Day-to-Day Variability of Fasting Plasma Glucose in Newly Diagnosed Type 2 Diabetic Subjects

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OBJECTIVE — To determine the day-to-day intraindividual variability of fasting plasma glucose (FPG) in newly diagnosed Caucasian type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS — A total of 193 newly diagnosed, previously untreated, Caucasian type 2 diabetic subjects (135 men, 58 women) had FPG measured on two consecutive days (FPG_1, FPG_2). Ethical approval and subjects' full informed consent were obtained. Subjects fasted for 12 h before each study day and rested for at least 30 min before blood was taken. Plasma glucose was analyzed by a glucose oxidase method with intra- and interassay coefficients of variation (CVs) <2%. Variability of FPG was assessed by comparison of percentage differences (PDs): PD = 100 ($FPG_2 - FPG_1$)/FPG_1, with averaged FPG (FPG_{aver} = [$FPG_1 + FPG_2$]/2). Biological and analytical variability were determined by use of $SD^2_{total} = SD^2_{biological} + SD^2_{analytical}$, where $SD^2_{analytical} \cong 2 \times (CV_{glucose\ measurement})^2$. Given normally distributed data with zero mean, 95% of daily percentage differences will be expected to fall within a range of ± 2 SD_{total}.

RESULTS — Subjects were age 54 ± 10 years (mean ± SD) and had BMI of 29.3 ± 5.3 kg/m^2. FPG values for both days were 12.2 ± 3.4 mmol/l (FPG_1) and 12.1 ± 3.3 mmol/l (FPG_2), with a mean paired difference (95% CI) of 0.1 (0.0 to 0.3) mmol/l. The variance of these differences increased with increasing FPG_{aver}. The PDs did not exhibit this effect and were normally distributed (mean −0.6% [−1.7 to 0.4]; SD 7.4% [6.8 to 8.3]), giving a 95% variability (2 SD) of 14.8%. Biological variability (2 $SD_{biological}$) was 13.7%. No significant difference in PD was found between men and women (mean difference 1.3% [−1.0 to 3.6]; SD_{male} 7.4%, SD_{female} 7.3%; $P = 0.62$).

CONCLUSIONS — A total of 95% of the FPG values for this group of newly diagnosed type 2 diabetic subjects varied within approximately ±15% on a daily basis, with ~14% caused by biological variability. As these results are expressed in percentage terms, subjects in the group with higher FPG values are likely to experience larger changes in FPG values measured from day to day. This variability should be considered when using FPG for the diagnosis and/or monitoring of response to treatment in patients with type 2 diabetes.

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Plasma glucose is widely used in conjunction with glycosylated hemoglobin as a measure of the adequacy of glycemic control in diabetes care. Its normalization is believed to be a reliable marker of good metabolic control in type 2 diabetes (1). A strong association of fasting plasma glucose (FPG) with the development of diabetic retinopathy has been observed in a number of populations, including Pima Indians (2) and Egyptians (3). The incidence of coronary artery disease is also strongly related to FPG, being markedly increased at an FPG level >6.9 mmol/l in the Paris Prospective Study (4). The American Diabetes Association (ADA) recommendations for the management of type 2 diabetes suggest an FPG value of <6.7 mmol/l as a measure of adequate glycemic control (5).

Recently, the ADA published revised criteria for the diagnosis of diabetes that include the possibility of diagnosing diabetes by use of an FPG value, with a confirmatory test on a subsequent day (6). A single FPG value was recommended for classifying patients as "normal" or "impaired fasting glucose" and for use in the diagnosis of diabetes in epidemiologic studies.

The measurement of FPG therefore is being encouraged for both the monitoring and diagnosis of different degrees of glucose intolerance. Consequently, the continued use of the oral glucose tolerance test (OGTT) in diabetic screening and diagnosis is being questioned (7). These recommendations necessitate an awareness of the variability of FPG. Therefore, we have examined the day-to-day variability of FPG in a group of newly diagnosed, previously untreated, type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS

— A total of 193 newly diagnosed previously untreated Caucasian type 2 diabetic subjects (135 men, 58 women) had FPG measured on two consecutive days (FPG_1, FPG_2). All investigations were approved by the local research ethics committee, and informed consent was obtained from all subjects.

