Nonfasting Plasma Glucose Is a Better Marker of Diabetic Control Than Fasting Plasma Glucose in Type 2 Diabetes

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OBJECTIVE — To evaluate the relative value of plasma glucose (PG) at different time points in assessing glucose control of type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — Glycemic profiles, i.e., PG at prebreakfast (8:00 A.M.), prelunch (11:00 A.M.), postlunch (2:00 P.M.), and extended postlunch (5:00 P.M.) times over the same day, were obtained in 66 type 2 diabetic patients on an ambulatory basis. The different time points of PG were compared with a measurement of HbA_{1c} made in a reference laboratory.

RESULTS — Extended postlunch PG was lower than prebreakfast PG (104 ± 21 vs. 133 ± 35 mg/dl, $P < 0.01$) in patients demonstrating good diabetic control ($HbA_{1c} \leq 7.0\%$), was not different from prebreakfast PG (149 ± 47 vs. 166 ± 26 mg/dl, NS) in patients demonstrating fair diabetic control ($7.0\% < HbA_{1c} \leq 8.5\%$), and was higher than prebreakfast PG (221 ± 62 vs. 199 ± 49 mg/dl, $P \leq 0.01$) in those demonstrating poor diabetic control ($HbA_{1c} \leq 8.5\%$). Prebreakfast, prelunch, postlunch, and extended postlunch PG values were all significantly correlated with HbA_{1c}. Multiple linear regression analysis demonstrated that postlunch PG and extended postlunch PG correlated significantly and independently with HbA_{1c}, but that prebreakfast PG and prelunch PG did not. Moreover, postlunch PG and extended postlunch PG demonstrated better sensitivity, specificity, and positive predictive value in predicting poor glycemic control than did prebreakfast PG or prelunch PG.

CONCLUSIONS — In type 2 diabetes, postlunch PG and extended postlunch PG are better predictors of glycemic control than fasting plasma glucose (FPG). We therefore suggest that they be more widely used to supplement, or substitute for, FPG in evaluating the metabolic control of type 2 diabetic patients.

In 1993, the results of the Diabetes Control and Complications Trial (DCCT) (1) confirmed that in patients with type 1 diabetes, plasma glucose (PG) levels should be tightly controlled to reduce the risk of microvascular complications. Although patients with type 2 diabetes were not studied in the DCCT, the DCCT results are increasingly applied to the management of people with type 2 diabetes. The theoretical expected benefit of glycemic normalization was therefore taken into account in the recent recommendations of the American Diabetes Association (ADA) (2) for type 2 diabetes. Before the DCCT, and until recently, acceptable therapeutic objectives were to maintain fasting or preprandial PG concentration at <7.8 mmol/l (140 mg/dl) and HbA_{1c} at <8%. The new guidelines recommend that fasting plasma glucose (FPG) levels and HbA_{1c} values be kept at <6.7 mmol/l (120 mg/dl) and <7%, respectively (3).

There is cogent evidence that normalization of FPG in type 2 diabetic patients does, in fact, indicate great improvement in two of the major abnormalities of the pathophysiology of the disease, i.e., peripheral insulin resistance and hepatic glucose overproduction (4). Moreover, the glucose-lowering effects of sulfonylurea drugs (5), metformin (6), and long-acting insulins (7) in the treatment of type 2 diabetes can all be shown to be largely accounted for by a reduction in FPG because the decrements in postprandial PG and FPG are very similar. For these reasons, normalization of FPG concentrations is believed to be a reliable marker of good metabolic control in type 2 diabetic patients (8). Consequently, in many interventional trials involving either dietary measures or antidiabetic drugs, FPG has been used in combination with HbA_{1c} to evaluate diabetic control (9,10). However, striving to achieve tight control of FPG in type 2 diabetic patients can increase the risk of hypoglycemia at other times of the day (9). Furthermore, although HbA_{1c} is considered the gold standard of long-term glycemic control in diabetic patients (11), the method suffers from two main drawbacks: *1*) its lack of standardization between laboratories (12) and *2*) its relative cost when a reliable method of measurement is used. Moreover, whereas well-standardized methods of measurement are available in most countries, many technical and economical problems remain to be solved before HbA_{1c} can be regarded as a simple, reproducible method available worldwide.

