

# Relationship of Postload Plasma Glucose to Mortality With 19-Yr Follow-Up

## Comparison of one versus two plasma glucose measurements in the Chicago Peoples Gas Company Study

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**OBJECTIVE**— To explore the relationship of one versus two postload plasma glucose measurements to 19-yr mortality in men in the Chicago Peoples Gas Company Study.

**RESEARCH DESIGN AND METHODS**— One-hour postload plasma glucose was measured twice (1.4 yr apart, 1965–1967) for 873 nondiabetic men 34–65 yr of age. Serum cholesterol, blood pressure, height, and weight were measured. Data on smoking habits were obtained. Mortality follow-up was complete through July 1986, 19 yr after second glucose load.

**RESULTS**— In prospective analyses, with each of three glucose values—first, second, and mean of first and second—coronary, cardiovascular, and all-cause age-adjusted mortality rates were higher in quintiles 3, 4, and 5 compared with quintile 1, with a significant linear trend. Multivariate analyses with glycemia as a continuous variable confirmed a positive independent association between plasma glucose and mortality endpoints with first measurement and mean of two values but not with second. With dichotomization of plasma glucose ( $\geq 11.2$  mM [ $\geq 200$  mg/dl]) for 30 men hyperglycemic both times, CHD and CVD death rates were significantly higher (odds ratios 2.3–2.7) compared with those for 758 men consistently nonhyperglycemic. In contrast, for those hyperglycemic once only, death rates were not significantly higher. Results of multivariate analyses were consistent with these findings.

**CONCLUSIONS**— These data indicate a significant relationship of asymptomatic hyperglycemia on repeat examinations to coronary and cardiovascular mortality independent of other factors measured in the study.

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CVD, CARDIOVASCULAR DISEASE; CHD, CORONARY HEART DISEASE; BMI, BODY MASS INDEX; IGT, IMPAIRED GLUCOSE TOLERANCE.

Although the role of clinical diabetes as an independent risk factor for major adult CVDs has been established, the relationship between asymptomatic hyperglycemia and CVD is unclear (1–3). For example, standardized analyses of cross-sectional and longitudinal data from 15 populations yielded inconsistent findings (2). Later studies have failed to provide conclusive evidence. Thus, reexamination of the Whitehall data suggested a threshold effect, with increased CHD mortality only for men with postload plasma glucose in the highest 5% of the distribution (4). Data of the Bedford Survey and the Chicago Heart Association Detection Project in Industry indicated an increase in CHD risk for women with postload hyperglycemia but not for men (3,5).

Possible causes of interstudy inconsistencies include lack of standardization of both methods and diagnostic criteria for assessing postload hyperglycemia and inadequate ability of a single blood glucose measurement to characterize an individual's glycemic status. The relatively large ratio of intra- to interindividual variation makes a single blood glucose measurement a limited tool for validly ranking individuals within a population; probability of misclassification is substantial (6,7). This can obscure a true low-order association between blood glucose and CVD risk. Increasing the number of measurements per person allows a more accurate characterization of the individual's true glycemic status. However, studies based on repeat plasma glucose measurements are rare.

This article presents data on the relationship of single and repeat 1-h postload plasma glucose determinations to mortality in the population of middle-aged men from the Chicago Peoples Gas Company Study.

### RESEARCH DESIGN AND METHODS

In 1965, 1-h plasma glucose response to a 50-g oral glucose load was introduced as part of the peri-

**Table 1—Descriptive statistics and correlation coefficients between measurements made at first and second examination**

	EXAMINATION		R*
	FIRST	SECOND	
PLASMA GLUCOSE 1-H POSTLOAD (MG/DL)	136.4 ± 37.7 (7.6 ± 2.1 )	142.9 ± 42.8 (8.0 ± 2.4 )	0.552
SERUM CHOLESTEROL (MG/DL)	226.7 ± 39.6 (5.9 ± 0.9 )	225.2 ± 38.1 (5.9 ± 1.0 )	0.715
BLOOD PRESSURE (MMHG)			
SYSTOLIC	131.7 ± 16.5	131.5 ± 17.6	0.751
DIASTOLIC	79.8 ± 9.7	78.9 ± 10.3	0.670
BMI (KG/M <sup>2</sup> )	27.1 ± 3.5	27.1 ± 3.6	0.961
AGE (YR)	51.1 ± 7.7	52.5 ± 7.4	

Values are means ± SD. SI units (mM) given in parentheses.

