

Is Glucose a Continuous Risk Factor for Cardiovascular Mortality?

Hyperglycemia has long been recognized as a strong risk factor for chronic eye, kidney, nerve, and cardiovascular disease. However, identification of the glucose thresholds above which the risk of these chronic diseases begins to increase has been controversial. Several population studies have clearly shown that a 2-h postchallenge glucose level of 11.1 mmol/l (200 mg/dl) or higher during an oral glucose tolerance test clearly identifies individuals at high risk for retinopathy and nephropathy. Indeed, the current definition of diabetes was based on these studies and on observations that a fasting plasma glucose level of 7.0 mmol/l has very high specificity for a 2-h glucose of 11.1 mmol/l (1). Thus diabetes is, by definition, a risk factor for eye and kidney disease (i.e., microvascular disease). Moreover, because the risk of microvascular disease rises with the plasma glucose, and falls as the glucose level is reduced in patients with both type 1 (2) and type 2 diabetes (3), plasma glucose within the diabetic range is a continuous and modifiable risk factor for microvascular disease.

Although several studies have also clearly shown that glucose levels that are higher than the diabetes threshold are a continuous risk factor for cardiovascular disease (4–7), the current definition of diabetes was not based on either the risk for cardiovascular disease or the risk of death from all causes. There is, therefore, no a priori reason for the diabetes glucose thresholds to be relevant to the risk for these outcomes, and there is no reason that the glucose-cardiovascular relationship should not extend below the diabetes thresholds. Indeed, there is a rapidly growing body of epidemiologic evidence demonstrating that the risk for both cardiovascular events and for atherosclerosis does extend below these microvascular thresholds (8–11).

Balkau et al. (12) add to the epidemiologic evidence in this issue of *Diabetes Care* through a new analysis of data from the Paris Prospective Study. They studied 7,018 men aged 44–55 years with no prior history of diabetes, who had a 75-g oral glucose tolerance test between 1967 and 1970

and who were followed for a mean period of 23 years from enrollment. Cause of death was determined prospectively in a standardized fashion and analyzed according to the results of the baseline fasting and postload glucose values.

At baseline, 4.4% of all participants had diabetic glucose tolerance tests, and a further 8.3% had impaired glucose tolerance. Fasting and 2-h glucose values of 5.25–5.75 and 4.75–5.25 mmol/l, respectively, were associated with the lowest all-cause mortality. Similar fasting and 2-h values of 4.5–5.5 and 5.5–6.5 mmol/l, respectively, were associated with the lowest coronary heart disease mortality. Data modeling showed that progressive increases in either fasting or 2-h glucose levels predicted significant increases in the risk of both total and coronary heart disease mortality. A significant relationship between fasting glucose and all-cause mortality, and between 2-h glucose and both all-cause and coronary heart disease mortality was maintained even after data from the participants with diabetic glucose tolerance tests were removed. The relationship between glucose levels and mortality was curvilinear.

This report concludes that glucose is a continuous risk factor for all-cause or coronary heart disease death in the upper levels of the nondiabetic distribution. For example, the hazard ratio of a fasting glucose of 7.0 mmol/l (126 mg/dl) compared with 6.0 mmol/l (108 mg/dl) was 1.24. There are insufficient numbers of events (and therefore insufficient power) to completely rule out the possibility that the glucose-mortality relationship might be driven by the highest nondiabetic glucose levels (for example by only those participants with impaired glucose tolerance or impaired fasting glucose). For example, using the data from this study, the hazard ratio for a 2-h glucose of 7.5 compared with 6.5 mmol/l is unlikely to be statistically significant. Nevertheless, the fact that the crude relative risks increase progressively across the range of glucose levels is consistent with a graded glucose-mortality relationship.

Such a graded relationship is highly similar to the relationships between cardiovascular risk and either cholesterol or blood

pressure levels previously demonstrated in a 12-year follow-up of 316,099 middle-aged men screened for the Multiple Risk Factor Intervention Trial (MRFIT) (13). This large amount of data was needed to demonstrate that even modest elevations in cholesterol or blood pressure predicted a sustained increased risk for coronary heart disease death. For example, the adjusted relative risks for coronary heart disease death of cholesterol levels of 4.7–5.2 mmol/l (182–202 mg/dl) and 5.2–5.7 mmol/l (203–220 mg/dl) compared with levels below 4.7 mmol/l (182 mg/dl) were 1.4 and 1.7, respectively. The adjusted relative risks of a diastolic blood pressure of 76–80 and 81–85 mm (compared with a diastolic blood pressure <76 mm) were 1.2 and 1.3, respectively. Curvilinear relationships were also noted for both of these variables.