For these reasons we have designed a study to evaluate the relative value of PG measurement at different times of the day in comparison with HbA_{1c} measurement in assessing the mean glycemic control of type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

Subjects

The 66 patients (42 men, 24 women), all of whom were regular visitors of the outpatient clinic of the Metabolic Disease Department of the University Hospital of Montpellier in France, were entered consecutively into the study. The patients, whose ages ranged from

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Abbreviations: ADA, American Diabetes Association; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; PG, plasma glucose

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Table 1—*Distribution of energy and of intake of main nutrients for daily meals*

	Breakfast	Lunch	Dinner
Average mealtime	8:00 A.M.	12:00 P.M.	7:30 P.M.
Calories	16.4 ± 7.3	41.1 ± 8.1	42.5 ± 6.5
Carbohydrates	26.6 ± 19.4	36.5 ± 12.9	36.9 ± 8.1
Fats	15.0 ± 9.7	39.2 ± 8.1	45.8 ± 10.5
Proteins	7.5 ± 3.2	46.7 ± 11.3	45.8 ± 10.5

Data are means ± SD, expressed as percentages of daily total calories, carbohydrates, fats, and proteins.

40 to 78 years (median, 60), were classified according to World Health Organization criteria (13) as having type 2 diabetes. BMI ranged from 18.5 to 40.3 kg/m^2 (median, 28.0). One month before enrollment, the dietary habits of each participant were checked by a 7-day diet record, and the patients received recommendations for continuing their usual diet throughout the entire period of the study. The dietary analysis was performed by dietitians using the food composition tables of Southgate and colleagues (14). The total caloric intake of the group considered as a whole was 1,839 ± 439 kcal/day (mean ± SD; range, 1,300–2,580 kcal per day) with 39.6 ± 7.3% as carbohydrates, 37.4 ± 7.3% as fats, 18.6 ± 2.4% as proteins, and 4.4 ± 3.2% as alcohol. The daily distribution of calories and of the intake of main nutrients for the different meals are indicated in Table 1. The average timing for meals was approximately 8:00 A.M. for breakfast, noon for lunch, and 7:30 P.M. for dinner, which corresponds to the usual distribution of meals within the general French population. Patients were treated for diabetes with diet alone (n = 6), diet plus either biguanides (n = 8) or sulfonylureas (n = 8), or diet plus a combination of these two drugs (n = 44). None of the patients were treated with insulin.

Protocol of the study and blood collections

Subjects were to have their blood sampled on an ambulatory basis to obtain glycemic profiles, i.e., PG measurements obtained on the same test day from 8:00 A.M. to 5:00 P.M. at 3-h intervals. The first sample was collected before breakfast at 8:00 A.M. (prebreakfast PG); the second, before lunch at 11:00 A.M. (prelunch PG); and the third, 2 h after the beginning of lunch, i.e., at 2:00 P.M. (postlunch PG). The last sample was collected at 5:00 P.M. (extended postlunch PG). Blood collections and glucose determinations were made at the patients' usual laboratories, and all individuals who participated in the study were counseled to maintain their usual living habits during the entire test day. In all laboratories, the standard glucose oxidase method was used to determine PG concentrations. Subjects were also requested to have their blood drawn for an HbA_{1c} measurement at the laboratory of biochemistry of the University Hospital of Montpellier as soon as possible after the test day, not allowing a time interval of >10 days from the test day (mean time interval ± SD = 3.4 ± 3.2 days). A high-pressure liquid chromatography assay was used to make all determinations of HbA_{1c} (normal range, 4–6%).