\*Product moment correlation coefficient.

odic examination of employees conducted by the Medical Department of the Peoples Gas Company in Chicago. Results are given for a cohort of 873 men 34–65 yr of age in 1965 who were tested by this method between 1965 and 1967. Men 34–49 yr old (40% of cohort) were surveyed biennially, and men 50–65 yr old (60% of cohort) were surveyed annually. Mean time interval between the two tests was 1.4 yr. At the periodic medical examination, the medical history included query about diagnoses of diabetes and/or myocardial infarction made by their personal private physicians; men with either or both of these diagnoses were excluded from this study. Blood was drawn 1 h after load, samples were collected in fluoridated tubes, and plasma was separated within 1 h. Plasma glucose was determined by automated chemistry with the modified Hoffman method (8). Serum cholesterol was determined by the Abell-Kendall method (9). The research laboratory was a regional reference center designated by the Lipid Standardization Program, Centers for Disease Control, Atlanta, Georgia. Quality-control procedures included internal standards to assess and help maintain stability of analytical measurement over time. Blood pressure was measured in a seated position; first and fifth Korot-

koff sounds were recorded, and the mean of three measurements was used in analysis. Height and weight were recorded; BMI was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Data were obtained on smoking habits. A 12-lead resting electrocardiogram was performed and coded according to the Minnesota code. Electrocardiogram abnormalities at baseline were defined by Whitehall ischemia criteria (codes Q1.1–1.3, 4.1–4.4, 5.1–5.3, 7.1) (2). Mortality follow-up was complete through July 1986, i.e., 19 yr after second examination with a glucose load. Death certificates were obtained for all decedents; one physician reviewed and classified causes of death without access to baseline data.

Results are age-adjusted mortality rates per 1000. Age adjustment was done by covariance analysis. Quintile analysis was used to assess relationship between plasma glucose and mortality. Rates were tested for significant differences and linear trend by standard methods (10). Additional univariate analyses were done with dichotomization of plasma glucose and definition of hyperglycemia as 1-h postload plasma glucose ≥200 mg/dl (11.2 mM). Proportional-hazards (Cox) regression analyses with plasma glucose either as a continuous or a categorical variable were used to assess the independent role of

plasma glucose as a cardiovascular risk factor. For these multivariate analyses, a complete data set on all variables was available on 838 men.

## RESULTS

### Descriptive statistics

Data on continuous variables for the cohort at the time of first and second tests are reported in Table 1, together with correlation coefficients between first and second measurements. At first survey, age-specific mean values for 1-h postload plasma glucose were 7.1 mM (126.7 mg/dl) for men 34–44 yr old, 7.5 mM (134.0 mg/dl) for men 45–59 yr old, and 144.7 mg/dl (8.1 mM) for men 55–64 yr old; this pattern prevailed at second survey also. For all 838 men, group mean plasma glucose was 7.6 mM (136.4 mg/dl) at first survey and 8.0 mM (142.9 mg/dl) at second examination. Changes for individuals were in both directions and—at least for those at the extremes in the first examination—partly reflected regression to the mean. Thus, differences in plasma glucose values between first and second measurements were 1.4, 1.0, 0.2, 0.1, and –0.9 mM, respectively (25, 17, 4, 2, and –16 mg/dl) for men in quintiles 1–5, respectively. Minimal or no changes were observed in mean BMI, serum cholesterol, and blood pressure. The correlation coefficient between the two measurements was lower for blood glucose than for any other variable. At both the first and second examinations, there were low-order (0.110–0.254) significant correlations of 1-h postload glucose with systolic blood pressure, diastolic blood pressure, BMI, and age (data not shown). Other low-order correlations between variables were in accordance with expectations based on previous findings for this and other samples of middle-aged American men.

