Acute Ischemic Heart Disease

Blood glucose: A strong risk factor for mortality in nondiabetic patients with cardiovascular disease

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Background The prognostic significance of blood glucose (BG) for nondiabetic patients in a stable chronic phase of cardiovascular disease (CVD) has been sparsely investigated, especially for glucose within the normal range. In particular, it is unknown if for these patients there is a graded relation of mortality to glucose or if there is a lower threshold.

Methods We used the Framingham Heart Study 30-year data to determine 2-year all-cause, cardiovascular mortality (CVM), and non-CVM risk adjusted for age, sex, and typical cardiovascular risk factors (systolic blood pressure, total cholesterol, body mass index, cigarette smoking, and use of antihypertensive drugs) by levels of random whole BG for non–glucose-intolerant subjects (glucose intolerance includes diabetes mellitus) with existing CVD.

Results There were steep graded relations of 2-year all-cause, CVM, and non-CVM to BG throughout the normal and subdiabetic range with no evidence of a lower threshold. Two-year mortality continuously increased from 2.99% at the bottom of the normal range (BG = 60 [plasma equivalent = 67] mg/dL) to 7.23% at the top of the normal range (89 [plasma equivalent = 100] mg/dL) (a 2.42-fold increase) and then continued to further continuously increase, reaching 11.38% at 119 [plasma equivalent = 133] mg/dL, the top of the glucose range considered (P for trend <.0001). There were analogous steep increases for CVM and non-CVM.

Conclusions Blood glucose, even within the normal range, is a strong independent predictor of 2-year all-cause, CVM, and non-CVM in nondiabetic subjects with CVD and therefore of prognostic significance for these high-risk patients. (Am Heart J 2005;150:209-14.)

It is well established that individuals with type 2 diabetes mellitus have an increased risk of all-cause and cardiovascular mortality (CVM).[1,2] Cardiovascular disease (CVD), including coronary artery disease, cerebrovascular disease, and peripheral vascular disease, is more prevalent among people with diabetes than in the general population.[3,4] Conversely, patients with coronary artery disease have been found to have higher rates of impaired glucose tolerance and diabetes than patients without atherosclerosis.[5] Given the impact of diabetes on CVD and mortality, the question of whether glucose level predicts mortality in people without diabetes is important. Most previous prospective studies of this question have focused on initially healthy subjects (mostly men younger than 60 years). These mainly have shown risk increases below the diabetes cut point starting in the upper regions of the normal range.[6-10]

A growing body of evidence suggests that glucose values below the diabetes cut point may be an important factor for mortality in patients with CVD.[1-16] Above-normal glucose levels below the diabetes cut point have been shown to carry increased mortality risk for patients in an acute phase of coronary heart disease [11-13] or undergoing percutaneous coronary intervention.[15] Only a few studies examined the role of glucose level to mortality in subjects in a chronic phase of CVD.[14,16] These have indicated risk increased across the 3 broad categories: normal, above normal but below the diabetes cut point, and above the diabetes cut point. The relations of all-cause mortality (mortality), CVM, and non-CVM to glucose, especially within the normal range, for nondiabetic patients in a stable chronic phase of CVD have been sparsely investigated; for these patients it is unknown if there is a graded association of mortality to glucose or if there is a threshold effect. In this study,

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Table I. Baseline pooled population characteristics by category of random whole BG* for non–glucose-intolerant subjects with CVD

	Glucose category (mg/dL)			
	<60	**60-69**	**70-79**	**79-89**
Mean glucose (mg/dL)	54.87 ± 4.29†	65.34 ± 2.78	74.82 ± 2.76	84.17 ± 2.88
No. of observations	39	293	753	807
No. of distinct subjects	35	220	491	553
Women (%)	38.46	37.88	41.43	45.60
Age (y)	59.24 ± 6.43	59.91 ± 7.33	60.39 ± 7.02	61.81 ± 6.74
Systolic blood pressure (mm Hg)	135.57 ± 23.14	144.99 ± 28.36	144.34 ± 25.65	147.08 ± 26.14
Total cholesterol (mg/dL)	254.795 ± 56.57	241.46 ± 44.57	241.45 ± 46.98	243.58 ± 49.09
Body mass index (kg/m^2)	25.15 ± 3.96	26.50 ± 4.33	26.10 ± 3.93	26.79 ± 4.26
Cigarette smokers (%)	15.38	19.11	29.08	22.80
Antihypertensive drug users (%)	25.71	19.78	21.83	26.42

*Multiply glucose values by 1.12 for plasma equivalent.
†Mean ± SD in category.

we used the Framingham Heart Study 30-year data to address this question.

