Fasting Blood Glucose: An Underestimated Risk Factor for Cardiovascular Death

Results from a 22-year follow-up of healthy nondiabetic men

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OBJECTIVE — Because of the available conflicting epidemiological data, we investigated the possible impact of fasting blood glucose as a risk factor for cardiovascular death in nondiabetic men. This study reports the results from a 22-year prospective study on fasting blood glucose as a predictor of cardiovascular death.

RESEARCH DESIGN AND METHODS — Of the 1,998 apparently healthy nondiabetic men (aged 40–59 years), a total of 1,973 with fasting blood glucose <110 mg/dl were included in the study in which also a number of conventional risk factors were measured at baseline.

RESULTS — After 22 years of follow-up, 483 men had died, 53% from cardiovascular diseases. After dividing men into quartiles of fasting blood glucose level, it was found that men in the highest glucose quartile (fasting blood glucose >85 mg/dl) had a significantly higher mortality rate from cardiovascular diseases compared with those in the three lowest quartiles. Even after adjusting for age, smoking habits, serum lipids, blood pressure, forced expiratory volume in 1 s, and physical fitness (Cox model), the relative risk of cardiovascular death for men with fasting blood glucose >85 mg/dl remained 1.4 (95% CI 1.04–1.8). Noncardiovascular deaths were unrelated to fasting blood glucose level.

CONCLUSIONS — Fasting blood glucose values in the upper normal range appears to be an important independent predictor of cardiovascular death in nondiabetic apparently healthy middle-aged men.

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Diabetes is associated with increased mortality from coronary heart disease and stroke (1–4). A similar association is found among nondiabetic subjects with raised blood glucose levels indicative of glucose intolerance, but below diagnostic levels for diabetes (5,6). The nature and strength of this association remains unsettled despite repeated attention (7,8), and has so far been observed only for those with blood glucose tolerance above the 80–95th percentile point (5,6). The role of fasting blood glucose in the development of cardiovascular disease in healthy subjects is even less known, mainly because of a paucity of studies correcting for established coronary heart disease risk factors such as smoking, blood lipids, blood pressure, age, BMI, and physical fitness. Because both fasting blood glucose level and glucose tolerance are essential in defining diabetes and either can be used diagnostically (9,10), it should be of interest to investigate this possible relationship further.

The present 22-year follow-up study in healthy men allows assessment of a possible relationship between fasting glucose level and cardiovascular death, after correcting for a number of confounding, accepted coronary risk factors.

RESEARCH DESIGN AND METHODS

Subjects

In 1972, all apparently healthy men aged 40–59 years working in five companies throughout Oslo, Norway, were invited to participate in a cardiovascular screening survey. The inclusion and exclusion criteria have been published in detail elsewhere (11). In brief, subjects with known or suspected coronary heart disease, other heart diseases, drug-treated hypertension, malignancy the last 5 years, advanced pulmonary disease, and other miscellaneous chronic diseases were excluded, as were men with disorders of the locomotor system preventing a symptom-limited bicycle exercise test. Specifically, men with a diagnosis of diabetes defined by glucosuria and/or fasting blood glucose ≥140 mg/dl were primarily excluded. Of the invited men, 2,341 fulfilled these criteria and 2,014 (86%) accepted to participate and were examined in the period 28 August 1972 to 25 March 1975. To meet the recently revised criteria for diagnosis of diabetes and impaired glucose homeostasis, men with fasting blood glucose ≥110 mg/dl (9) at baseline (see RESULTS) were later excluded from the present analysis. Informed consent was obtained from all participants.

Examination

The examination took place at the University Hospital of Oslo between 7:30 and 10:00 A.M. after at least 12 h of overnight fasting and 8 h of abstaining from smoking. The examination program, described in detail elsewhere (11), included a comprehensive questionnaire on various health issues, a complete clinical examination, chest X ray, measurements of resting heart

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Abbreviations: ICD, *International Classification of Diseases*; ROC, receiver operating characteristic; RR, relative risks.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline variables in 1,973 healthy men aged 40–59 years related to fasting blood glucose level (quartiles)*