Data analysis

The data were analyzed to evaluate the accuracy of PG at each time point in predicting the mean metabolic control value as estimated by HbA_{1c}. Metabolic control values were considered to be good or poor according to whether HbA_{1c} levels were ≤7.0 or >8.5%, respectively. When HbA_{1c} percentages were both >7.0 and ≤8.5%, the patients were considered as having fair metabolic control.

Unless otherwise stated, all results are given as means ± SD. Statistical analyses were made using Statview software. Simple linear regression analysis was used to examine the relationship of PG to HbA_{1c} at each time point. Multiple linear regression analysis was performed to determine which of the various PG values were significant and independent predictors of HbA_{1c}. From this analysis, partial regression coefficients (β-coefficients) were obtained for each variable, and the statistical strength (P value) of each coefficient was further calculated by t testing (15). Statistical significance of the differences among PG concentrations at different time points were tested by one-way analysis of variance followed by the two-tailed Student's t test.

RESULTS — When the 66 glycemic profiles were considered as a whole, prebreakfast PG and extended postlunch PG were significantly lower than prelunch PG and postlunch PG (Table 2). In the subset of patients exhibiting good metabolic control (HbA_{1c} ≤7.0%), extended postlunch PG was significantly lower than both prebreakfast PG (104 ± 21 mg/dl vs. 133 ± 35 mg/dl, $P < 0.01$) and PG at the other time points (prelunch and postlunch). In this group the extended postlunch time point was the only one associated with a normal PG, i.e., <120 mg/dl (99% CI, 92–119 mg/dl). In the subset of patients demonstrating fair metabolic control (7.0% < HbA_{1c} ≤ 8.5%), extended postlunch PG (149 ± 47 mg/dl) was not significantly different from prebreakfast PG (166 ± 26 mg/dl) and was >120 mg/dl (95% CI, 127–171 mg/dl). In the patients exhibiting poor glycemic control (HbA_{1c} >8.5%), extended postlunch PG (221 ± 62 mg/dl)

Table 2—*PG concentrations correlated with glycemic control*

	All	Glycemic control		
		Good (HbA_{1c} ≤ 7.0%)	Fair (7.0% < HbA_{1c} ≤ 8.5%)	Poor (HbA_{1c} ≥ 8.5%)
n	66	20	20	26
Prebreakfast PG	169 ± 47	133 ± 35*	166 ± 26	199 ± 49*
Prelunch PG	216 ± 73*†	158 ± 48*†	212 ± 54*†	263 ± 69*†
Postlunch PG	197 ± 80*†	131 ± 29*	179 ± 46*	263 ± 79*†
Extended postlunch PG	164 ± 69	104 ± 21†	149 ± 47	221 ± 62†

Data are means ± SD. *Significantly different from extended postlunch PG ($P \leq 0.05$); †significantly different from prebreakfast PG ($P \leq 0.05$).

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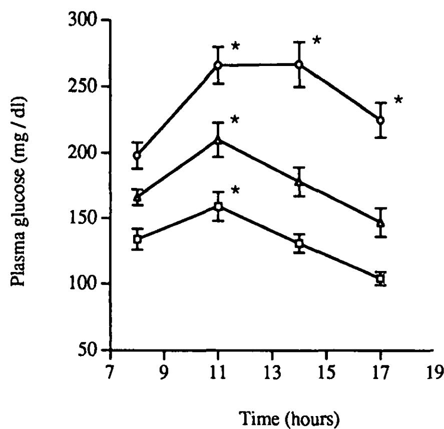

Figure 1—*Mean glycemic profile correlated with the level of glycemic control. □, good control; △, fair control; ○, poor control. Bars represent SE. *Significantly different from prebreakfast PG (P ≤ 0.05).*