Methods

Background

The methodology of the Framingham Heart Study has been previously described.[17] In brief, the Framingham target population consisted primarily of white, urban, middle-class Americans. In 1948, a sample of 5209 subjects was selected from Framingham and these subjects were given biennial exams. Framingham determined glucose values using a sample of random (ie, casual) whole blood by Nelson's method,[18] which were therefore approximately 11% lower than plasma values.[19] Using the first 15 examinations, we used the Framingham investigators' pooling of repeated observations (PRO) method,[20,21] which considered each examination as a separate ministudy and pooled the observations, to determine the relation of all-cause, CVM, and non-CVM to blood glucose (BG) over a 2-year period. This method, which can only be used if (as in Framingham) there are repeated measurements over successive intervals of fixed length, has close affinities with survival analysis with time-varying covariates. In essence, subjects are followed up over successive 2-year intervals (with updated covariates at the start of each interval) until death or the end of the 30-year period occurs. In this manner, all deaths that accrue over 30 years of follow-up are used to provide accurate estimates of 2-year risks. Glucose was not measured at examinations 5, 11, and 13.

Framingham classified a subject as "glucose intolerant" at a given examination if any of the following conditions held: (a) previous or current diagnosis of diabetes, (b) definite or trace glucose in urine, (c) BG ≥120 mg/dL. Using the Framingham classifications, CVD consisted of coronary heart disease, stroke, congestive heart failure, and intermittent claudication. Coronary heart disease consisted of myocardial infarction, coronary insufficiency, sudden death, and angina pectoris. Cardiovascular disease status was ascertained by direct examination by 2 or more Framingham physicians using a variety of techniques as detailed by Dawber.[17]

Statistical analyses

We considered the pooled population of subjects who at time of examination were between 45 and 74 years old, had existing (ie, clinically diagnosed) CVD, and were non–glucose intolerant. Subjects entered this pooled population upon contracting CVD if they were non–glucose intolerant and exited at death or the onset of glucose intolerance. This pooled population was divided into 6 age-sex groups: (1) males 45 to 54, (2) males 55 to 64, (3) males 65 to 74, (4) females 45 to 54, (5) females 55 to 64, and (6) females 65 to 74 years old. The relation of various mortality risks to BG was investigated by considering the logit of risk as a function (not necessarily linear) of BG as a continuous covariate as well as with BG categorically. The categories were: <60, 60 to 69, 70 to 79, 80 to 89, 90 to 99, 100 to 109, and 109 to 119 mg/dL (multiply by 1.12 for plasma equivalents). All models were fitted by logistic regression using Stata 8 software. Age-sex group was always entered categorically, and all models were adjusted for age-sex group, systolic blood pressure, total cholesterol, body mass index, cigarette smoking, use of antihypertensive drugs, and period (ie, examination). Significance of terms was decided by likelihood ratio tests and 2-sided Wald tests.

Results

In all, there were 2732 observations that satisfied the pooled population requirements (Table I) yielding a total of 140 cardiovascular and 61 noncardiovascular deaths (Table II). None of the subjects in the pooled population were using hypoglycemic agents and essentially none were using lipid-lowering agents. Table I gives baseline characteristics by category of BG of the variables in the pooled population used for adjustments in our models. Age, body mass index, systolic blood pressure, percent women, and percent using antihypertensive drugs tended to increase with increasing BG. Table II gives the number of events by BG category for the pooled population.