Diagnosis of diabetes had been made according to 1985 World Health Organiza-

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Abbreviations: ADA, American Diabetes Association; CV, coefficient of variation; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PD, percentage difference; WHO, World Health Organization.

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

Table 1—*Demographic data for 193 newly diagnosed Caucasian type 2 diabetic subjects (135 men, 58 women)*

	Mean ± SD	Median	Minimum	Maximum	*n*
Age (years)	54 ± 10	54	26	78	193
BMI (kg/m²)	29.3 ± 5.3	28.9	17.1	48.7	193
Systolic blood pressure (mmHg)	139 ± 21	140	92	210	192
Diastolic blood pressure (mmHg)	85 ± 11	85	58	120	192
$Cholesterol_{total}$ (mmol/l)	5.4 ± 1.3	5.3	3.0	9.8	186
$Triglycerides_{total}$ (mmol/l)	2.2 ± 1.4	1.8	0.4	10.7	186
HbA_1 (%)	11.2 ± 2.4	11.0	6.7	17.3	179

tion (WHO) criteria (8) before the study. All subjects were islet cell antibody negative. Subjects took part in the study within 2 weeks of diagnosis with no intervening treatment.

Subjects fasted for 12 h before each study day and rested for at least 30 min before blood was taken. Each subject's weight and height were determined and BMI was calculated. Supine systolic and diastolic blood pressures were recorded to the nearest 2 mmHg. A 17-gauge Luer-lock venflon was inserted into either anticubital fossa, and samples were taken for plasma glucose, HbA_1, total serum cholesterol, and total serum triglycerides. HbA_1 was determined chromatographically (9). Total cholesterol and triglyceride levels were measured by enzymatic techniques (10,11).

For glucose measurement, blood was taken into fluoride oxalate, placed in a refrigerated (4°C) centrifuge, and spun at 2,000*g* for 5 min. The plasma was then aliquoted into plain tubes and stored at −20°C until assayed by a glucose oxidase method (12) with intra- and interassay coefficients of variation (CVs) <2%. On average, the time between sampling and freezing was 10 min. Samples were handled identically on the two study days.

To avoid spurious correlations (13), variability of FPG was assessed by comparison of percentage differences (PDs): PD = 100 $(FPG_2 - FPG_1)/FPG_1$, with averaged FPG ($FPG_{aver} = [FPG_1 + FPG_2]/2$). Biological and analytic variability were determined by use of $SD^2_{total} = SD^2_{biological} + SD^2_{analytical}$, where $SD^2_{analytical} \cong 2 \times (CV_{glucose\ measurement})^2$. Given normally distributed data with zero mean, 95% of daily percentage differences will be expected to fall within a range of ± 2 SD. Levene's test for equality of variances was used to compare the variability of men and women. Data analysis was performed using SPSS software, version 7.5 (SPSS, Chicago).

RESULTS — Summary data for this group of type 2 diabetic subjects are given in Table 1, and FPG values are summarized in Table 2. A nonsignificant mean paired difference of 0.1 (0.0 to 0.3) mmol/l was found. FPG values for both days are illustrated in Fig. 1 together with the line of identity. The high correlation ($r = 0.96$, $P < 0.0001$) between the two FPG values should not be overinterpreted in the case of method comparison or repeatability studies (14).

Some increase in the variance of the differences with increasing FPG is evident in Fig. 1. To assess the significance of this, the absolute values of the differences ($|FPG_2 - FPG_1|$) were plotted against FPG_{aver} (Fig. 2). The slope of the regression line was positive and significantly different from zero ($P < 0.0001$), indicating increasing variance with increasing FPG. This was also confirmed by an "errors in variables" regression analysis, which accounts for the fact that both variables are subject to measurement error. The variance was stabilized by considering percentage differences (Fig. 3). The 95% CI for the regression line includes the zero line and is tight. Normality of the PDs was assessed graphically, and no significant departure from normality was found. The mean PD was −0.6% (−1.7 to 0.4) with SD 7.4% (6.8 to 8.3), giving 95% limits of variability (2 SD) of ±14.8%. As expected, 181 of 193 (94%) of the PDs lie within this range. Figure 4 illustrates the distribution of PD values. A glucose measurement CV of 2% implied a 95% biological variability (2 $SD_{biological}$) of 13.7%.

