Fasting Plasma Glucose Variability Predicts 10-Year Survival of Type 2 Diabetic Patients

The Verona Diabetes Study

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OBJECTIVE — In the present study, we evaluated whether the coefficient of variation (CV) of fasting plasma glucose (FPG) over a 3-year period was a significant predictor of mortality in type 2 diabetic patients aged 56–74 years.

RESEARCH DESIGN AND METHODS — All type 2 diabetic patients (n = 1,409) aged 56–74 years attending the Verona Diabetes Clinic and having at least two FPG determinations in each of the years 1984–1986 were followed for 10 years (1987–1996) to assess total and cause-specific mortality. Patients were grouped into tertiles of mean and CV of FPG during 1984–1986. These parameters as well as sex, age, diabetes duration, insulin treatment, smoking, hypertension, and hypercholesterolemia were included in multivariate survival analyses.

RESULTS — During the follow-up, 468 patients died. The CV of FPG was an independent predictor of total, cardiovascular, and cancer mortality. Mean FPG was a predictor of total mortality only when the CV of FPG was not included in the analyses.

CONCLUSIONS — Long-term variability of fasting glucose is an independent predictor of mortality in patients with type 2 diabetes. The CV of FPG might be considered a useful additional parameter in the management of these patients.

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Hyperglycemia predicts mortality from all causes (1), and particularly from cardiovascular diseases (2), in patients with type 2 diabetes. Recently, the U.K. Prospective Diabetes Study (UKPDS) conclusively showed that mean HbA_{1c} predicts myocardial infarction in type 2 diabetes (3). However, when HbA_{1c} was reduced by intensive treatment, a significant decrease in microvascular complications, but not in diabetes-related mortality or myocardial infarction, was observed (4).

We reported that fasting plasma glucose (FPG) variability, as assessed by the coefficient of variation (CV) of FPG over a period of three years, was an independent predictor of all-cause (5) and cardiovascular mortality (6) in patients with type 2 diabetes aged ≥75 years. Interestingly, when the CV of FPG was introduced in a multivariate survival analysis, mean FPG was not a significant predictor of mortality. The potential clinical implication of this observation is considerable; however, it is crucial that what was observed in elderly patients, who represent only 20–25% of type 2 diabetes (7,8), be confirmed in younger patients.

In the present study, we examined a cohort of patients aged 56–74 years, which is the age-range including ~60% of the diabetic population (7,8), with the aim to establish whether mean FPG and/or the CV of FPG over a period of 3 years independently predicted mortality during the next 10 years.

RESEARCH DESIGN AND METHODS

Subjects

This is an observational study carried out within the framework of the Verona Diabetes Study, a population-based survey on diabetes prevalence and diabetes-related mortality (5–8).

The cohort under study included 1,409 type 2 diabetes patients diagnosed according to standard criteria (9). These subjects (652 men, 757 women; age 56–74 years), regularly attended the Verona Diabetes Clinic, and had ≥2 FPG determinations per year from 1 January 1984 to 31 December 1986. Subjects irregularly attending the Diabetic Clinic, with fewer FPG determinations were excluded (n = 917). First referral to the Diabetes Clinic was suggested by family physicians, while subsequent visits were scheduled by physicians of the Diabetes Clinic, with 3.68 ± 1.24 visits/year per patient. The therapeutic guidelines for type 2 diabetes at the Diabetes Clinic followed a stepwise approach. Diet was prescribed as first-line therapy in all patients. Oral hypoglycemic agents (OHA) were introduced as a second step and insulin was prescribed when OHA failed, first with a bedtime injection associated with OHA and subsequently, if necessary, with more complex regimens. In general, the switch to the next step was dictated by FPG persistently >9–10 mmol/l.

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Abbreviations: CV, coefficient of variation; FPG, fasting plasma glucose; OHA, oral hypoglycemic agents; RR, relative risk; UKPDS, U.K. Prospective Diabetes Study.