## Relationship of postload plasma glucose to mortality

Table 2—Nineteen-year age-adjusted mortality (rate/1000) by 1-h postload plasma glucose quintiles at 1st and 2nd measurements and average of 2 measurements (N = 873)

EXAMINATION QUINTILE	PLASMA GLUCOSE		CHD		CVD		ALL CAUSES	
	(MG/DL)	(MM)	DEATHS	RATE	DEATHS	RATE	DEATHS	RATE
<b>FIRST</b>								
1 (N = 185)	91.4	5.1	18	113.2	19	125.0	43	279.8
2 (N = 166)	114.1	6.4	14	87.3	17	106.6	44	273.8
3 (N = 182)	132.3	7.4	22	120.4	27	147.7	57	311.8
4 (N = 171)	153.3	8.6	33	181.4	44	241.1	72	386.6
5 (N = 169)	194.9	10.9	31	175.4	37	207.6	75	419.7
QUINTILE 5/QUINTILE 1 RISK RATIO*			1.69		1.84		1.64	
95% CONFIDENCE LIMIT*			0.94, 3.04		1.05, 3.23		1.12, 2.40	
$\chi^2$ FOR LINEAR TREND			6.3†		9.0‡		11.7§	
<b>SECOND</b>								
1 (N = 173)	93.2	5.2	16	98.3	18	112.4	41	254.1
2 (N = 183)	117.4	6.6	16	92.4	20	116.5	49	282.5
3 (N = 165)	135.8	7.6	26	159.5	34	208.9	60	369.4
4 (N = 180)	158.8	8.9	25	137.2	31	169.7	63	344.8
5 (N = 172)	210.1	11.8	35	192.3	41	222.2	78	420.5
Q5/Q1 RISK RATIO*			2.14		2.18		1.81	
95% CONFIDENCE LIMIT*			1.18, 3.89		1.25, 3.80		1.24, 2.65	
$\chi^2$ FOR LINEAR TREND			8.7‡		9.4‡		12.7§	
<b>AVERAGE QUINTILE</b>								
1 (N = 179)	97.3	5.4	17	106.9	18	117.8	42	270.2
2 (N = 171)	118.9	6.7	17	100.2	20	118.0	43	253.7
3 (N = 173)	134.7	7.5	19	117.3	26	161.0	52	322.8
4 (N = 182)	154.9	8.7	33	174.5	41	215.5	81	424.8
5 (N = 168)	194.4	10.9	32	176.8	39	212.3	73	393.6
Q5/Q1 RISK RATIO*			1.76		1.96		1.56	
95% CONFIDENCE LIMITS			0.97, 3.20		1.11, 3.45		1.06, 2.30	
$\chi^2$ FOR LINEAR TREND			8.9‡		9.9‡		12.6§	
<b>ALL</b>			118		135.2		144	
					164.9		291	
							333.3	

\*Determined with proportional-hazards (Cox) regression model, including age and indicators for quintiles.

†P < 0.05.

‡P < 0.01.

§P < 0.001.

### Prospective analyses: plasma glucose from 1965 to 1967 and mortality by cause-quintile analyses

A graded association with a significant linear trend was observed between plasma glucose and age-adjusted mortality rates with all three plasma glucose assessments (Table 2). In all nine analyses, rates were higher for quintiles 3–5 compared with quintiles 1 and 2, with Q5/Q1 risk ratios in the range 1.6–2.2. No stronger association was de-

tected between plasma glucose and mortality endpoints with use of the average of two measurements compared with the use of the first or second measurement only.

### Analyses with dichotomization of plasma glucose.

With dichotomization of the cohort based on plasma glucose of 11.2 mM (200 mg/dl) as the cutoff point and identification of three subgroups based on response at both surveys, 785 men were

nonhyperglycemic at both surveys; 85 were hyperglycemic at one survey only; and 30 were hyperglycemic at both surveys. Chart review showed that, at previous periodic medical examinations, 29 of these 30 were assessed as nondiabetic and the other as suspect diabetic. Of the 85 men who were hyperglycemic at one survey only, 24 were hyperglycemic at the first examination only, of whom 9 (38%) subsequently died; 61 were hyperglycemic at the second examination only, of whom 25 (41%) subsequently

**Table 3—Classification of men based on 2 measurements of postload plasma glucose (glucose values and 19-yr age-adjusted mortality [rates/1000])**