No significant difference was found when PDs for men and women were compared (mean difference 1.3% [−1.0 to 3.6]; variability 2 SD_{male} 14.8%, 2 SD_{female} 14.6%, $P = 0.62$).

CONCLUSIONS — This study indicates that 95% of FPG values for members of this group of type 2 diabetic subjects varied within approximately ±15% on two consecutive days. The daily biological variability comprised 14 of the 15% total variability and represents a limit to the accuracy with which daily FPG can be assessed. Diet or lifestyle changes are unlikely to have had a significant effect on the results because of the relatively short time period between the two tests. Thus, the bulk of the variability is probably due to other unexplained intraindividual biological factors that influence FPG, including the "dawn phenomenon" (15). Under "field" conditions, where glucose measurement CVs may not be as stringent as in the laboratory, the observed variability would be even larger. For instance, had a glucose measurement method with a CV of 4% been used, then a 95% variability on the order of 18% would be expected.

Diagnosis of diabetes was made according to 1985 World Health Organization (WHO) criteria, and measurements for this study were taken within 2 weeks of diagnosis. In addition to the natural variability described in this study, the effect of recent diagnosis may also explain some of the low FPG values seen in Fig. 1.

Surprisingly, very few published studies have attempted to address the issue of FPG variability, despite its widespread use as an index of glycemic control. Olefsky and Reaven (16) assessed the reproducibility of the OGTT by repeating the test at 48-h intervals in 31 nondiabetic adults. The

Table 2—*Summaries of FPG data and their paired differences*

	Mean ± SD	Median	Minimum	Maximum
FPG_1 (mmol/l)	12.2 ± 3.4	11.7	6.0	22.8
FPG_2 (mmol/l)	12.1 ± 3.3	11.5	6.2	20.5
ΔFPG (mmol/l)	−0.1 ± 0.9	−0.1	−3.2	2.9
PD (%)	−0.6 ± 7.4	−1.2	−19.0	23.9

$n = 193$. ΔFPG, $FPG_2 - FPG_1$.

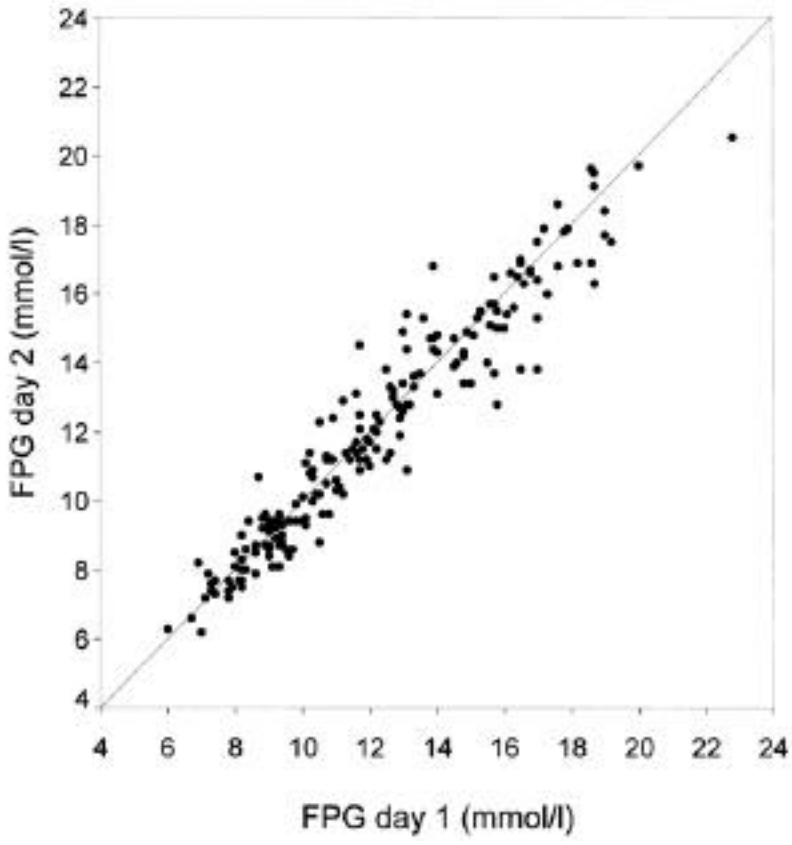

Figure 1—*FPG values measured on consecutive days. The identity line is also shown.*

mean FPG was identical on the two occasions, and 22 of 31 (71%) subjects varied by <10%, 30 of 31 (97%) subjects varied by <20%, and only one subject varied by >20%. The variability of the 2-h plasma glucose value was higher with only 14 of 31 (45%) subjects varying by <10% and 12 of 31 (39%) subjects varying by >20%. For comparison, in our study FPG varied by <10% in 162 of 193 (84%) subjects and <20% in 190 of 193 (98%) subjects, as illustrated in Fig. 4. Three subjects varied by >20%.