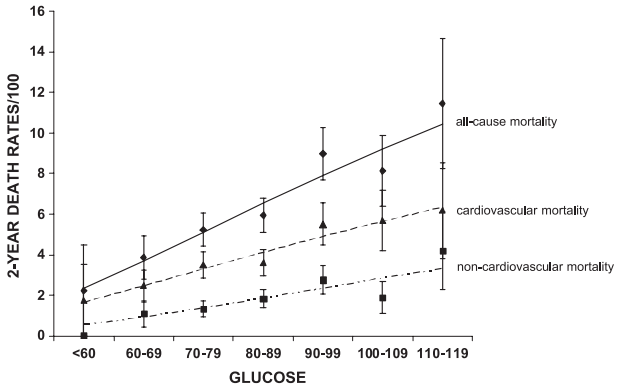
Glucose cetegory (mg/dL)				
90-99	**100-109**	**109-119**	**Total**	***P* (trend)**
93.77 ± 2.80	103.66 ± 2.84	114.08 ± 2.95	83.72 ± 12.84	
494	251	95	2,732	
390	216	86	985	
47.17	48.21	36.84	43.74	.035
62.56 ± 6.59	63.10 ± 6.62	62.81 ± 6.87	61.56 ± 6.93	<.001
147.49 ± 27.05	147.20 ± 26.60	141.22 ± 21.02	145.81 ± 26.31	.178
239.62 ± 4778	238.30 ± 49.00	233.20 ± 48.43	241.37±47.33	.034
27.39 ± 5.00	27.55 ± 5.42	27.02 ± 4.65	26.72 ± 4.48	<.001
24.49	22.71	23.16	24.34	.67
30.61	31.58	28.72	25.79	<.001

Table II. Deaths by category of whole BG* for the pooled population of non–glucose-intolerant subjects with CVD

Glucose category (mg/dL)	No. of observations	CVM	Non-CVM	All deaths
<60	39	2	0	2
60-69	293	11	3	14
70-79	753	38	12	50
80-89	807	36	18	54
90-99	494	30	17	47
100-109	251	16	6	22
109-119	95	7	5	12
Total	2732	140	61	201

*Multiply by 1.12 for plasma equivalent.

Figure 1

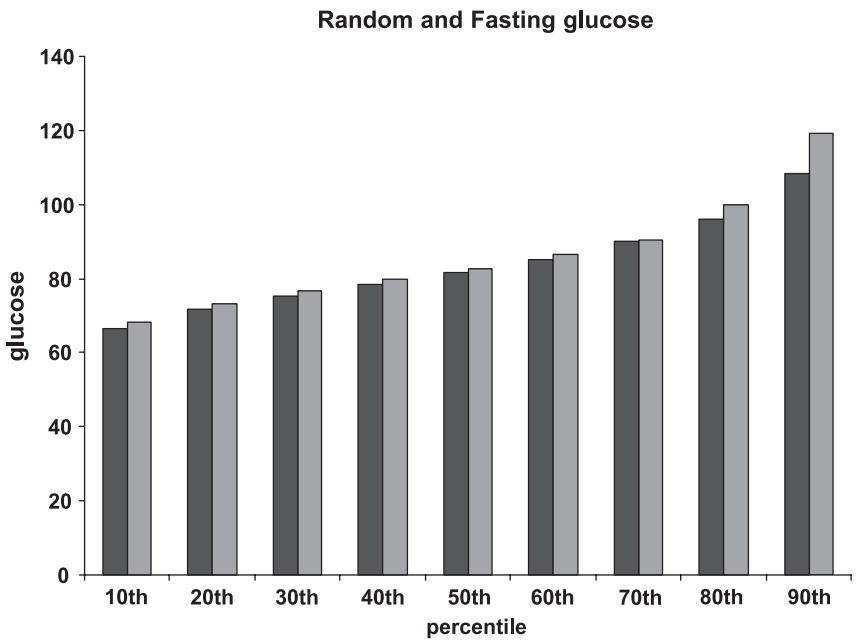


Adjusted 2-year all-cause mortality, CVM, and non-CVM rates (in percent) to random whole BG (mg/dL) for non–glucose-intolerant subjects with CVD (multiply glucose values by 1.12 for plasma equivalents). Shown for each outcome are the categorical rates and their standard errors together with the continuous fits using the saturation model. Starting at glucose <60 mg/dL, all risks rise steeply with increasing glucose.