GLYCEMIC STATUS	PLASMA GLUCOSE		CHD		CVD		ALL CAUSES	
	(MG/DL)	(MM)	DEATHS	RATE	DEATHS	RATE	DEATHS	RATE
NORMOGLYCEMIC TWICE (N = 758)*	130.4	7.3	96	128.9	118	158.9	240	323.1
HYPERGLYCEMIC ONCE ONLY (N = 85)	187.0	10.5	13	138.0	16	166.8	34	356.9
HYPERGLYCEMIC TWICE (N = 30)	239.3	13.4	9	285.7	10	312.8	17	525.3
RISK RATIO (HYPERGLYCEMIC TWICE VS. NONE)†			2.42		2.13		1.78	
95% CONFIDENCE LIMITS			1.22–4.80		1.11–4.08		1.09–2.92	

\*Normoglycemia is 1-h postload plasma glucose <11.2 mM (<200 mg/dl).

†Risk ratio determined with Cox regression model including age and indicators for number of hyperglycemic measurements.

died. The percentages dying of CHD and CVD were also similar for both groups of men. For the 24 men who were hyperglycemic at first survey only, average weight at second survey (average interval 1.3 yr) was 1.1 kg (2.4 lbs) lower; average systolic blood pressure was 0.2 mmHg higher; average diastolic blood pressure was 2.0 mmHg lower; and average serum total cholesterol was 1.0 mM (17.2 mg/dl) lower. These findings indicate that changes in diet probably played a role in producing the lower plasma glucose levels at second survey for at least some of these 24 men.

For the 30 men who were hyperglycemic at both surveys (3.4% of cohort), age-adjusted mortality rates were consistently and significantly higher compared with rates for the 758 men who were normoglycemic at both examinations, with risk ratios ranging from 1.8 for all-cause mortality to 2.4 for CHD mortality (Table 3). In contrast to the findings for the 30 men with persistent hyperglycemia, for the 85 men with hyperglycemia at one examination only (either first or second), rates were not significantly different from those for normoglycemic men.

#### Multivariate regression analyses

Multivariate proportional-hazards (Cox) regression analyses to assess relationship of postload plasma glucose to CHD, CVD, and total mortality with control for major CVD risk factors indicated that,

with plasma glucose as a continuous variable, a significant independent relationship of glycemia to mortality existed based on first but not second measurement (Table 4). With use of the mean of both glucose measurements, glycemia was related significantly to CHD, CVD, and all-cause mortality.

With plasma glucose used as a dichotomized variable in Cox multivariate analyses, hyperglycemia at both examinations was related significantly and independently to CHD and CVD mortality, unlike once only hyperglycemia (Table 5).

**CONCLUSIONS**— This study addressed the unresolved issue of whether postload plasma glucose is a significant independent risk factor for mortality in middle-aged American men. It explored this matter with results from two examinations done 1–2 yr apart in 873 men of the Chicago Peoples Gas Company Study. In univariate analyses, results of the two examinations were consistent in showing a significant positive relationship of glycemia to 19-yr coronary, cardiovascular, and all-cause mortality, but in multivariate analyses with control for other risk factors, results from each of the two examinations were inconsistent. That is, a positive independent significant relationship of glycemia to the three 19-yr mortality endpoints was observed, based on glycemia data from the first examination, but no significant indepen-

dent relationship based on the second examination. When findings from the two examinations were considered together, there was a significant independent relationship of glycemia to 19-yr mortality. This was the finding for all three mortality endpoints, with plasma glucose considered a continuous variable, and for CHD and CVD mortality with glycemia as a dichotomized variable. For the former analysis, each man's mean glucose level from the two examinations was used. For the latter, each man was classified as consistently hyperglycemic (no or yes) based on 1-h plasma glucose  $\geq 11.2$  mM ( $\geq 200$  mg/dl) in both examinations.