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

Table 1—*Main demographic and clinical characteristics at baseline (31 December 1986) of type 2 diabetic patients, aged 56–74 years, included and not included in the study, and of survivors and decedents after 10-year follow-up*

	Subjects					
	Not included in study	Included in study	*P*	Survivors	Decedents	*P*
n	917	1,409	—	941	468	—
Male sex	466 (50.8)	652 (46.3)	0.034	416 (44.2)	236 (50.4)	0.031
Age (years)	65.7 ± 5.4	66.4 ± 5.1	0.003	65.7 ± 5.0	67.8 ± 5.0	<0.001
Duration of diabetes (years)	8.0 ± 6.5 (0.5–32.5)	12.3 ± 6.3 (2.5–40.5)	<0.001	12 ± 6.2 (2.5–40.5)	13 ± 6.5 (2.5–38.5)	0.004
BMI (kg/m^2)	28.2 ± 4.5 (17.2–58.7)	27.9 ± 4.2 (17.1–50.7)	0.043	28.0 ± 4.1 (17.1–50.7)	27.6 ± 4.3 (17.1–45.8)	0.124
Hypertension	531 (57.9)	801 (56.8)	0.637	514 (54.6)	287 (61.3)	0.019
Hypercholesterolemia	49.8	48.6	0.104	305 (49.5)	140 (46.7)	0.439
Smokers	240 (26.2)	308 (21.9)	0.019	220 (23.4)	88 (18.8)	0.055
Therapy	—	—	<0.001	—	—	<0.001
Diet	205 (22.4)	73 (5.2)	—	55 (5.8)	18 (3.8)	—
OHA	685 (74.7)	1,188 (84.3)	—	810 (86.1)	378 (80.8)	—
Insulin	13 (1.4)	58 (4.1)	—	29 (3.1)	29 (6.2)	—
Insulin + OHA	14 (1.5)	90 (6.4)	—	47 (5)	43 (9.2)	—
FPG						
Mean (mmol/l) (1984–1986)	8.4 ± 2.3	8.9 ± 2.3	<0.001	8.7 ± 2.2	9.2 ± 2.5	<0.001
CV (%) (1984–1986)	—	17.0 ± 9.8	—	16.2 ± 9.7	18.7 ± 9.8	<0.001
Slope (mmol · l^{-1} · year^{-1})	—	−0.04 ± 0.93	—	−0.06 ± 0.85	−0.02 ± 1.07	0.463
<3.9 mmol/l	9 (1.0)	35 (2.5)	0.012	20 (2.1)	15 (3.2)	0.275
Deaths in 10 years from:						
All causes	309 (33.7)	468 (33.2)	0.822	—	468 (100.0)	—
Cardiovascular diseases	123 (13.4)	180 (12.8)	0.659	—	180 (38.5)	—
Malignancies	84 (9.2)	129 (9.2)	0.999	—	129 (27.6)	—
Diabetes	39 (4.3)	75 (5.3)	0.280	—	75 (16.0)	—
Digestive diseases	26 (2.8)	24 (1.7)	0.079	—	24 (5.1)	—
Respiratory diseases	14 (1.5)	22 (1.6)	0.999	—	22 (4.7)	—
All other causes	23 (2.5)	38 (2.7)	0.895	—	38 (8.1)	—

Data are *n*, means ± SD (range), *n* (%), or %. Hypertension is defined as blood pressure ≥160/90 mmHg or use of antihypertensive drugs. Hypercholesterolemia (total cholesterol ≥240 mg/dl or use of lipid-lowering drugs) is given for subjects with plasma total cholesterol available at baseline (*n* = 916 for subjects included in the study and 642 for subjects not included in the study).

Main clinical characteristics at baseline of the cohort under study and subjects excluded from the analysis are summarized in Table 1. Marginal differences were found in age, sex distribution, smoking habits, and number of FPG values <3.9 mmol/l, while slightly greater differences were found with respect to diabetes duration, therapy, and mean FPG. Total and cause-specific mortality was similar.

FPG determinations

FPG was repeatedly measured in a consistent fashion in the three years preceding the mortality follow-up. Venous blood was withdrawn from an antecubital vein after a 10-h overnight fast, collected in tubes containing EDTA and fluoride and centrifuged within 2 h. Plasma glucose was assayed with a glucose-oxidase method (Boehringer, Mannheim, Germany).

The total number of FPG measurements during the years 1984–1986, which were available in the clinical records of patients under study and which were collected for analysis, was 16,184 (per-patient mean ± SD 11.5 ± 3.6; median 11.0; range 6–41). For each patient, the mean, CV, and regression coefficient (slope) of FPG over the years were calculated.

Mortality assessment

Patients were followed prospectively from 1 January 1987 to 31 December 1996 to assess all-cause and cause-specific mortality. The life status was ascertained on 31 December 1996 by reviewing death certificates of the Registry Office and mortality records of the Social Health Unit. Patients who had died were identified by name, birthdate, and National Health Code. A total of 74 patients (5.3%) lost to follow-up were arbitrarily considered alive.