The hypothesis that there is a graded relationship between glucose and cardiovascular disease that begins at normal levels and rises into the diabetic range is consistent with other data. An early report of the Whitehall Study (14) demonstrated a 1.5- to twofold increase in coronary heart disease and stroke mortality after 10 years in men whose postload (50 g) capillary glucose was as low as 5.4 mmol/l. A 22-year follow-up study showed that nondiabetic men with fasting glucose levels >4.7 mmol/l (85 mg/dl) had a 1.4-fold higher risk of cardiovascular mortality than men with lower glucose values (15). Another epidemiologic study with data from a follow-up period of 14 years (16) demonstrated that men with fasting glucose levels of 6.1–6.6 mmol/l (110–119 mg/dl) and 6.7–7.2 mmol/l (120–129 mg/dl) had a ~1.3- and ~1.5-fold higher adjusted risk of ischemic heart disease mortality than men with glucose levels <5.5 mmol/l (100 mg/dl). Finally, a recent systematic overview and metaregression analysis of several epidemiologic studies (the majority of which followed nondiabetic men) also confirmed a graded relationship between fasting and postprandial glucose levels and cardiovascular risk (17). Therefore, if there is a dysglycemic level above which individuals are at risk for cardiovascular disease, it may be as low as 5.5 mmol/l for

fasting values and 6.5 mmol/l for 2-h values (i.e., substantially below both the diabetes threshold and the impaired glucose tolerance threshold).

This relationship between progressive increases in glucose and mortality risk has several implications. First, the majority of these studies have been done in men; the degree to which these conclusions apply to women is, therefore, unclear. Second, up to 25% of men aged 45–64 years without a clinical diagnosis of diabetes have a fasting glucose level >5.7 mmol/l (103 mg/dl), and up to 50% have a 2-h glucose level >5.9 mmol/l (107 mg/dl) (18). Thus, a substantial fraction of men in the general population have at least one easily measured metabolic risk factor for coronary heart disease mortality. Identification of these higher-risk men could identify individuals in whom initiating cardiovascular screening or prevention programs may be appropriate. Third, although no cardiovascular studies of interventions that lower glucose in nondiabetic people have been reported, this may be important for high-risk patients (for example, those with a previous myocardial infarction). Indeed, the fact that cardioprotective interventions such as exercise, weight loss, and smoking cessation also improve glucose tolerance supports this possibility. Moreover, studies such as the Cholesterol and Recurrent Events (CARE) Study, which demonstrate the benefits of lipid lowering in high-risk patients with average lipid values (19), support the hypothesis that a similar approach directed at glucose is worth studying. Fourth, demonstration that glucose is a continuous risk factor for coronary heart disease and all-cause mortality provides no information on whether it causes these outcomes. Several alternative explanations may account for the observed relationship (9,17).

Cardiovascular disease will develop in 49% of middle-aged men during their lifetime (20). There are clearly many classic and emerging risk factors of this disease, some of which are modifiable. As new risk factors are identified, new insights into this disease and new opportunities for primary and secondary prevention will appear. This study provides another reason to add glu-

cose to the list of established continuous cardiovascular risk factors.

HERTZEL C. GERSTEIN, MD, MSC, FRCPC

From the Division of Endocrinology and Metabolism, McMaster University, and the Preventive Cardiology and Therapeutics Research Program, Hamilton Civic Hospitals Research Center, Hamilton, Ontario, Canada.

Address correspondence to Dr. H.C. Gerstein, Department of Medicine, Room 3V38, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5, Canada. E-mail: gerstein@fhs.csu.mcmaster.ca.

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. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
3. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
4. Wei M, Gaskill SP, Haffner SM, and Stern MP: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio Heart Study. *Diabetes Care* 21:1167–1172, 1998
5. Moss SE, Klein R, Klein BEK, Meuer SM: The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 154:2473–2479, 1994
6. Kuusisto J, Mykkanen L, Pyorala K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
7. Andersson DKG, Svardssudd K: Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 18:1534–1543, 1995
8. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. *Diabetes Care* 360:360–367, 1998
9. Haffner SM: The importance of hyperglycemia in the nonfasting state to the development of cardiovascular disease. *Endocr Rev* 19:583–592, 1998
10. Vitelli LL, Shahar E, Heiss G, McGovern PG, Brancati FL, Eckfeldt JH, Folsom AR, Atherosclerosis Risk in Communities (ARIC) Study Investigators: Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals: the

Atherosclerosis Risk in Communities Study. *Diabetes Care* 20:1454–1458, 1997

11. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kubota M, Kajimoto Y, Kamada T: Asymptomatic hyperglycaemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia* 38:585–591, 1995
12. Balkau B, Bertrais S, Ducimetiere P, Eschwege E: Is there a glycemic threshold for mortality risk? *Diabetes Care* 22:696–699, 1999
13. Neaton JD, Wentworth D, MRFIT Research Group: Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. *Arch Intern Med* 152:56–64, 1992
14. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary-heart-disease risk and impaired glucose tolerance: the Whitehall Study. *Lancet* 8183:1373–1376, 1980
15. Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, Erikssen J, Thaulow E: Fasting blood glucose: an underestimated risk factor for cardiovascular death: results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care* 22:45–49, 1999
16. Scheidt-Nave C, Barrett-Connor E, Wingard DL, Cohn BA, Edelstein SL: Sex differences in fasting glycemia as a risk factor for ischemic heart disease death. *Am J Epidemiol* 133:565–576, 1991
17. Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999
18. Cowie CC, Harris MI: Physical and metabolic characteristics of persons with diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Washington, DC, U.S. Govt. Printing Office, 1995, p. 117–164 (NIH publ. no. 95-1468)
19. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun CC, Davis BR, Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335:1001–1009, 1996
20. Lloyd-Jones DM, Larson MG, Beiser A, Levy D: Lifetime risk of developing coronary heart disease. *Lancet* 353:89–92, 1999