As to the inconsistent findings in multivariate analyses in the first compared with the second Peoples Gas Company cohort examinations, considered separately, the following comments seem relevant: These findings are concordant with the inconsistency in results of similar multivariate analyses across population samples, e.g., for the 11 populations assessed in the joint report of the International Collaborative Group (2,11). In most but not all of these population samples, with use of a single glycemia measurement, plasma glucose was not a significant independent risk factor for coronary or cardiovascular mortality. This was the finding when the glycemia value was a fasting, 1-h postload, or 2-h postload one. Therefore, it is not likely that the inconsistency in this study of

## Relationship of postload plasma glucose to mortality

**Table 4—Proportional-hazards regression analyses, coefficients, plasma glucose, other risk factors, and 19-yr mortality by cause**

	EXAMINATION		AVERAGE
	FIRST	SECOND	
<b>CHD</b>			
PLASMA GLUCOSE (MG/DL)	0.0058	0.0031	0.0055*
AGE (YR)	0.0584†	0.0660†	0.0598†
SERUM CHOLESTEROL (MG/DL)	0.0082†	0.0056*	0.0081†
SYSTOLIC BLOOD PRESSURE (MMHG)	0.0237†	0.0169‡	0.0223†
BMI (KG/M <sup>2</sup> )	-0.1440	-0.2163	-0.2129
BMI <sup>2</sup>	0.0024	0.0040	0.0037
CIGARETTES/DAY	0.0242‡	0.0254†	0.0244†
WHITEHALL ELECTROCARDIOGRAM ISCHEMIA (0,1)	0.4773*	0.6053*	0.5150*
<b>CVD</b>			
PLASMA GLUCOSE (MG/DL)	0.0060‡	0.0024	0.0050*
AGE (YR)	0.0670†	0.0750†	0.0684†
SERUM CHOLESTEROL (MG/DL)	0.0079†	0.0060‡	0.0081
SYSTOLIC BLOOD PRESSURE (MMHG)	0.0262†	0.0195†	0.0252†
BMI (KG/M <sup>2</sup> )	-0.1330	-0.1859	-0.1865
BMI <sup>2</sup>	0.0022	0.0034	0.0032
CIGARETTES/DAY	0.0265†	0.0280†	0.0268†
WHITEHALL ELECTROCARDIOGRAM ISCHEMIA (0,1)	0.5575*	0.6774‡	0.5882‡
<b>ALL CAUSES</b>			
PLASMA GLUCOSE (MG/DL)	0.0044‡	0.0019	0.0037*
AGE (YR)	0.0811†	0.0841†	0.0811†
SERUM CHOLESTEROL (MG/DL)	0.0018	0.0012	0.0018
SYSTOLIC BLOOD PRESSURE (MMHG)	0.0118†	0.0126†	0.0135†
BMI (KG/M <sup>2</sup> )	-0.3237*	-0.4084‡	-0.3969‡
BMI <sup>2</sup>	0.0057*	0.0073‡	0.0070‡
CIGARETTES/DAY	0.0287†	0.0304†	0.0292†
WHITEHALL ELECTROCARDIOGRAM ISCHEMIA (0,1)	0.5125‡	0.5823†	0.5358‡

\*P < 0.05.

†P < 0.001.

‡P < 0.01.

Peoples Gas Company men is primarily because of use of 1-h postload plasma glucose values rather than 2-h or fasting values. It may be attributable partly to possible changes in life-style (e.g., diet, exercise) made by these 24 men based on their learning of this finding; their lower group mean values for weight, serum cholesterol, and diastolic blood pressure at second compared with first survey indicate that this happened to at least some men between 1965 and 1967. Impact on subsequent mortality risk cannot be

measured. In any case, for the remaining 61 of the 85 men who were hyperglycemic once only, hyperglycemia occurred at the second survey, not the first; precluding a role for preventive life-style change, at least before 1967. Furthermore, no changes were observed between first and second examinations for mean BMI, serum cholesterol, and blood pressure in the entire group of 873 men (Table 1), suggesting that changes in life-style happened rarely among these men between 1965 and 1967. Another possi-