Owens et al. (17) assessed the reproducibility of serial meal and OGTTs in normal male subjects. There was no significant difference between the FPG values of the meal test (mean ± SD on day 1, 4.88 ± 0.34 mmol/l; on day 2, 4.66 ± 0.27 mmol/l). Similarly, there was no significant difference between the FPG values of the OGTT (on day 1, 5.06 ± 0.21 mmol/l; on day 2, 4.79 ± 0.29 mmol/l).

Recently, Mooy et al. (18) studied the intraindividual variation of glucose, specific insulin, and proinsulin by two OGTTs given at intervals ranging from 2 to 6 weeks. In 80 newly diagnosed type 2 diabetic subjects, the variability of FPG (2 SD) was ~20%. For normal subjects and subjects with impaired glucose tolerance, the FPG variabilities were 14 and 16%, respectively.

These studies show a fairly consistent picture of an FPG variability of 14–20% at different time intervals and in different glucose tolerance categories, although no studies specifically considered the day-to-day variability of FPG in type 2 diabetic subjects.

This variability should be carefully considered when monitoring glycemic control in patients with diabetes and also when using FPG for diagnostic purposes as recommended by the ADA (5,6). The present study is particularly relevant to type 2 diabetic patients, the major sector of the diabetic population, as it addresses the daily variability of FPG in subjects similar to those who are likely to have diagnosis and/or management based on FPG values. For instance, if a recommended FPG cutoff value of 7.0 mmol/l is strictly adhered to, a 95% variability of 14.8% would mean that a patient with an FPG value in the nondiabetic range of $7 \times (1 - 0.148) = 6.0$ to 6.9 mmol/l may well have a subsequent FPG value above the diagnostic criterion. Similarly, FPG values up to $7 \times (1 + 0.148) = 8.0$ mmol/l should be treated cautiously. Two of the subjects in this study had FPG values on either side of the cutoff value, with values of 6.9 and 8.2 (FPG_1) and 7.0 and 6.2 (FPG_2). It should be emphasized that the range 6.0–8.0 mmol/l represents 95% of the data and that occasional values will still fall outside this range, as seen in one of the above subjects. It should also be noted that a higher proportion of "borderline" results is likely to occur in practice because the current study focuses on a

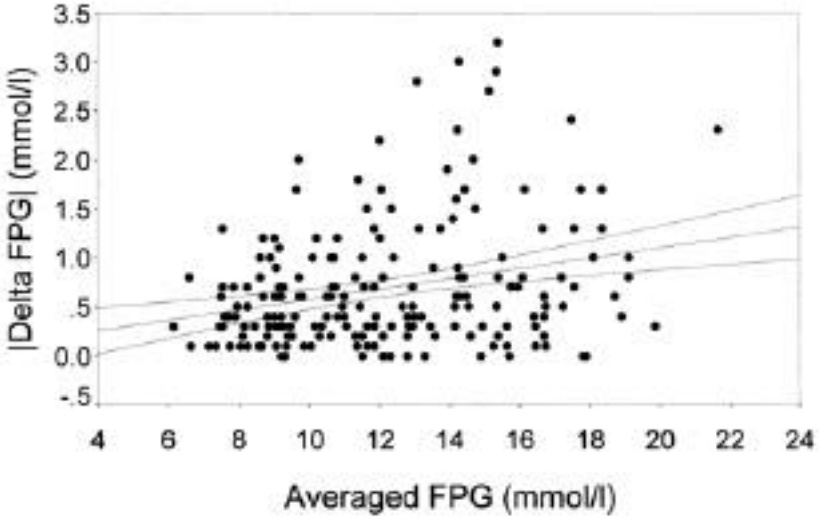

Figure 2—*Regression of the absolute differences, $|FPG_2 - FPG_1|$, against averaged FPG, indicating increasing variance with increasing FPG. The regression equation is $|FPG_2 - FPG_1| = 0.05\ FPG_{aver} + 0.05$. The 95% CI for the regression is also shown.*