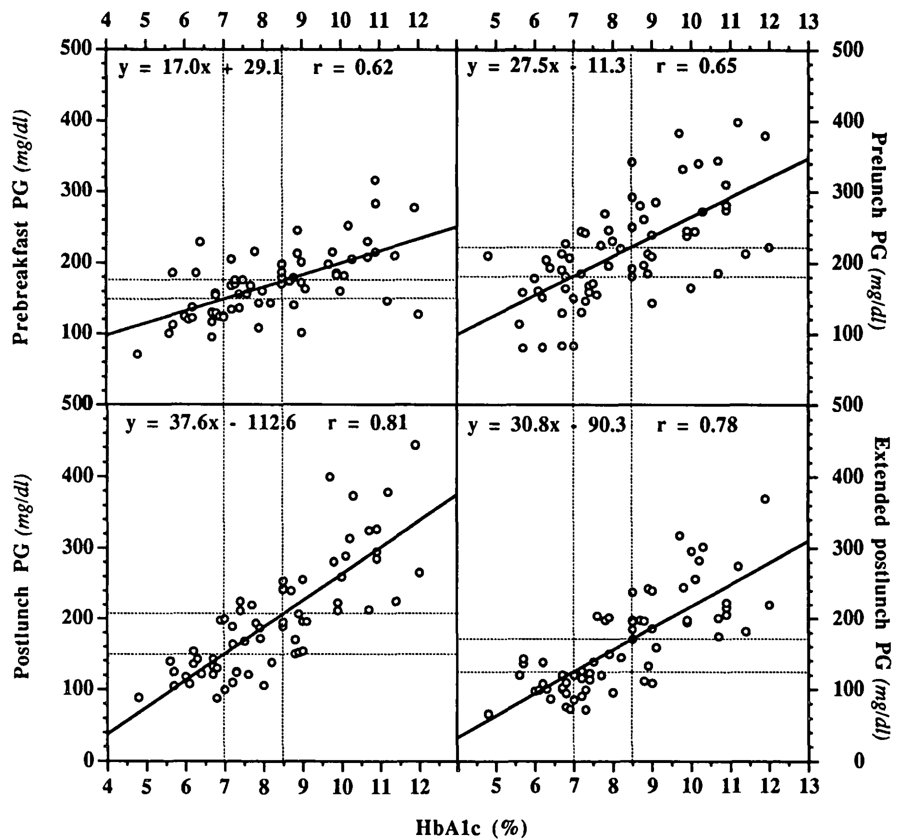

Figure 2—*Plots and regression lines of glycemia at the various time points (prebreakfast PG, prelunch PG, postlunch PG, and extended postlunch PG) correlated with HbA_{1c}.*

was higher ($P < 0.05$) than prebreakfast PG (199 ± 49 mg/dl). In each group, prelunch PG was significantly higher than prebreakfast and extended postlunch PG, while postlunch PG was significantly higher than extended postlunch PG (Table 2). The mean glycemic profiles corresponding to the various levels of glycemic control (good, fair, and poor) are represented in Fig. 1.

The prebreakfast, prelunch, postlunch, and extended postlunch PG values were all significantly and linearly correlated with HbA_{1c} (Fig. 2). Prebreakfast PG had the weakest correlation with HbA_{1c} ($r = 0.62$), and postlunch PG showed the strongest correlation ($r = 0.81$) with HbA_{1c} (Fig. 2), but the correlation coefficients were not significantly different. Nevertheless, the multiple linear regression analysis showed that postlunch PG and extended postlunch PG correlated significantly and independently with HbA_{1c} values, while prebreakfast PG and prelunch PG did not (Table 3).

We calculated the expected values of PG at each time point (prebreakfast, prelunch, postlunch, and extended postlunch) for HbA_{1c} levels of 7.0 and 8.5%, according to the corresponding regression line (Table 4). We then used these values to make additional classifications of the patients within the good, fair, and poor glycemic control subgroups (Table 5). Postlunch PG and extended postlunch PG had better sensitivity, specificity, and positive predictive values than prebreakfast PG and prelunch PG in predicting poor glycemic control. Furthermore, of the measurements of HbA_{1c} reflecting good glycemic control, 25 and 35% corresponded to a prebreakfast PG value or a prelunch PG value, respectively, in either the fair or the poor control range. This percentage fell to 15% when postlunch PG or extended postlunch PG was considered.