The underlying cause reported on the death certificate was regarded as the cause of death. When more than one underlying cause was reported, the first one was chosen. All death certificates were reviewed by a certified nosologist, according to the *International Classification of Diseases, Ninth Revision.* Causes of death were grouped into cardiovascular diseases (codes 390–459), malignant neoplasms (140–208), diabetes mellitus (250), digestive diseases (520–579), respiratory diseases (460–519), and other causes (all other codes).

Statistical analysis

Patients were grouped into tertiles of mean FPG (<7.61, 7.61–9.36, and >9.36 mmol/l) and the CV of FPG (<11.7, 11.7–18.7, and >18.7%).

BMI, total cholesterol (data available only in 916 patients), smoking, hypertension, and diabetes therapy at baseline were recorded. Hypertension was defined by blood pressure ≥160/90 mmHg, measured after 5 min in the sitting position, or by use of antihypertensive medications. Hypercholesterolemia was defined by total cholesterol ≥240 mg/dl or by use of lipid-lowering drugs.

Table 2—*Demographic and clinical characteristics and 10-year mortality from all causes for type 2 diabetic patients as a function of mean FPG and of the CV of FPG, 1984–1986*

	Tertiles of mean FPG				Tertiles of CV of FPG			
	I	II	III	*P*	I	II	III	*P*
n	469	470	470	—	469	470	470	—
Male sex	270 (57.6)	223 (47.4)	159 (33.8)	<0.001	225 (48.0)	232 (49.4)	195 (41.5)	0.036
Age (years)	66.9 ± 5	66.4 ± 5.1	65.9 ± 5.2	0.012	66.5 ± 5	66.1 ± 5.3	66.4 ± 5.1	0.454
Duration of diabetes (years)	11.2 ± 6.1	11.8 ± 6.3	13.9 ± 6.2	<0.001	11.6 ± 5.6	12.2 ± 6.3	13.1 ± 6.8	0.001
BMI (kg/m^2)	27.5 ± 3.8	27.8 ± 4.3	28.3 ± 4.4	0.014	28.0 ± 4.1	27.8 ± 3.9	27.7 ± 4.4	0.457
Hypertension	247 (52.7)	276 (58.7)	278 (59.1)	0.081	248 (52.9)	278 (59.1)	275 (58.5)	0.102
Hypercholesterolemia	144 (47.2)	152 (49.7)	149 (48.9)	0.825	158 (51.8)	140 (45.8)	147 (48.2)	0.322
Smokers	113 (24.1)	103 (21.9)	92 (19.6)	0.246	94 (20.0)	113 (24.0)	70 (21.5)	0.324
Therapy	—	—	—	<0.001	—	—	—	<0.001
Diet	61 (13.0)	11 (2.3)	1 (0.2)	—	55 (11.7)	13 (2.8)	5 (1.2)	—
OHA	400 (85.3)	435 (92.6)	353 (75.1)	—	409 (87.2)	431 (91.7)	348 (74)	—
Insulin	4 (0.9)	11 (2.3)	43 (9.1)	—	1 (0.2)	8 (1.7)	49 (10.4)	—
Insulin + OHA	4 (0.9)	13 (2.8)	73 (15.5)	—	4 (0.9)	18 (3.8)	68 (14.5)	—
FPG								
Mean (mmol/l)	6.7 ± 0.6	8.4 ± 0.5	11.4 ± 1.9	—	7.7 ± 1.7	9.0 ± 2.3	9.8 ± 2.3	<0.001
CV (%)	13.0 ± 8.1	17.7 ± 10.5	20.3 ± 9.3	<0.001	8.5 ± 2.1	14.8 ± 1.9	27.7 ± 9.4	—
<3.9 mmol/l	12 (2.6)	13 (2.8)	10 (2.1)	0.814	0 (0)	1 (0.2)	34 (7.2)	<0.001
Slope (mmol · l^{-1} · year^{-1})	−0.07 ± 0.53	−0.06 ± 0.86	−0.01 ± 1.25	0.551	0.01 ± 0.32	0.05 ± 0.66	−0.21 ± 1.42	<0.001
Deaths in 10 years from all causes	142 (30.3)	143 (30.4)	183 (38.9)	0.005	111 (23.7)	171 (36.4)	186 (39.6)	<0.001

Data are *n*, means ± SD, or *n* (%). Hypercholesterolemia (*n* = 916) and hypertension are as defined in Table 1.

