Is There a Glycemic Threshold for Mortality Risk?

BEVERLEY BALKAU, PHD
SANDRINE BERTRAIS, MSC
PIERRE DUCIMETIERE, PHD
EVELINE ESCHWEGE, MD

OBJECTIVE — To determine whether there are thresholds for fasting and for 2-h glucose above which the risk of death from all causes and from coronary heart disease (CHD) increases.

RESEARCH DESIGN AND METHODS — We studied 23-year mortality data from the Paris Prospective Study of the 7,018 men, aged 44–55 years, who were not known as diabetic at the baseline examination. The effect of glucose concentrations on mortality was studied using the observed relative risks and an age-adjusted Cox proportional hazards model.

RESULTS — For all causes of death, there were J-shaped relationships with both fasting and 2-h glucose concentrations, and the lowest observed death rates were in the intervals centered on 5.5 mmol/l for fasting glucose and 5.0 mmol/l for 2-h glucose. The death rates for CHD were low in this population: for fasting glucose, the hazards ratio was best modeled by a positive linear relationship; for 2-h glucose, it was modeled by a J-shaped curve and the lowest observed death rate was in the interval centered on 6.0 mmol/l.

CONCLUSIONS — In the Paris Prospective Study, there were no clear thresholds for fasting or 2-h glucose concentrations above which mortality sharply increased; in the upper levels of the glucose distributions, the risk of death progressively increased with increasing fasting and 2-h glucose concentrations.

Diabetes Care 22:696–699, 1999

The current American Diabetes Association (ADA) criteria for defining diabetes from fasting plasma glucose concentrations, namely ≥7.0 mmol/l, were based on the observation that the incidence and prevalence of retinopathy increased at a fasting glucose concentration of ~7 mmol/l; for the 2-h glucose concentration that follows a 75-g oral glucose tolerance test, the corresponding level was close to 11 mmol/l (1). In addition, in Pima Indians, the fasting concentration of 7.2 mmol/l was found to maximize the sum of the sensitivity and specificity for existing retinopathy (2). The choice of glucose thresholds to define diabetes was based on the prevalence and incidence of retinopathy, because the incidence of retinopathy, a specific complication of diabetes, is closely related to glucose concentrations. However, we challenge the concept that microvascular complications are the most important criteria. We believe that perhaps the ultimate criteria should be longevity, although we do not dispute the importance of the associated quality of life of diabetic patients with microvascular, or even macrovascular, disease. We take the title of this article from that of an editorial in *Diabetes Care* by Harris and Eastman (3), who commented on our joint analysis of data from the Whitehall Study (U.K.), the Paris Prospective Study, and the Helsinki Policemen Study (4). In that study, we showed that in nondiabetic subjects, the risks of early death and death by coronary heart disease (CHD) were increased in the upper percentiles of the fasting and 2-h glucose distributions, but we did not describe the risks associated with glucose concentrations in the lower 80% of the distributions, nor did we include the subjects who were classified as diabetic during baseline screening; moreover, because of the different methods used in the three studies, we were not able to look at the risks associated with actual plasma glucose concentrations. The aim of the present analysis was to determine whether there was a sharp increase in mortality, and in mortality from CHD, above certain fasting and/or 2-h glucose concentrations, as in the relationship between glucose concentration and the incidence of retinopathy (1,2).

RESEARCH DESIGN AND METHODS

Study population

We analyzed data from the Paris Prospective Study for 7,018 men, 44–55 years old at baseline, who have been followed for causes of death for an average of 23 years (5). These men were examined during the years 1967–1970, had not previously been identified as diabetic, and had baseline glucose concentrations measured both during a fasting state and 2 h after receiving a 75-g oral glucose tolerance load.