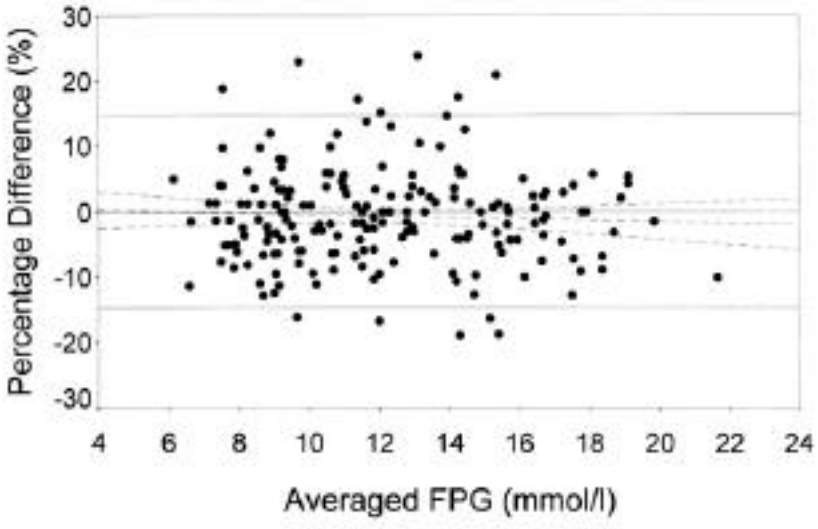

Figure 3—*Percentage differences between the two FPG values versus averaged FPG. The regression confidence interval (– – –) is tight around the zero line, indicating constant variability with increasing FPG. The 95% variability region (±14.8%, ——) is also shown.*

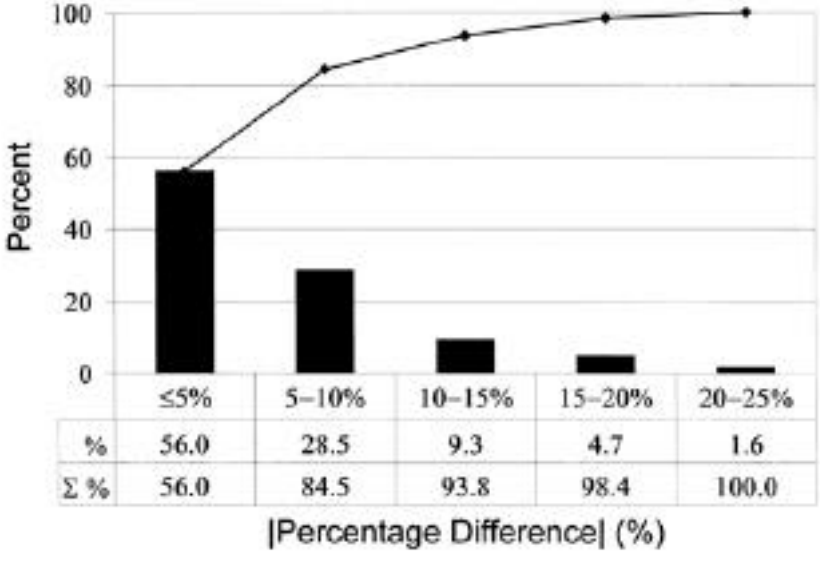

Figure 4—*Distribution (■) and cumulative distribution (——) of the absolute value percentage differences (PD = 100 [FPG$_2$ − FPG$_1$]/FPG$_1$). Approximately 95% of the data fall below 14.8%.*

group of subjects already selected by a set of diagnostic criteria that includes an FPG cutoff value. FPG values in the range 6.0–8.0 mmol/l should prompt either a repeat FPG or an OGTT. The possible financial burden of such an approach is a concern, but it should be weighed against the cost benefits of early diagnosis, early treatment, and screening for complications in diabetic patients (19).

In conclusion, we found that FPG varied on consecutive days by up to 15% in 95% of this group of newly diagnosed, Caucasian type 2 subjects. We have suggested that this variability should be taken into consideration when either the diagnosis of diabetes or the assessment of glycemic control is based on FPG values.

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