	Quartile I (52–73 mg/dl)	Quartile II (74–79 mg/dl)	Quartile III (80–85 mg/dl)	Quartile IV (86–109 mg/dl)	*P* values for trend
n	470	563	483	457	—
Fasting blood glucose (mg/dl)	70	77	82	90	—
Age (years)	50 ± 5.6	49 ± 5.5	50 ± 5.7	50 ± 5.2	0.63
Systolic blood pressure (mmHg)	127 ± 16	128 ± 17	131 ± 18	134 ± 18	<0.0001
Diastolic blood pressure (mmHg)	86 ± 10	86 ± 10	87 ± 11	89 ± 10	<0.0001
Resting heart rate (beats/min)	59 ± 8	61 ± 9	61 ± 10	65 ± 11	<0.0001
Smokers (%)	43.4	45.8	43.9	40.7	0.46*
Cholesterol (mmol/l)	6.56 ± 1.16	6.53 ± 1.17	6.70 ± 1.26	6.75 ± 1.16	0.0091
Triglycerides (mmol/l)	1.27 ± 0.67	1.28 ± 0.76	1.29 ± 0.66	1.43 ± 0.70	0.0003
BMI	24.0 ± 2.6	24.3 ± 2.7	24.7 ± 2.8	24.6 ± 2.8	0.87
Physical fitness (J/kg)	1,480 ± 5.78	1,470 ± 569	1,431 ± 569	1,352 ± 500	0.35
FEV1 (ml)	3,835 ± 788	3,448 ± 835	3,394 ± 805	3,377 ± 757	0.20

Data are means ± SD or %, except fasting blood glucose, which is given as median. *Difference between quartile I and IV.

rate and blood pressure, spirographic measurements, resting and exercise electrocardiogram, and a panel of fasting blood tests.

Venous whole-blood samples were analyzed immediately after they had been drawn, and blood glucose was determined by the glucose oxidase method according to Hjelm and de Verdier (12). Two samples taken ~30 min apart were analyzed. Assay procedures for lipid analyses have been described (13). BMI was calculated as body weight (kilogram) divided by squared height (meter). Physical fitness was defined as working capacity (kilojoules) divided by body weight (kilogram), defining working capacity as the cumulated work performed during the exercise test (14).

Follow-up and mortality data

Mortality and morbidity data were collected after having been granted legal permission from the Norwegian Board of Health and the Norwegian Data Inspectorate. Mortality data were obtained from Statistics Norway, which has a complete coverage of all deaths occurring in Norway, with a maximum delay of completeness of ≤6 months. All death certificates were coded according to the *International Classification of Diseases* (ICD), *Ninth Revision*. Cardiovascular mortality included documented death from ischemic heart disease (ICD 410–414), stroke (ICD 430,431, and 436), and sudden death (ICD 798.1), defined as either occurring unexpectedly and unwitnessed within 24 h of being seen alive and well, or if witnessed, within 1 h of the onset of symptoms. Deaths from all other causes were classified as noncardiovascular. Early and late morbidity data were collected from patient records in all relevant Norwegian hospitals. The closing date of the present follow-up was 31 December 1994.

Statistical methods

First, the association between the fasting blood glucose level and mortality (from cardiovascular and noncardiovascular causes) was assessed by presenting mortality related to blood glucose quartiles.

Second, the association between time until death (from cardiovascular causes or noncardiovascular causes) and the fasting blood glucose level corrected for possible differences in age and other selected variables was investigated by means of a proportional hazards model. All variables introduced into the model were selected from previous knowledge on their associations with cardiovascular disease mortality, and all are presented.

The results are presented as relative risks (RRs). For continuous variables, the RRs of cardiovascular death associated with a deviation of 2 SDs from the mean value are presented after adjustment for all other variables in the model. For discrete variables (smoking status and fasting blood glucose), the RRs of death between groups are presented. Fasting blood glucose was analyzed as a binary variable, comparing quartile IV versus quartiles I–III (i.e., fasting blood glucose >85 vs. ≤85 mg/dl). If an interaction was found to be significant, a stratified Cox model related to the actual variable was performed. All *P* values are two-tailed and the significance level chosen is 5%.

The proportional hazards assumption was checked for all models by a graphical plot of $\log[-\log S(t)]$ and $\log(t)$ for the variables included in the model and were found to be adequately met, where $S(t)$ denotes the survival function (S) on time (t) (15). Correlations are calculated with Fisher's r to z (16).