Until the end of 1988, information on causes of death was obtained from the family and treating physicians. The causes of death were classified after review by a medical panel; for missing causes and for deaths occurring after 1989, the officially certified causes of death were used where available. Causes of death were coded according to the *International Classification of Diseases* (*ICD*), *Eighth Revision* (5a), and the *ICD, Ninth Revision* (6): CHD corresponded to codes 410–414, and as is customary in France, the following additional categories were used (codes from the *ICD, Eighth Revision,* are given): congestive heart failure (427.0), left ventricular failure (427.1), acute edema of lung (519.1), symptoms referable to the

From Institut National de la Santé et de la Recherche Médicale (INSERM) U258, Villejuif, France.
Address correspondence and reprint requests to Beverley Balkau, PhD, INSERM U258, 16 Avenue Paul Vaillant-Couturier, 94807 Villejuif cedex, France. E-mail: balkau@vjf.inserm.fr.
Received for publication 3 September 1998 and accepted in revised form 21 December 1998.
Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; ICD, International Classification of Diseases; IFG, impaired fasting glucose, IGT, impaired glucose tolerance.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Downloaded from http://diabetesjournals.org/care/article-pdf/22/5/696/449575/10332668.pdf by guest on 18 May 2022

Table 1—*Distribution of the 7,018 men not known as diabetic, according to fasting and 2-h glucose categories for the diagnosis of diabetes, IGT, IFG, and normoglycemia: the Paris Prospective Study*

	2-h glucose (mmol/l)			
Fasting glucose (mmol/l)	Normal (≤7.7)	IGT (7.8–11.0)	Diabetes (≥11.1)	Overall
Normal (≤6.0)	5,204	326	45	5,575 (79)
IFG (6.1–6.9)	927	253	23	1,203 (17)
Diabetes (7.0–7.7)	72	56	32	160 (2)
Diabetes (≥7.8)	10	10	60	80 (1)
Overall	6,213 (89)	645 (9)	160 (2)	7,018

Data are *n* or *n* (%).

cardiovascular and lymphatic systems (782), and sudden death (795).

Statistical analysis

The observed death rate was calculated using the number of person-years of follow-up as the denominator for each glucose class. The observed relative risks for all causes of death were calculated by intervals of width of 0.5 mmol/l, with reference to the interval centered on 5.5 mmol/l; for death by CHD, intervals of width of 1.0 mmol/l were used, and the reference interval was centered on 5.0 mmol/l. An age-adjusted Cox proportional hazards model was used to assess the effect of the glucose levels (logarithmically transformed to ensure more symmetrical distributions) on the time until death. By using a χ^2 log-likelihood ratio test and comparing nested models, we tested whether the hazards ratios for mortality were adequately explained by just the linear term in the logarithm of glucose, or whether a squared logarithmic term should be added. The hazards ratios were determined with reference to 5.5 mmol/l for all causes of death, and 5.0 mmol/l for death by CHD, for easy comparison with the observed relative risks. Hazards ratios and their 95% CIs were also calculated for specific fasting and 2-h glucose concentrations, after adjusting for age alone; further adjustments were made for other risk factors when the data were available (n = 6,981): systolic blood pressure, cholesterol concentration, iliac circumference, and current smoking.

RESULTS — None of the 7,018 men had previously been identified as diabetic; 240 (3.4%) had undiagnosed diabetes, defined as fasting glucose ≥7.0 mmol/l; and 1,203 (17%) had impaired fasting glucose (IFG), defined as fasting glucose from 6.1 to 6.9 mmol/l (Table 1). If the 2-h glucose alone were used to diagnose diabetes, 160 (2.3%) subjects would be identified as diabetic (2-h glucose ≥11.1 mmol/l), and 645 (9%) would be classified as having impaired glucose tolerance (IGT) (2-h glucose from 7.8 to 11.0 mmol/l). According to the current ADA criteria, which are based on both fasting and 2-h glucose concentrations (1), a total of 308 diabetic men were screened, giving a prevalence of undiagnosed diabetes of 4.4%.