Univariate survival analysis was performed by Kaplan-Meier method and log-rank test. Multivariate survival analysis was accomplished by Poisson regression model (10) including tertiles of mean FPG and the CV of FPG, the slope of FPG, sex, age (years), diabetes duration (years), insulin treatment (yes/no), cigarette smoking (yes/no), hypertension (yes/no), and hypercholesterolemia (yes/no) as independent variables. Mortality from all causes, cardiovascular diseases, malignancies, and all other causes (combined) was used as end points in separate survival analyses. Results were expressed as relative risk (RR). For continuous variables, RR was calculated on the basis of an increase in the values of 1 SD. The interaction terms between mean FPG and the CV of FPG as well as sex and either mean FPG or the CV of FPG were entered in the model. The Poisson regression model was chosen because the hazard associated with some variables showed a significant interaction with time. Other statistics were carried out by unpaired Student's *t test*, χ^2 test, and one-way analysis of variance. Statistical analyses were performed with statistical packages SPSS (11) and EGRET (11a).

RESULTS — By the end of follow-up, 468 patients (236 men, 232 women) had died. Overall mortality was 39.7/1,000 person-years (44.6 men, 35.7 women). Cardiovascular diseases were the leading cause of death, followed by malignancies and diabetes. Altogether these causes accounted for 82% of all deaths. Decedents were slightly but significantly older, presented a longer duration of diabetes, included a larger proportion of men and of hypertensive patients, and were more frequently insulin-treated (Table 1). In addition, patients who died had higher mean FPG and CV of FPG, while the slope of FPG was not different.

The proportion of women and of insulin-treated patients, as well as the duration of diabetes, significantly increased across tertiles of both the mean and CV of FPG (Table 2). Age significantly decreased, and BMI significantly increased only across tertiles of mean FPG. CV of FPG significantly increased across tertiles of mean FPG, whereas mean FPG significantly increased across tertiles of the CV of FPG. However, the overall relationship between these two parameters was rather weak (r^2 = 0.09). Patients with occasionally low fasting glycemia (<3.9 mmol/l), who were uniformly distributed across tertiles of mean FPG, almost completely segregated into the top tertile of the CV of FPG. The slope of FPG was similar across tertiles of mean FPG and was slightly negative in the upper tertile of the CV of FPG. Hypertension, hypercholesterolemia, and smoking did not significantly differ in tertiles of the mean or the CV of FPG. Deaths from all causes increased significantly across tertiles of both the mean and CV of FPG (Table 2).

In the 10-year survival analysis carried out by the Kaplan-Meier method (Fig. 1), patients in the top tertile of mean FPG experienced higher mortality (P = 0.005) than patients of the other two tertiles, who displayed a similar survival during the follow-up. Patients of the lower tertile of the CV of FPG had a longer survival ($P < 0.001$) than patients of the other two tertiles, who did not show substantial differences.

Multivariate survival analysis carried out by Poisson regression model (Table 3) showed that the CV, but not mean FPG, was an independent predictor of mortality. In particular, patients in the middle and the upper tertiles of CV of FPG had an ~65% higher risk of all-cause mortality than patients in the lower tertile ($P <$ 0.001). Remarkably, mean FPG was an