Receiver operating characteristic was calculated from crude mortality data, and the cut-off value was chosen as that which maximizes the sum of the sensitivity and the specificity.

All models were computed with use of the proportional hazards regression (PHREG) procedure for a linear model in the SAS computer package (17) and the Survival Tools in the StatView package (18).

RESULTS

For various reasons, 16 of the 2,014 men did not have fasting blood glucose values measured and were primarily excluded. Median fasting blood glucose was 79 mg/dl (range 52–146 mg/dl, except one outlier at 190 mg/dl). The first of the two measured fasting blood glucose values were used (alternative use of the other or the mean of the two values gave virtually identical results). A total of 25 individuals had fasting blood glucose ≥110 mg/dl and were subsequently excluded, leaving 1,973 individuals for the present analysis (the 25 individuals excluded were identical in the two samples).

During the 22-year follow-up (range 20–23 years) a total of 476 men (24.1%) died, 249 men (12.8%) from cardiovascular disease (151 men from coronary heart disease, 68 died suddenly, and 30 died from stroke).

A number of parameters are presented for each quartile of fasting blood glucose (Table 1). Age was almost identical in all quartiles. With increasing glucose values, a definite pattern was observed, namely,

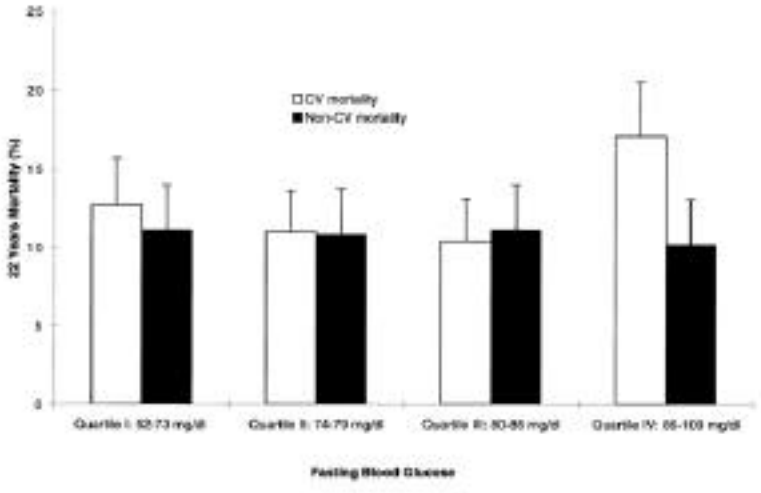

Figure 1—*Crude 22 years cardiovascular and noncardiovascular mortality according to fasting blood glucose quartiles. Error bars indicate 95% CI. CV, cardiovascular.*

increase in blood pressure, resting heart rate, cholesterol, and triglycerides. The apparent differences in physical fitness and forced expiratory volume in 1 s were not statistically significant. Men with the highest glucose values had the most unfavorable risk factor pattern, except for smoking, which if anything, showed a reversed risk pattern.

Figure 1 shows that noncardiovascular mortality rates were independent of fasting blood glucose. Virtually identical cardiovascular and noncardiovascular mortality rates were observed in the three lowest quartiles, while cardiovascular mortality was significantly higher among men from quartile IV (>85 mg/dl) compared with quartiles I-III (>85 mg/dl) (17.1 vs. 11.0%; $P = 0.0014$).

Cumulative age-adjusted cardiovascular mortality rates over 22 years of observation are presented in Fig. 2, comparing quartile IV with quartiles I+II+III. From 6 years onward, the curves deviate consistently.

On the basis of the Cox analysis, the independent risk contribution of baseline variables related to specific changes or comparisons are presented in Table 2.

Fasting blood glucose >85 mg/dl was associated with a relative risk of 1.4 (95% CI 1.04–1.8) after adjustment for all variables in the model, a level similar to established risk factors like cholesterol and blood pressure. Forced expiratory volume in 1 s (FEV1) and physical fitness were strong predictors of survival, whereas the RRs for triglycerides, BMI, and resting heart rate were not significantly different from unity.