Figure 1 exhibits the adjusted categorical rates of mortality, CVM, and non-CVM to category of BG. There was a definitive, strong, graded relation of mortality to BG (estimate = 0.0235, SE = 0.0059, $P < .0001$) with no evidence of a lower threshold. There was also a definitive graded relation when the lowest and highest glucose categories (BG <60 and BG ≥110 mg/dL were dropped) ($P = .002$) showing that the steep increase over the entire range was not due to just the influence of end points, but, as indicated in Figure 1, there was a smooth steady increase throughout the entire range. The continuous fits were slightly improved (as judged by log likelihood and Akaike's Information Criterion [AIC]) by considering risk as a linear function of the variable BG/(1 + BG) rather than BG itself (saturation model). According to the saturation model (Figure 1) the adjusted mortality rate increased from 2.99% for BG = 60 [plasma equivalent = 67] mg/dL to 7.23% for BG = 89 [plasma equivalent = 100] mg/dL, a 2.42-fold increase over the normal range. Risk continued to steadily increase, reaching 11.38% for BG = 119 [plasma equivalent = 134] mg/dL. Overall, there was a 3.81-fold increase from BG = 60 to BG = 119 mg/dL.

The relation of CVM to BG was very similar to that for mortality (Figure 1). Non-CVM also exhibited a steep graded relation to BG (P for trend = .019) with risk increasing from 0.55% for BG <60 [plasma equivalent = 67] mg/dL to 3.53% for BG = 119 [plasma equivalent = 134] mg/dL (Figure 1).

Figure 2



Percentiles of age- and sex-adjusted random and fasting BG for the Framingham cohort. The black bars show random values at each percentile and the gray bars show fasting values. There were very little differences between these percentiles.

Adding interactions between BG and other covariates in the models showed no interactions were significant. Fasting glucose values were determined at 4 of the 15 examinations. Using these determinations, we compared the percentiles of fasting and random glucose values for each age-sex group. As illustrated in Figure 2, the age- and sex-adjusted random percentiles very closely approximated those for fasting, with the random percentiles being slightly lower. In addition, *t* tests for the difference between random and fasting glucose for each age-sex group showed there were no significant differences. Using χ^2 tests, we found that there were no significant differences in the glucose distributions between those with different forms of CVD. In particular, there was no evidence that those with more severe CVD (eg, stroke or coronary heart disease [CHD] other than angina) had higher glucose values than those with more moderate disease (eg, angina or intermittent claudication).

Discussion

Currently, nondiabetic glucose levels are not considered particularly relevant in the prognosis for subjects with established CVD. Our finding of large, continuous, steady increases of various relatively short-term, adjusted mortality risks with increasing BG commencing at the bottom of the normal range for non–glucose-intolerant subjects who are primarily in a stable chronic phase of CVD suggests that this view may need revision. For these subjects there is no evidence of a lower threshold: adjusted 2-year mortality is 2.42-fold higher (7.23%) at 89 [plasma equivalent = 100] mg/dL than at 60 mg/dL (2.99%) [plasma equivalent = 67] and is 3.81-fold higher (11.38%) at 119 [plasma equivalent = 134] mg/dL than at 60 mg/dL, with analogous steep increases for CVM and non-CVM. Consequently, BG may provide a new and powerful predictor of mortality in these high-risk subjects.