The ADA's objective of achieving an HbA_{1c} level of <7.0% was obtained in 30% (20 of 66) of the patients, but the objective of achieving an FPG value <120 mg/dl was obtained in only 9% (6 of 66) of the patients. Hence, only 29% of the patients who had an HbA_{1c} ≤7.0% concomitantly demonstrated a prebreakfast PG value <120 mg/dl. When the extended postlunch PG is considered, the association of a value <120 mg/dl with an HbA_{1c} level ≤7.0% was found in 24% (16 of 66) of the determinations. In 80% (16 of 20) of the patients with an HbA_{1c} level ≤7.0%, the extended postlunch PG value was <120 mg/dl.

CONCLUSIONS — The results of this study indicate that good glycemic control (HbA_{1c} ≤7.0%) is characterized by an extended postlunch PG value lower than the prebreakfast PG value, whereas poor glycemic control is associated with an extended postlunch PG value higher than the prebreakfast PG value. This observation means that the extended postlunch PG increases more than prebreakfast PG when the glycemic control is worsening. Although 20 of 66 HbA_{1c} values were effectively below the goal of 7.0%, only 6 HbA_{1c} values were associated with a prebreakfast PG value <120 mg/dl, whereas 16 HbA_{1c} values were

Table 3—*Multivariate predictors of HbA_{1c} by multiple linear regression analysis*

Variable	Partial regression coefficient (β)	SD of β	P value
Prebreakfast PG	0.605	0.339	0.079
Prelunch PG	0.238	0.243	0.332
Postlunch PG	0.845	0.314	0.009
Extended postlunch PG	0.731	0.332	0.032

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Table 4—*Expected values of prebreakfast, prelunch, postlunch, and extended postlunch PG for HbA_{1c} levels of 7.0 and 8.5%*

	HbA_{1c} (%)	
PG (mg/dl)	7.0	8.5
Prebreakfast	148	174
Prelunch	181	223
Postlunch	151	207
Extended postlunch	125	172

Data are derived from the corresponding regression lines.

Table 5—*Agreement in clinical classification between PG at the different time points and HbA_{1c}*

	HbA_{1c}			
	Good	Fair	Poor	Total
n	20	20	26	66
Prebreakfast PG				
Good (<148 mg/dl)	15 (62)	5 (21)	4 (16)	24 (100)
Fair (148–174 mg/dl)	2 (15)	7 (54)	4 (31)	13 (100)
Poor (>174 mg/dl)	3 (10)	8 (28)	18 (62)	29 (100)
Prelunch PG				
Good (<181 mg/dl)	13 (59)	7 (32)	2 (9)	22 (100)
Fair (181–223 mg/dl)	6 (35)	4 (23)	7 (41)	17 (100)
Poor (>223 mg/dl)	1 (4)	9 (33)	17 (63)	27 (100)
Postlunch PG				
Good (<151 mg/dl)	17 (71)	6 (25)	1 (4)	24 (100)
Fair (151–207 mg/dl)	3 (18)	8 (47)	6 (35)	17 (100)
Poor (>207 mg/dl)	0 (0)	6 (24)	19 (76)	24 (100)
Extended postlunch PG				
Good (<125 mg/dl)	17 (63)	8 (30)	2 (7)	27 (100)
Fair (125–172 mg/dl)	3 (30)	5 (50)	2 (20)	10 (100)
Poor (>172 mg/dl)	0 (0)	7 (24)	22 (76)	29 (100)

Data in parentheses represent the percentages of patients within a given PG range for each of the HbA_{1c} categories.