Because of the same age distribution in all quartiles of fasting blood glucose, an interaction between age and fasting blood glucose on cardiovascular death was possible. An interaction term was introduced in the previous model and it was found to be significant ($P < 0.0001$). A stratified Cox model with strata defined by the age-groups 40–49 and 50–59 years was therefore investigated. The RR for fasting blood glucose >85 mg/dl was 2.1 (95% CI 1.3–3.3) for age-group 40–49 years and 1.1 (95% CI 0.80–1.5) for age-group 50–59 years, after adjustment for all other variables in the model.

The cut-off value of 85 mg/dl is arbitrary, representing only the interquartile boundary between quartiles III and IV. A receiver operating characteristic (ROC) analysis (detailed data not shown), maximizing the sum of specificity and sensitivity, suggests that a more appropriate threshold value for demonstrating increased risk in this material is 88 mg/dl. By comparing subjects above and below this value in the Cox model, the RR was 1.5 (95% CI 1.2–2.0).

The prevalence of known diabetes at the time of death in men with fasting blood glucose >85 mg/dl (quartile IV) is presented in Table 3; data from the 25 excluded individuals with fasting blood glucose ≥110 mg/dl at baseline are also presented.

In this fourth quartile, 15 of the 75 who died from cardiovascular causes had a diagnosis of diabetes at the time of death; 11 appeared on the death certificates and 4 in hospital records only.

CONCLUSIONS

— Subjects with a diagnosis of diabetes have a substantially increased cardiovascular morbidity and mortality, as have subjects with glucose tolerance in the upper (normal) range (19–21). The present report extends these experiences even further by showing a marked increase in cardiovascular mortality in apparently healthy men with fasting blood

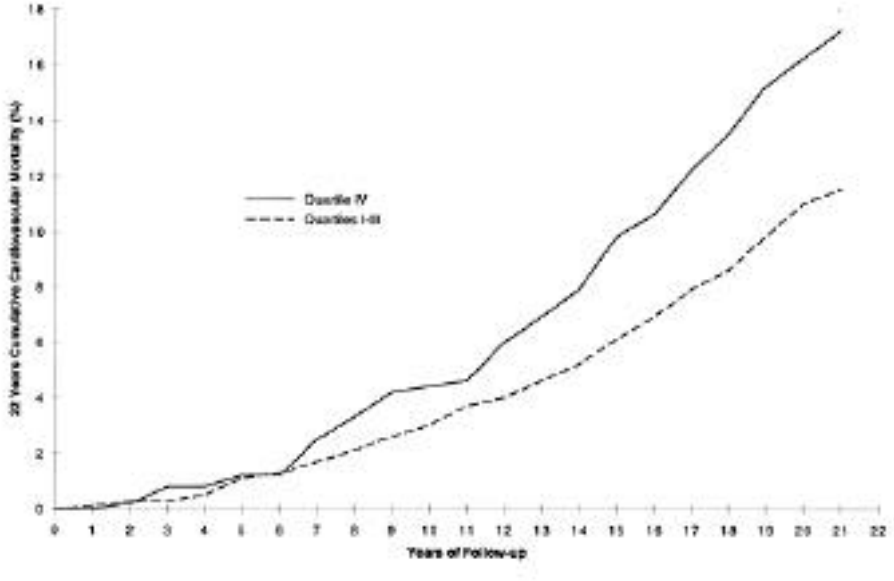

Figure 2—*Age-adjusted 22 years cumulative cardiovascular mortality comparing fasting blood glucose quartiles I–III (≤85 mg/dl) with quartile IV (>85 mg/dl).*

Table 2—*RRs of death from cardiovascular causes in 1,973 healthy men during 22-year follow-up, associated with specific changes (2 SDs or comparisons between groups) of baseline variables*

	RR	95% CI	*P* value
Fasting blood glucose (>85 vs. ≤85 mg/dl)	1.4	1.04–1.8	0.025
Age (increase of 10 years)	2.2	1.7–2.9	<0.0001
Smoking (vs. nonsmoking)	1.7	1.3–2.2	<0.001
Systolic blood pressure (increase of 35 mmHg)	1.5	1.2–2.0	<0.01
Cholesterol (increase of 2.4 mmol/l)	1.4	1.1–1.8	0.008
FEV1 (increase of 1,484 ml)	0.77	0.59–0.99	0.036
Physical fitness (increase of 1,140 J/kg)	0.54	0.37–0.79	0.001
Triglycerides (increase of 1.3 mmol/l)	1.1	1.00–1.5	0.15
BMI (increase of 2.8 kg/m^2)	1.0	0.88–1.1	0.83
Resting heart rate (increase of 10 beats)	1.0	0.91–1.2	0.95