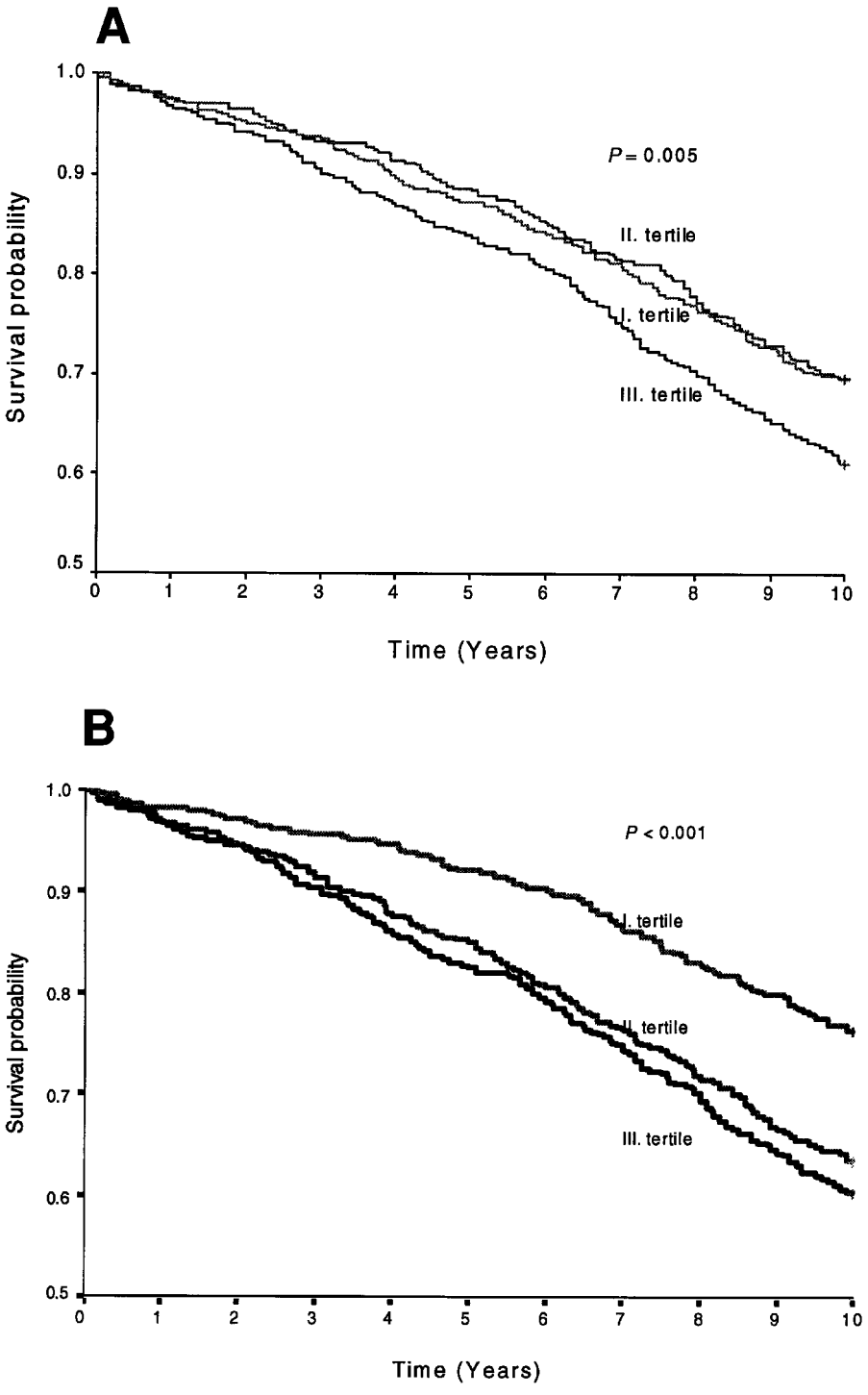

Figure 1—*Kaplan-Meier estimates of survival probability in 1,409 type 2 diabetic patients from Verona, Italy, 1 January 1987 through 31 December 1996. Patients were grouped into tertiles according to mean FPG (*A*) and CV of FPG (*B*) during the 3 years (1 January 1984 through 31 December 1986) preceding the mortality follow-up. The log-rank test revealed significant differences in survival among tertiles of mean FPG (*P* = 0.005) and of the CV of FPG (*P* < 0.001).*

independent predictor of all-cause mortality only when the CV was not included in the model (RR for tertile III vs. I = 1.36; 95% C.I. 1.07–1.74; *P* = 0.018).

Analysis of cause-specific mortality (Table 3) revealed that the excess mortality associated with higher CV of FPG was mainly explained by an excess mortality from cardiovascular diseases (*P* = 0.019) and malignancies (*P* = 0.024). The results were unchanged after exclusion of subjects who died within the first 2 years of follow-up (RR for tertile III vs. I = 1.85; 95% CI 1.09–3.14).

Other predictors of mortality were male sex (all-cause mortality, mortality from malignancies, and mortality from other causes combined), age (all categories of cause of death), insulin treatment (all-cause mortality and mortality from other causes combined), and hypertension (mortality from cardiovascular diseases).

When the interaction terms between the mean and CV of FPG and between sex and these parameters of glucose control were entered in the models, none of these terms turned out to be a predictor of mortality. When insulin-treated subjects were excluded from the analyses, results did not change (data not shown).