Overall, there were 1,924 deaths, of which 347 were from CHD. The observed all-cause mortality was lowest for subjects with fasting glucose of 5.25–5.75 mmol/l, and for subjects with 2-h glucose of 4.75–5.25 mmol/l (Fig. 1). Modeling with glucose as a continuous variable showed a statistically significant curvilinear relationship between both fasting and 2-h glucose concentrations and all-cause mortality (χ^2 = 5.6, df = 1, $P < 0.02$; χ^2 = 40.9, df = 1, $P < 0.0001$, respectively). A subject with a fasting glucose level of 7.8 mmol/l (previously the fasting glucose level for defining diabetes) had a risk of death 40% greater than a subject with a fasting glucose level of 6.0 mmol/l (the upper limit of normal, according to the ADA criteria [1]) (Table 2). When other risk factors were taken into account, the relationship was no longer curvilinear for fasting glucose (χ^2 = 2.7, df = 1, $P < 0.1$), but fasting glucose remained

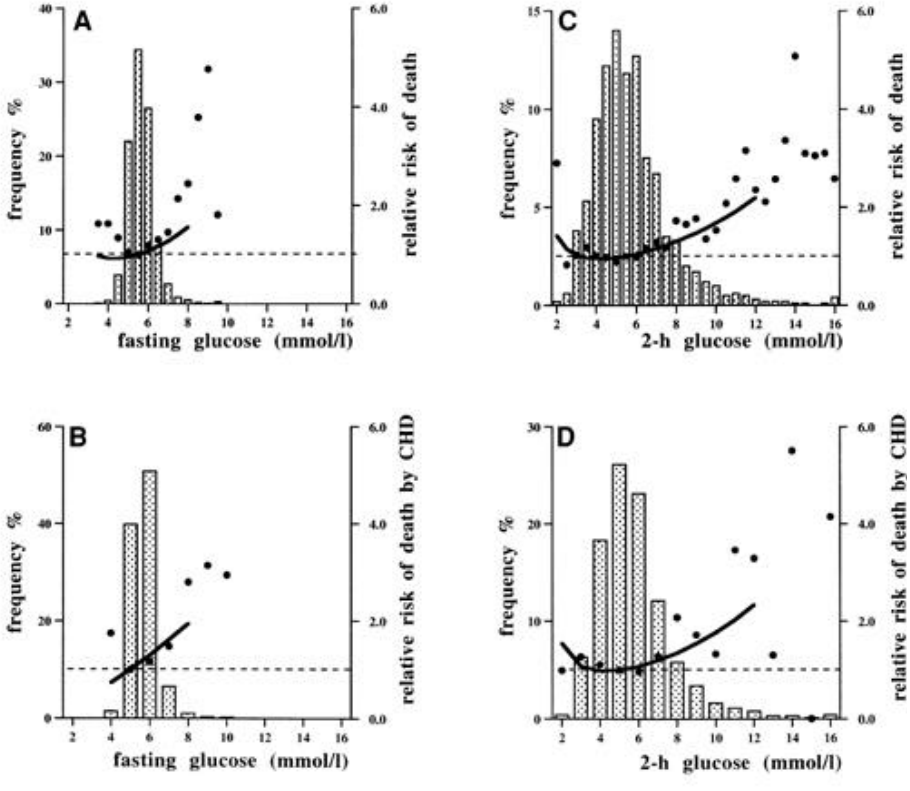

Figure 1—*Fasting and 2-h glucose distributions, and relative risks of death by all causes and by death from CHD, observed (●) and predicted by the Cox model (—). Data are from the Paris Prospective Study.*

Downloaded from http://diabetesjournals.org/care/article-pdf/22/5/696/449575/10332668.pdf by guest on 18 May 2022

Table 2—*Hazard ratio and 95% CIs for all causes of death and for death by CHD for given fasting and 2-h glucose concentration: the Paris Prospective Study*