Several studies have shown above-normal glucose levels below the diabetes cut point carry increased mortality risk for patients in an acute phase of coronary heart disease [11-13] or undergoing percutaneous coronary intervention.[15] Fisman et al[14] were the first to recognize the important connection between nondiabetic glucose levels and mortality in subjects in a stable chronic-phase CVD. They divided nondiabetic subjects with ischemic heart disease into 3 categories of fasting plasma glucose (<110, 110 to 126, and >126 mg/dL) and showed that mortality sharply increased across these 3 categories. Subsequent studies[15,16] also found mortality increases across these categories. Our results both confirm and expand these earlier findings. First, they show that there is a strong association between mortality and BG for patients in a chronic phase of any form of CVD. Two, they quantitatively extend earlier findings by showing

not only are there increases across the 3 categories stated above, but there is in fact a continuous, steep graded relation of various mortality risks to BG that extends throughout the entire normal and subdiabetic range, with no indication of a lower threshold. In particular, there is a steep increase in these risks from the bottom to the top of the normal range.

The fact that we excluded subjects with glucose intolerance (in particular, all diabetic patients) and adjusted for various cardiovascular risk factors (age, sex, systolic blood pressure, total cholesterol, body mass index, cigarette smoking, and use of antihypertensive drugs) makes it unlikely that the strong associations of the various mortalities to glucose observed here are due to confounding with known risk factors, although in an observational study that possibility can never be definitely excluded. The mechanism(s) by which glucose may directly increase mortality risk in subjects with CVD is unclear and warrants further investigation. Glucose may have direct harmful effects on vascular endothelium or atherosclerotic plaques, mediated by nonenzymatic glycosylation of low-density lipoprotein cholesterol and other apolipoproteins and clotting factors.[6] Other mechanisms by which elevated glucose may exacerbate atherosclerosis or heart failure include increased oxidative stress, activation of the polyol pathway, and basement membrane alterations.[22] Alternatively, insulin resistance may be the factor that worsens CVD, with elevated glucose levels serving as a marker of insulin resistance. Studies have shown that hyperinsulinemia, independent of other risk factors, is also a predictor of coronary heart disease among healthy subjects.[23] Insulin resistance may exacerbate myocardial ischemic damage by causing decreased glucose utilization and increased free fatty acid utilization, increasing oxygen demand and reducing contractility.[24] Hyperinsulinemia has been associated with decreased fibrinolysis via increased levels of plasminogen activator inhibitor-1.[25] We were unable to assess the effect of insulin resistance per se on mortality because insulin levels were not measured in the Framingham Heart Study.

Although we have insufficient data to accurately assess the relations of various cause-specific CVMs to BG or to examine cause-specific non-CVMs we speculate that the increase in non-CVM with glucose may be due to renal disease mortality, which is not considered a CVD in the Framingham classifications.

Previous prospective studies[6-10,26,27] on the relation of nondiabetic glucose levels to mortality have been almost exclusively on primarily healthy subjects and therefore are not directly comparable with the findings here on subjects with CVD. The results of these studies have reported mixed associations of mortality to glucose. Most of these studies[6,7,26] showed that risk increases began only in the upper normal range. The increases were of magnitude about 50%. This contrasts markedly with the results reported here for subjects with CVD in which risk increase starts at the bottom of the normal range and is approximately 242% higher at the top of the normal range: BG = 89 [plasma equivalent = 100] mg/dL.

Study limitations

Our findings may not apply to subjects of different racial and socioeconomic groups than those in the Framingham population (mostly white middle class) or to younger or older (<45 or >74 years old) subjects than in our population. As with all observational studies, although the analyses here demonstrate a strong link between BG and mortality for CVD subjects, they cannot prove that it is causal. Potentially, use of random instead of fasting glucose could have compromised our analyses by introducing additional random errors (due to glucose fluctuations in relation to time of last meal) that would dilute or even eliminate any association of glucose to mortality. This obviously did not occur; we found very strong associations between BG and the various mortalities. Fasting glucose values were available at 4 of the examination cycles. A direct comparison of the percentiles of random and fasting glucose values (Figure 2) as well as a comparison of their distributions by age-sex group showed that there were no significant differences between the 2 glucose measurements and that random glucose very closely approximated fasting glucose. Thus, we believe that in our case the use of random instead of fasting glucose had little impact on our analyses.

