principal cause of death to be due to an acute or recent MI or to fresh coronary occlusion without formation of a MI; *2*) an acute or recent MI with documented electrocardiographic (ECG) or enzyme evidence, terminating in death within 1 mo after onset of the episode, but without autopsy confirmation; *3*) sudden death within 24 h after the onset of coronary-type chest pain, but without documented ECG or enzyme evidence of acute MI or without autopsy confirmation; *4*) sudden death (not accompanied by coronary-type chest pain) within 1 h for an asymptomatic or apparently healthy person in the absence of other attributable causes; and 5) death due to chronic congestive heart failure or dysrhythmia in men who had previously experienced any of the specified manifestations of CHD in the absence of other cardiovascular diseases considered to be the underlying cause of death.

Nonfatal MI was defined as *1*) acute coronary-type chest pain with diagnostic serial ECG changes or enzyme elevation that did not lead to death within 1 mo of the onset of the episode or *2*) temporal changes in the ECG considered to be diagnostic of an interim MI with or without compatible history.

Serum glucose was determined by the autoanalyzer N-2B method with a modification of Hoffman's potassium ferricyanide method (8) in venous blood, sampled 1 h after ingestion of a 50-g glucose solution, administered throughout the day without regard to fasting status. The required information to apply the National Diabetes Data Group criteria (9) to define glucose tolerance was not available.

Age-adjusted mean levels of several selected covariates were compared across quintiles of glucose with analysis of covariance models including logistic regression for binary responses (10). Quintile 1 range was 40–114 mg/dl; quintile 2, 115–133 mg/dl; quintile 3, 134–156 mg/dl; quintile 4, 157–189 mg/dl; and quintile 5, 190–532 mg/dl. Covariates included total cholesterol, body mass [wt (kg)/ht ($m^2$)], hypertensive status (blood pressure consistently >160/90 mmHg), cigarette use, ECG evidence of left ventricular hypertrophy, and hematocrit.

To estimate the independent effects of 1-h postchallenge glucose on both fatal CHD and combined fatal and nonfatal events, proportional hazards models were used to follow subjects for the first development of an event over 12 yr of follow-up (11). One analysis followed subjects for fatal CHD only, and the second followed subjects for either fatal CHD or nonfatal MI. Comparisons were made controlling for the above covariates and for age alone. Age was adjusted to the age distribution of the entire study population.

## RESULTS

Table 1 shows the distribution of glucose after a 50-g challenge in Honolulu, Puerto Rico (12), and the Health Examination Survey in 1962–1965 (13) studies. Data from Puerto Rico and the Health Examination Survey were obtained in the fasting state from men aged 55–64 yr. Distribution of glucose in Honolulu men, however, is similar to that in the Puerto Rican men, whereas the national probability data displayed a lower percentage of high values. Although laboratory variability cannot be discounted, differences in the distribution of glucose may reflect true population differences or methodological differences. The Puerto Rican laboratory, which was standardized with the Centers for Disease Control program, appears to yield results similar to those from the Honolulu study.

Table 2 presents age-adjusted 12-yr incidence rates (per 1000) of fatal CHD and combined fatal CHD and nonfatal MI by 1-h serum glucose levels. A stepwise increase was noted for both fatal CHD and combined events. The age-adjusted rate of fatal CHD nearly doubled from quintile 1 to quintile 3 ($P < .05$) and was three times higher in quintile 5 than in quintile 1 ($P < .001$). A less abrupt but similar increasing trend was noted for combined events ($P < .01$).

Table 3 shows age-adjusted mean levels of the major CHD risk factors by glucose level. Neither total cholesterol concentration nor the proportion of current smokers exhibited a consistent trend with increasing glucose level. The proportion of hypertensive subjects rose with each quintile, however, as did mean body mass ($P < .001$ for each), although the absolute increase in body mass was small. Frequency of left ventricular hypertrophy was significantly higher in quintiles 4 and 5, as was the mean hematocrit concentration ($P < .001$ for each).

Table 4 presents both the age-adjusted and risk-factor–

TABLE 2
Twelve-year age-adjusted incidence of fatal CHD and combined fatal CHD and nonfatal MI by casual 1-h serum glucose

| Quintile (glucose) | Number at risk | Fatal CHD | Events (*n*) | Fatal CHD and nonfatal MI | Events (*n*) |
|---|---|---|---|---|---|
| 1 (40–114 mg/dl) | 1306 | 9.30 | 12 | 35.6 | 43 |
| 2 (115–133 mg/dl) | 1248 | 12.2 | 15 | 40.0 | 49 |
| 3 (134–156 mg/dl) | 1262 | 17.1 | 22 | 48.9 | 62 |
| 4 (157–189 mg/dl) | 1288 | 20.7 | 28 | 52.6 | 69 |
| 5 (190–532 mg/dl) | 1290 | 30.3 | 42* | 59.9 | 80* |

Values are rate per 1000. CHD, coronary heart disease; MI, myocardial infarction.
*$P < .001$, test for linear trend.