	Death by all causes		Death by CHD	
	Adjusted for age	Adjusted for age and risk factors*	Adjusted for age	Adjusted for age and risk factors*
Fasting glucose (mmol/l)				
7.8 vs. 6.0	1.40 (1.22–1.61)	1.31 (1.02–1.36)	1.42 (1.15–1.82)	1.04 (0.81–1.33)
7.0 vs. 6.0	1.19 (1.09–1.30)	1.08 (1.01–1.15)	1.24 (1.09–1.42)	1.02 (0.88–1.18)
2-h glucose (mmol/l)				
11.1 vs. 7.7	1.55 (1.46–1.65)	1.38 (1.29–1.47)	1.58 (1.37–1.83)	1.31 (1.11–1.53)

Data are hazard ratios (95% CI). *Risk factors were systolic blood pressure, cholesterol concentration, iliac circumference, and current smoking.

a significant predictor of mortality (χ^2 = 5.0, df = 1, $P < 0.03$). For 2-h glucose, a concentration of 11.1 mmol/l carried a 55% higher risk than 7.7 mmol/l (Table 2). The relationship remained curvilinear for the 2-h glucose after adjustment was made for other risk factors (χ^2 = 22.6, df = 1, $P <$ 0.0001). For both fasting and 2-h glucose concentrations, the hazards ratios were lower after adjustment for the other risk factors (Table 2).

The lowest CHD death rates were observed in the intervals 4.5–5.5 mmol/l for fasting glucose and 5.5–6.5 mmol/l for 2-h glucose (Fig. 1). Fasting glucose and CHD mortality were positively and linearly associated (χ^2 = 9.4, df = 1, $P <$ 0.002), with no significant curvilinear relationship (χ^2 = 0.08, df = 1, $P < 0.4$). For the 2-h glucose concentration, there was a curvilinear relationship for the risk of death by CHD (χ^2 = 8.7, df = 1, $P <$ 0.003). A fasting glucose concentration of 7.8 mmol/l carried a 42% higher risk for death by CHD than did a concentration of 6.0 mmol/l; however, this association was no longer significant after adjusting for other risk factors (χ^2 = 0.01, df = 1, $P <$ 0.9). For the 2-h glucose concentration, the risk increased by 58% in passing from 7.7 to 11.1 mmol/l; after adjustment for other risk factors, the curvilinear relationship remained significant (χ^2 = 4.9, df = 1, $P < 0.03$), but the hazards ratio was lower (Table 2).

CONCLUSIONS — It is noteworthy that the relationship between glucose concentration and mortality followed a J-shaped curve, except for fasting glucose concentration and death from CHD, which had a positive and linear relationship. The observed and the modeled relative risks were higher at very low glucose levels, and the lowest death rates correspond to glucose levels well below the World Health Organization's fasting and 2-h glucose criteria (7), and even below the new ADA fasting glucose criterion (1) for the definition of diabetes. The modeled relationship between fasting glucose concentration and CHD mortality was linear, although a higher death rate was observed in the lowest fasting glucose class; the number of CHD deaths may have been too low to show a significant curvilinear relationship.

This analysis of the Paris Prospective Study includes 308 undiagnosed diabetic patients, and they had higher all-cause and CHD mortality rates. This finding is in concordance with the results from the U.K. Prospective Diabetes Study, where coronary artery disease and fatal myocardial infarction were significantly more frequent in diabetic subjects with higher baseline fasting glucose concentrations (8). When the 308 men with newly diagnosed diabetes were excluded from the analyses, there were still positive and curvilinear relationships between glucose concentrations and both all-cause and CHD mortality, except for fasting glucose concentration and CHD mortality, for which there was no statistically significant relationship.

Death rates were higher for the men with the lowest glucose concentrations. The men with either fasting or 2-h glucose concentrations ≤4.75 or ≤2.75 mmol/l, respectively, had lower mean values of systolic blood pressure, cholesterol concentration, and iliac circumference, and fewer of them smoked (29 vs. 43%). However, there were more men with suspected cirrhosis in this group (8.7 vs. 5.4%, $P < 0.0001$). Cirrhosis is known to be associated with lower postabsorptive glucose concentrations, although hypoglycemia is unusual (9). The curvilinear relationship between 2-h glucose concentrations and both all-cause and CHD mortality remained when the men with these low 2-h glucose concentrations were removed from the analysis, whereas there was no longer a statistically significant relationship between fasting glucose concentration and CHD. The liver is central in glucose homeostasis, and cirrhosis is also associated with high glucose concentrations, as we have already shown in this cohort (10).