ble explanation for the inconsistency in relationship of first versus second survey glycemia values to mortality is random variation. This cannot be ruled out, particularly given the high ratio of intra- to interindividual variability of the 1-h postload plasma glucose and the consequent considerable probability of misclassifying individuals with use of only a single measurement. Whatever the several mechanisms, the possibility that random variation explains the inconsistency between first and second survey multivariate findings on glycemia and risk of death is supported by the positive results on glycemia and risks in this study with use of two glycemia measurements for each man. These data indicate the ability of two values to overcome, to a degree, the misclassification arising with only one value. This inference is supported by data showing that GHb values, which reflect integrated blood glucose values over a period of weeks, were higher in people with consistent postload hyperglycemia in two tests ~2 mo apart (12). Because, to our knowledge, no other prospective population studies have reported long-term mortality findings with use of more than one baseline glycemia value, the foregoing suggestion about a main reason for the independent positive Peoples Gas Company result with data from two surveys is hypothetical, pending further research.

The baseline data of this study on 1-h postload glycemia were collected in 1965–1967, well before development of present criteria for IGT based on assessment of fasting and postload glycemia values (13–15). Both World Health Organization and U.S. reports note that, for diagnostic purposes, at least two tests should be done. The findings of this study underscore the soundness of this recommendation, as do the conclusions of reviews noting the instability of the IGT designation based on one test (7,16). They also indicate that for epidemiological research focused on individuals, given the high ratio of intra- to interindividual variability of glycemia,

**Table 5—Proportional-hazards regression analyses, coefficients, classification of men based on 2 measurements of 1-h postload plasma glucose, with control for other risk factors, 19-yr mortality by cause**

	CHD	CVD	ALL CAUSES
HYPERGLYCEMIA ONCE ONLY	-0.2785	-0.2637	-0.0590
HYPERGLYCEMIA TWICE	0.8096*	0.7008*	0.4420
AGE (YR)	0.0649†	0.0732†	0.0841†
SERUM CHOLESTEROL (MG/DL)	0.0082†	0.0082†	0.0019
SYSTOLIC BLOOD PRESSURE (MMHG)	0.0250†	0.0277†	0.0150†
BMI (KG/M <sup>2</sup> )	-0.2395	-0.2138	-0.4108†
BMI <sup>2</sup>	0.0043	0.0037	0.0073†
CIGARETTES/DAY	0.0256†	0.0281†	0.0300†
WHITEHALL ELECTROCARDIOGRAM ISCHEMIA (0,1)	0.4666	0.5452*	0.5227†

Hyperglycemia is 1-h postload plasma glucose  $\geq 200$  mg/dl ( $\geq 11.2$  mM).

\*P < 0.05.

†P < 0.001.

‡P < 0.01.

more than one measurement per person of this parameter is needed. One study yielded data bearing on the possible generalizable meaning of the glycemia values reported herein for the 30 middle-aged men classified as consistently hyperglycemic based on two postload plasma glucose values, both  $\geq 11.2$  mM ( $\geq 200$  mg/dl). In a Naples health-examination survey of telephone company employees, repeat oral glucose tolerance testing was done on 67 men and women with IGT at first test (criteria of the European Association for the Study of Diabetes) (13); 45 met these criteria again at second test. Their mean 1-h postload (75-g) whole-blood glucose was  $11.8 \pm 2.6$  mM ( $211 \pm 47$  mg/dl) (O.V., K.J.R., J.S., unpublished observations).

Because whole-blood values average  $\sim 1.1$  mM (20 mg/dl) lower than plasma levels, this finding is similar to the mean of this study for the 30 men with consistent hyperglycemia 1-h postload (50 g), i.e., 13.4 mM (239 mg/dl). These data indicate that consistent hyperglycemia, as defined in this study, very likely identifies people in the upper range of the IGT distribution as currently defined.

The possibility remains that other

factors associated with hyperglycemia not measured in this study (e.g., serum insulin, serum proinsulin, triglycerides, high-density lipoprotein cholesterol, insulin resistance) may account at least in part for the association between consistent hyperglycemia and CHD and CVD mortality. The concept that hyperglycemia and CVD are related causally has been challenged, at least for diabetic patients, and a hypothesis has been put forward that both conditions may share common antecedents (17).

In conclusion, findings from this study indicate that hyperglycemia defined based on repeat measurements, in contrast to a single measurement, identifies a more homogeneous group of people with more severe metabolic abnormalities and with higher cardiovascular risk.

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