The above-described analyses were repeated in a subset of 1,075 patients who were prospectively followed from 1986 (baseline) to 1996. These subjects had ≥2 FPG measurements per year at the Diabetes Clinic during years 1987–1989, were alive on 1 January 1990, and were followed up for mortality until 31 December 1996. The results of these supplementary analyses were similar to those previously reported. The RR of total mortality associated with upper versus lower tertile of the CV of FPG in multivariate analysis was 1.85 (95% C.I. 1.33–2.56).

CONCLUSIONS — The preliminary observation that glucose variability predicted 5-year mortality in elderly type 2 diabetes subjects (5,6) prompted us to confirm the result over a period of 10 years in patients aged 56–74 years, who represent the largest segment of the diabetic population (7,8).

Consistent with other studies (1,2), we found that hyperglycemia (high mean FPG) was a predictor of mortality. However, when the survival analyses included both the mean and CV of FPG, only the latter was an independent predictor of mortality. This does not necessarily mean that the severity of hyperglycemia was not important in determining the outcome in type 2 diabetes, but indicates that the prognostic value of mean FPG was lower than that of the CV. Indeed, our data suggest that the CV of FPG might be more reliable than the mean in assessing the relationship between long-term glucose control and survival. On the other hand, the CV of FPG might be a

Table 3—*RRs (95% CI) for death from all causes, from cardiovascular diseases, from malignancies, and from all other causes in type 2 diabetes patients, aged 56–74 years after adjustment for all other variables included in the model*

Variable	All causes	*P*	Cardiovascular diseases	*P*	Malignancies	*P*	All other causes	*P*
n	468	—	180	—	129	—	159	—
Sex (women vs. men)	0.66 (0.54–0.81)	<0.001	0.79 (0.58–1.09)	0.156	0.51 (0.35–0.75)	<0.001	0.66 (0.47–0.92)	0.015
Age (years) (1 SD = 5.14 years)	1.45 (1.31–1.60)	<0.001	1.66 (1.41–1.97)	<0.001	1.22 (1.01–1.47)	0.035	1.47 (1.23–1.74)	<0.001
Diabetes duration (years) (1 SD = 6.28 years)	1.01 (0.92–1.11)	0.858	1.09 (0.93–1.26)	0.285	0.99 (0.82–1.19)	0.885	0.94 (0.80–1.11)	0.487
Insulin treatment (yes vs. no)	1.59 (1.19–2.13)	0.002	1.06 (0.62–1.83)	0.826	0.81 (0.41–1.61)	0.542	3.07 (2.00–4.72)	<0.001
Smoking (yes vs. no)	0.85 (0.66–1.10)	0.208	1.00 (0.65–1.52)	0.983	0.85 (0.54–1.33)	0.464	0.71 (0.45–1.14)	0.144
Hypertension (yes vs. no)	1.16 (0.96–1.41)	0.121	1.50 (1.09–2.06)	0.013	0.79 (0.55–1.12)	0.189	1.23 (0.89–1.71)	0.207
Slope of FPG	1.06 (0.97–1.16)	0.232	1.08 (0.92–1.27)	0.342	1.11 (0.92–1.35)	0.284	1.01 (0.88–1.17)	0.823
Mean FPG	—	0.148	—	0.444	—	0.380	—	0.296
Tertile II vs. tertile I	0.89 (0.70–1.14)	—	0.85 (0.58–1.24)	—	0.75 (0.48–1.17)	—	1.15 (0.73–1.79)	—
Tertile III vs. tertile I	1.12 (0.87–1.45)	—	1.07 (0.71–1.6)	—	0.96 (0.60–1.53)	—	1.43 (0.89–2.28)	—
CV of FPG	—	<0.001	—	0.019	—	0.024	—	0.052
Tertile II vs. tertile I	1.67 (1.30–2.14)	—	1.73 (1.18–2.55)	—	1.71 (1.08–2.71)	—	1.60 (1.01–2.54)	—
Tertile III vs. tertile I	1.68 (1.29–2.18)	—	1.53 (1.00–2.33)	—	1.86 (1.14–3.03)	—	1.75 (1.08–2.81)	—

RR and significance of differences were derived from the Poisson regression analyses. Calculation of the RR for age and diabetes duration was based on an increase of 1 SD. *P*, significance of each variable in the Poisson regression model after adjustment for all other variables.

feature of glucose control ("variability") distinct from hyperglycemia. It is noteworthy that in the UKPDS, HbA_{1c} reduction by intensive treatment yielded a significant reduction in microvascular complications but not in mortality (4). According to our data, it could be hypothesized that in the UKPDS the beneficial effect of lower FPG by intensive treatment has been partially blunted by higher glucose variability.