The observed relative risks at high glucose concentrations appeared to rise more steeply than the modeled curves. With few exceptions, the observed relative risk increased with increasing glucose concentrations. For fasting glucose concentrations and all causes of death, we could estimate by visual interpolation between the observed relative risks that a fasting glucose concentration of 7.5 mmol/l corresponds to a relative risk of 2.0; for CHD mortality, the corresponding fasting glucose concentration would be 8 mmol/l. For the 2-h glucose concentration, the observed relative risk reached 2.0 for all-cause mortality, with a corresponding 2-h glucose level of 10.5 mmol/l for CHD mortality. These cutoff points corresponding to a relative risk of 2.0 are very close to the criteria for defining diabetes. Furthermore, for fasting glucose concentrations above ~7–8 mmol/l, the observed death rates were higher than in the remainder of the population; for the 2-h glucose concentration, the corresponding values were ~10–11 mmol/l.

There is no doubt that the increasing all-cause and CHD mortality associated with increasing concentrations of both fasting and 2-h glucose is in part due to the worsening risk factor profile with increasing glucose concentrations (11). The hazards ratios decreased after adjustment was made for other risk factors, but the fasting glucose levels still carried a statistically significant risk for all causes of death, as did

Downloaded from http://diabetesjournals.org/care/article-pdf/22/5/696/449575/10332668.pdf by guest on 18 May 2022

the 2-h glucose concentration for both all-cause and CHD mortality.

In the Paris Prospective Study, there was no clear concentration of either fasting or 2-h plasma glucose above which the risk of death or death by CHD sharply increased. These results do not challenge the existing diagnostic criteria for diabetes of 7.0 mmol/l for fasting and 11.1 mmol/l for 2-h glucose concentrations, which were based on data that showed a sharp increase in retinopathy incidence and prevalence.

Acknowledgments — The authors wish to thank Anne Forhan for providing technical assistance and Louise Mennen for carefully reading the manuscript.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
2. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308:1323–1328, 1994
3. Harris MI, Eastman RC: Is there a glycemic threshold for mortality risk? (Editorial) *Diabetes Care* 21:331–333, 1998
4. Balkau B, Shipley M, Jarrett RJ, Pyörälä K, Pyörälä M, Forhan A, Eschwège E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
5. Balkau B, Eschwège E, Papoz L, Richard J-L, Claude J-R, Warnet J-M, Ducimetière P: Risk factors for early death in non-insulin dependent diabetes and men with known glucose tolerance status. *BMJ* 307:295–299, 1993

5a. World Health Organization: *International Classification of Diseases, 8th Revision*. Geneva, World Health Org., 1965

6. World Health Organization: *International Classification of Diseases, 9th Revision*. Geneva, World Health Org., 1975
7. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
8. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR, for the United Kingdom Prospective Diabetes Study Group: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study. *BMJ* 316:823–828, 1998
9. Cryer PE: Glucose homeostasis and hypoglycemia. In *Williams' Textbook of Endocrinology*. 8th ed. Wilson JD, Foster DW, Eds. Philadelphia, WB Saunders, 1992, p. 1223–1253
10. Balkau B, Eschwège E, Fontbonne A, Claude J-R, Warnet J-M: Cardiovascular and alcohol-related deaths in abnormal glucose tolerant and diabetic subjects. *Diabetologia* 35:39–44, 1992
11. Balkau B, Eschwège E, Tichet J, Marre M, the D.E.S.I.R. Study Group: Proposed criteria for the diagnosis of diabetes: evidence from a French epidemiological study (D.E.S.I.R.). *Diabetes Metab* 23:428–434, 1997

Downloaded from http://diabetesjournals.org/care/article-pdf/22/5/696/449575/10332668.pdf by guest on 18 May 2022