TABLE 3
Age-adjusted levels of risk factors by quintile of 1-h serum glucose

| | Quintile | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Total cholesterol (mg/dl) | 215.2 ± 37.2 | 216.0 ± 35.2 | 217.2 ± 38.0 | 219.2 ± 36.1* | 217.3 ± 40.0 |
| Body mass (kg/m²) | 23.3 ± 2.9 | 23.5 ± 2.9† | 23.6 ± 3.0† | 23.8 ± 3.1‡ | 23.9 ± 3.4‡ |
| Smokers (%) | 46.2 ± 50.0 | 42.5 ± 49.5† | 42.6 ± 49.6 | 47.1 ± 50.0 | 49.5 ± 50.0 |
| Hypertensive (%) | 10.3 ± 29.4 | 11.9 ± 32.3 | 16.5 ± 36.9‡ | 16.5 ± 37.3‡ | 20.8 ± 41.2‡ |
| Left ventricular hypertrophy (%) | 0.6 ± 7.8 | 0.7 ± 7.9 | 0.5 ± 7.4 | 1.6 ± 12.6† | 1.7 ± 13.3* |
| Hematocrit (mg/dl) | 44.3 ± 2.9 | 44.3 ± 2.9 | 44.5 ± 3.0 | 44.7 ± 3.0‡ | 45.1 ± 3.1‡ |
| 1-h glucose (mg/dl) | 99.7 ± 12.1 | 123.9 ± 5.5 | 144.7 ± 6.6 | 171.7 ± 9.6 | 230.7 ± 42.8 |

Values are means ± SD.
*$P < .01$, †$P < .05$, ‡$P < .001$, significant differences compared with quintile 1.

adjusted relative risks for each quintile of postchallenge glucose level, with quintile 1 as the reference category. As shown, there was a consistent, graded increase in the adjusted relative risk of both fatal CHD and combined fatal CHD and nonfatal MI. This trend remained significant after adjustment for other risk factors ($P < .001$). When 1-h glucose was considered as a continuous variable, a significant association was noted with both fatal CHD and combined fatal CHD and nonfatal MI ($P < .001$). No evidence of a threshold effect was noted.

## DISCUSSION

Previous results from the Honolulu Heart Program have shown that diagnosed diabetes and glucose concentrations above the 90th percentile (225 mg/dl) were predictive of CHD mortality over 9 yr (14). This report excluded subjects known to be diabetic and examined the relationship of postchallenge glucose to fatal CHD and nonfatal MI. Prevalence of known diabetes at baseline was 8%, and national data suggest that an equal proportion may be undiagnosed (15). Thus, many individuals above the 90th percentile of 1-h glucose may have undiagnosed diabetes and share a similar degree of risk for CHD with known diabetic men.

Whether an excess risk of CHD exists at more modest elevations of glucose is not known. Current data suggest a monotonically increasing risk of heart disease with increasing serum glucose.

The role of asymptomatic hyperglycemia in the etiology of CHD has been reviewed by the International Collaborative Group (5). Although a clear association was not found, few of the studies examined contained adequate numbers of coronary events to yield sufficient statistical power. Data from the Whitehall study suggest a threshold effect of glucose on the risk of CHD death in men (2). The Busselton study reported that in older men and women, 1-h (but not 2-h) glucose >200 mg/dl was related to cardiovascular disease end points occurring in 12 yr (16). The Helsinki policemen's study found that 1-h glucose was significantly associated with both fatal and nonfatal events in analyses uncontrolled for confounding risk factors (17). The Tecumseh study reported, however, an excess of coronary mortality among those with high blood glucose after adjusting for other risk factors (18). Although fasting blood glucose was linearly related to risk of cardiovascular disease among men in the Rancho Bernardo study (4), the Puerto Rico Heart Health study failed to find an effect of elevated glucose on risk of CHD death in nondiabetic men (12). Our results, therefore, are among the first to suggest that the risk of CHD increases monotonically with increases in postchallenge glucose concentration. Furthermore, a threshold effect was not detected in our data after comparing various subgroups of glucose quintiles.

Although an independent role for hyperglycemia remains unclear, the disparity between studies may partly result from dissimilar methodologies and low statistical power to detect a true association. Furthermore, Liu et al. (19) have shown that the ability of an oral glucose tolerance test to characterize an individual's glycemic status is relatively low and that it is possible that insulin or the ratio of insulin to glucose may be better able to quantitate glucose homeostasis within an individual (16,17,20).

In summary, our findings show that 1-h glucose was related in a continuously increasing fashion to the risk of fatal CHD alone and when combined with nonfatal MI. The excess in fatal coronary events among hyperglycemic subjects observed in this and other studies indicates that elevated glucose concentration itself may be atherogenic or that glucose may be reflecting underlying disturbances in carbohydrate metabolism (e.g., hyperinsulinemia or insulin resistance) or other metabolic derangements that have yet to be fully defined. Such factors may include alterations in the concentration or composition of HDL cholesterol (which would not

TABLE 4
Estimated relative risk and 95% confidence limits of fatal CHD and combined fatal CHD and nonfatal MI by 1-h postchallenge glucose with quintile 1 as reference

| Quintile | Fatal CHD | Fatal CHD and nonfatal MI |
|---|---|---|
| 2 | | |
| Age adjusted | 1.1 (0.5, 2.3) | 1.2 (0.8, 1.8) |
| Risk-factor adjusted | 1.1 (0.5, 2.3) | 1.2 (0.8, 1.8) |
| 3 | | |
| Age adjusted | 1.6 (0.8, 3.2) | 1.4 (0.9, 2.1) |
| Risk-factor adjusted | 1.4 (0.7, 2.8) | 1.3 (0.9, 1.9) |
| 4 | | |
| Age adjusted | 2.0* (1.0, 3.7) | 1.6* (1.1, 2.3) |
| Risk-factor adjusted | 1.7 (0.9, 3.2) | 1.4 (0.9, 2.0) |
| 5 | | |
| Age adjusted | 3.0† (1.6, 5.5) | 1.8‡ (1.2, 2.6) |
| Risk-factor adjusted | 2.4† (1.3, 4.6) | 1.5* (1.1, 2.1) |

Ninety-five percent confidence limits given in parentheses. CHD, coronary heart disease; MI, myocardial infarction.
*$P < .05$, †$P < .001$, ‡$P < .01$, excess risk relative to those in quintile 1.

be accounted for in the adjustment for total cholesterol), clotting or platelet abnormalities, or disturbances in apolipoprotein metabolism.

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