It could be speculated that the CV and mean of FPG are strongly interrelated and both are the expression of the severity of hyperglycemia. However, the relation between the two parameters was weak ($r^2 = 0.09$), and the introduction of interaction terms in the multivariate analyses did not change the results. Thus, it seems that the CV and mean of FPG describe different aspects of long-term glucose control, i.e., severity of hyperglycemia (mean) and glucose variability (CV). In this respect, the lack of significance of the interaction terms between the mean and CV supports the conclusion that variability is detrimental both when glucose control is apparently "good" (low mean FPG), and when it is "poor" (high mean FPG).

One might hypothesize that the association between glucose variability and mortality underlies a worsening of FPG over time in subjects with high CV of FPG. This is not the case, as the slope of FPG in the upper tertile of the CV of FPG was actually slightly negative (-0.21 mmol $\cdot$ $l^{-1} \cdot year^{-1}$).

Mortality in the middle and upper tertiles of the CV of FPG was similar. This result suggests the existence of a threshold for increased mortality at a relatively low CV of FPG. In other words, stability seems to be protective and a moderate variability seems to be already harmful.

The CV of FPG was an independent predictor of death from cardiovascular diseases and malignancies. Association with cardiovascular mortality is not surprising (6), whereas the association with mortality from malignancies is less obvious. On purely theoretical grounds, two hypotheses may be put forward: *1*) malignancies result in glucose variability through several mechanisms (e.g., impaired feeding, deterioration of nutritional status, involvement of organs controlling glucose homeostasis, use of medications with a detrimental effect on glucose control, etc.); and *2*) glucose variability favors the development and/or the progression of cancer through still unidentified mechanisms. So far, the latter hypothesis is not supported by any experimental or clinical data.

At present it is unknown whether these associations are causal or not. The association of FPG variability with excess mortality could be an epiphenomenon of a severe underlying illness. We reasoned that in this case the exclusion from the analyses of subjects deceased within the first two years of follow-up should blunt the association between mortality and CV-FPG. However, the CV of FPG turned out to be also a significant predictor of late mortality. Thus, one might speculate that FPG fluctuations over time are harmful.

Several pathophysiological mechanisms can be hypothesized to explain the association between FPG variability and mortality. First, glucose variability could simply be an indicator of irregular compliance to therapy due to a variety of reasons (poor health education, low socioeconomic status, erratic food intake, lack of economic resources, insufficient awareness of the severity of the disease). Second, glucose variability might depend on the interference exerted by alcohol abuse, concomitant use of medications affecting glucose metabolism, or comorbidity. Third, glucose variability might be implicated, through mechanisms still poorly understood, in diabetes complications. Fourth, a pathophysiological factor or process influencing mortality might have an effect on FPG in a manner that is not directly related to the severity of hyperglycemia. We do not have much information about the second, third, and fourth issues. As to the first one, the number of medical examinations during the study period, i.e., an indicator of compliance, was higher rather than lower in subjects with high CV of FPG as compared with subjects with low

CV (13.1 vs. 10.1 examinations in upper vs. lower CV tertiles).

The association between the CV of FPG and cardiovascular mortality could result from more frequent hypoglycemia, which predisposes to adverse outcomes (12). Indeed, nearly all patients with occasional low FPG at the Diabetes Clinic fell in the top tertile of CV. This could indicate a predisposition to hypoglycemic events in everyday life. Thus, the association between the CV of FPG and cardiovascular mortality could be partially explained by fatal hypoglycemia in subjects with high glucose variability.

Experimental data on the harmful effect of glucose variability are scarce. However, ambient glucose fluctuations yielded retinal and kidney damage in cell studies (13–15). It might also be that in humans, glucose variability exerts a deleterious effect on various tissues, thereby contributing to fatal events.

In conclusion, the results of the present study suggest that the CV of FPG might be included in the evaluation of glucose control in type 2 diabetes patients, to better predict survival. Whether maintenance of a stable glucose level over time can improve survival in diabetic patients remains to be demonstrated. A clinical trial comparing stable versus unstable glycemia would be conclusive to prove that glucose "stability" actually reduces mortality.

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