Clinical implications

The strong association between BG within the normal range and 2-year mortality for subjects with CVD is potentially of clinical importance. The findings here show that BG even in the normal range is a strong independent predictor of mortality in all subjects with CVD. As with the established risk factors of blood pressure and cholesterol, the rule "lower is better" seems to also apply to BG in these patients. Thus, BG is of prognostic significance for mortality in these high-risk subjects. More importantly, since BG is a modifiable risk factor, if this association is causal, it raises the intriguing possibility that vigorous reductions in BG might lead to substantial reduction in 2-year mortality for CVD subjects. However, whether the reductions in mortality suggested by the observational findings reported here can be realized by interventions can only be answered by suitable randomized trials. We hope that our findings will encourage further investigation into these possibilities.

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References

1. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100: 1134-46.
2. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ 2001;322:15-8.
3. Marso SP. Optimizing the diabetic formulary: beyond aspirin and insulin. J Am Coll Cardiol 2002;40:652-61.
4. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes 1999;48:937-42.
5. Gerstein HC, Pais P, Pogue J, et al. Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study. J Am Coll Cardiol 1999;33:612-9.
6. Coutinho M, Gerstein HC, Wang Y, et al. 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 1999;22:233-40.
7. Bjornholt JV, Erikssen G, Aaser E, et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. Diabetes Care 1999;22:45-9.
8. Donahue RP, Abbott RD, Reed DM, et al. Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. Diabetes 1987;36:689-92.
9. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care 1999;22:920-4.
10. Balkau B, Bertrais S, Ducimetiere P, et al. Is there a glycemic threshold for mortality risk? Diabetes Care 1999;22:696-9.
11. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773-8.
12. Zindrou D, Taylor KM, Bagger JP. Admission plasma glucose: an independent risk factor in nondiabetic women after coronary artery bypass grafting. Diabetes Care 2001;24:1634-9.
13. Zeller M, Cottin Y, Brindisi MC, et al. Impaired fasting glucose and cardiogenic shock in patients with acute myocardial infarction. Eur Heart J 2004;25:308-12.
14. Fisman EZ, Motro M, Tenenbaum A, et al. Impaired fasting glucose concentration in non-diabetic patients with ischemic heart disease: a marker for a worse prognosis. Am Heart J 2001;141:485-90.
15. Muhlestein JB, Anderson JL, Horne BD, et al. Effect of fasting glucose levels on mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2003;146:351-8.
16. Arcavi L, Behar S, Caspi A, et al. High fasting glucose levels as a predictor of worse clinical outcome in patients with coronary heart disease: results from the Bezafibrate Infarction Prevention (BIP) study. Am Heart J 2004;147:239-45.
17. Dawber TR. The Framingham Study: the epidemiology of atherosclerotic disease. Harvard University Press: Cambridge; 1980.
18. Nelson NA. Photometric adaptation of the Somogyi method for the determination of glucose. J Biol Chem 1944;153:375-80.
19. Kuwa K, Nakayama T, Hoshino T, et al. Relationships of glucose concentrations in capillary whole blood, venous whole blood and venous plasma. Clin Chim Acta 2001;307:187-92.
20. Cupples LA, D'Agostino RB, Anderson K, et al. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. Stat Med 1988;7:205-22.
21. D'Agostino RB, Lee ML, Belanger AJ, et al. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9:1501-15.
22. King GL, Wakasaki H. Theoretical mechanisms by which hyperglycemia and insulin resistance could cause cardiovascular diseases in diabetes. Diabetes Care 1999;22(Suppl 3):C31-7.
23. Pyorala M, Miettinen H, Laakso M, et al. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Circulation 1998;98:398-404.
24. Oliver MF, Opie LH. Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 1994;343:155-8.
25. Jokl R, Laimins M, Klein RL, et al. Platelet plasminogen activator inhibitor 1 in patients with type II diabetes. Diabetes Care 1994;17:818-23.
26. Balkau B, Shipley M, Jarrett RJ, et al. 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 1998;21:360-7.
27. Wei M, Gibbons LW, Mitchell TL, et al. Low fasting plasma glucose level as a predictor of cardiovascular disease and all-cause mortality. Circulation 2000;101:2047-52.