FEV1, forced expiratory volume in 1 s.

glucose values markedly lower than hitherto acknowledged as carrying increased risk. A similar pattern, with a step increase in risk, is described in the Whitehall Study (21) for higher percentiles of 2-h postload values in nondiabetic men. An ROC suggests the threshold for increased risk to be ~88 mg/dl (i.e., well below the criteria for diabetes and even also for impaired fasting glycemia [9,10]). Unexpectedly, this association appears primarily to occur among men age 40−49 years. This might represent a more rigorous selection effect in the men age 50–59 years than in younger men age 40–49 years. The former have remained healthy for 10 more years. However, this observation remains speculative and should possibly be pursued in other studies.

A few previous studies have related fasting blood glucose levels to mortality data. Our findings are in accordance with Barrett-Connor et al. (22) who demonstrated a positive association between fasting plasma glucose and mortality from coronary heart disease after correcting for age, cholesterol, systolic blood pressure, obesity, and smoking, but are of variance with The Paris Prospective Study (19). The differences may be related to variations in methods, populations/cohorts studied, and follow-up times, which by and large are in the range of 9–11 years in most previous studies. Our 22-year observation may be more appropriate for studying the development of coronary atherosclerotic disease, which generally is a slow pathoanatomic process that may take a long time to reach an end-stage in healthy populations. As seen in Fig. 2, the RR reaches 1.5 after 7 years' observation, but the low number of deaths makes the statistical power low.

Undoubtedly, there is an association between impaired glucose tolerance and cardiovascular disease. Thus 2-h postload glucose values in the upper 5% range were associated with increased cardiovascular mortality in the Whitehall Study (21) as were values in the upper 20% range in the Paris Prospective Study (5). However, it is difficult to decide which test is the best for assessing cardiovascular risk. Oral glucose tolerance tests may be fraught with greater variability than fasting blood glucose measurements, although fasting blood glucose values are closely correlated to 2-h postglucose load values in individuals <65 years of age (23,24); our men were all <60 years. Conceivably, fasting blood glucose reflects the total exposure of the endothelium to variation in glucose level in a different way than the 2-h postload level (and the casual blood glucose value). If so, this could explain why fasting blood glucose in the present study shows an association to cardiovascular mortality at lower percentiles of the distribution than reported in studies using 2-h postload values.

Of the 75 who died from a cardiovascular cause in the upper fasting blood glucose quartile, 15 had a diagnosis of diabetes at the time of death. Therefore, the development of overt diabetes late in life may at least in part explain the risk associated with having a fasting blood glucose >85 mg/dl in the present study. To study whether the development of diabetes explains the excess risk, one would have to describe its development in the total material. However, it is remarkable that the 7 deaths in the 25 excluded men, with fasting blood glucose between 110 and 139, all were cardiovascular and all 7 had become diabetic. In the present study, the search for diabetes among the decedents was meticulous, and late undiagnosed diabetes should only occasionally have been overlooked in patients who died outside hospital.

It should be emphasized that the present study deals with the independent contribution of the fasting glucose level. An important additional observation was that subjects with blood glucose in the upper normal range show a clustering of several unfavorable other cardiovascular risk traits, such as elevated blood pressure, increased blood lipids, etc. Necessarily, such traits might increase cardiovascular risk even further in subjects with high fasting blood glucose values. Without correcting statistically for these associations, a high contribution would spuriously have been ascribed to fasting blood glucose alone.

The recognition of fasting blood glucose as an important risk factor for cardiovascular disease at a level certainly within but even below the recently extended range of diabetes and impaired glucose homeostasis (9) may carry causal significance and preventive importance.

Table 3—*Cardiovascular deaths and diabetes in quartile IV (including the subgroup with impaired fasting blood glucose) and the individuals excluded from the analysis because of fasting blood glucose≥110 mg/dl*

Fasting blood glucose (mg/dl)	*n*	Cardiovascular death	Cardiovascular death and a diagnosis of diabetes
86–99	408	65	8
100–109	49	10	7
110–126*	20	4	4
126–139*	5	3	3

*Individuals excluded (9).

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