associated with an extended postlunch PG value <120 mg/dl. Hence, good mean glycemic control, as assessed by an HbA_{1c} value ≤7.0%, does not necessarily imply a normalization of prebreakfast PG. Our observations agree with the suggestion of the authors of the U.K. Prospective Diabetes Study (16) that normalization of fasting blood glucose is difficult to achieve because the higher doses of sulfonylurea or insulin required to overcome insulin resistance may increase the risk of hypoglycemia. However, it should be noted first that such a risk does not occur when acarbose or metformin are used as monotherapy, and second that commonsense therapeutic measures such as eating or snacking at regular intervals and avoiding excessive alcohol intake can almost always prevent or minimize sulfonylurea- or insulin-induced hypoglycemic episodes. Nevertheless, these dietary measures may increase the risk of weight gain, especially in type 2 diabetic patients. Many clinical and pathophysiological data have indicated that fasting blood glucose and HbA_{1c} measurements are reliable markers of diabetic control, but surprisingly, the question remains of whether measurements of postlunch PG and extended postlunch PG, with or without HbA_{1c} determinations, might be an equal or a better indicator of diabetic control.

From a clinical point of view, our results confirm those reported by Gonen et al. (17), who found a strong relationship ($r = 0.74$) between FPG and HbA_1 in 55 diabetic patients. This figure is slightly better than that observed in our study ($r = 0.62$ between prebreakfast PG and HbA_{1c}). The slight difference may be due to a greater PG variability in our results, because PG measurements were made in different laboratories. Moreover, most of the patients in the study by Gonen et al. were treated with insulin, whereas none of our patients were treated with insulin. In another study of non–insulin-treated type 2 diabetic patients, Paisey et al. (18) found a correlation coefficient of 0.86 by averaging at least three fasting capillary blood glucose measurements obtained over several weeks and testing their relationship with the HbA_1 percentages evaluated at the end of the test period. The correlation is similar to that observed in our study between HbA_{1c} and a single ambulatory measurement of either postlunch PG ($r = 0.81$) or extended postlunch PG ($r = 0.78$).

Furthermore, our data show that the correlation between PG and HbA_{1c} was always better with nonfasting PG than with FPG. This result was confirmed by multiple linear regression analysis, because only the postlunch PG and extended postlunch PG correlated significantly and independently with the HbA_{1c} values. An explanation for these differences can be provided by the pathophysiological features of type 2 diabetes, which include both peripheral insulin resistance and impairment of endogenous insulin secretion (19,20). The respective contribution of each of these two defects has long been controversial. A large body of evidence supports the view that hepatic glucose production is excessive in type 2 diabetes, either on an absolute basis or in relationship to the concurrent FPG level (4,20,21). Furthermore, it has been clearly established that the FPG correlates positively with hepatic glucose overproduction and negatively with metabolic clearance of glucose (4). Therefore, normalization of FPG in type 2 diabetes can be considered a reflection of both a profound improvement in the insulin sensitivity of peripheral tissues and a marked reduction in glucose hepatic overproduction. Post-

Table 6—*Sensitivity, specificity, and positive predictive value of prebreakfast, prelunch, postlunch, and extended postlunch PG in predicting poor control of HbA_{1c}*

PG	Sensitivity	Specificity	Positive predictive value
Prebreakfast	69	85	62
Prelunch	65	86	63
Postlunch	73	92	76
Extended postlunch	85	90	76

Data are % and are based on the glycemic thesholds defined in Table 4. Poor control of HbA_{1c} is defined as ≥8.5%.

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prandial PG depends altogether on insulin resistance, hepatic glucose output, and insulin secretory capacity of the pancreas in response to meals (20,22). Hence, postprandial PG rather than FPG would better reflect the overall pathophysiological process of the disease, i.e., insulin resistance, inadequately suppressed hepatic glucose output, and defective insulin response to meals. In addition, under normal circumstances, an individual is in the fasting state only during the second part of the night, whereas he or she is in a postprandial or postabsorptive state for the remainder of the day. This could give a rationale to our results, which indicate, first, that postlunch PG and extended postlunch PG correlate better than prebreakfast PG with overall diabetic control as estimated from HbA_{1c} and, second, that these parameters have a better sensitivity, specificity, and positive predictive value in predicting glycemic control.

For the foregoing reasons, we strongly suggest that postlunch or extended postlunch PG values should be more widely used in estimating the glycemic control of an individual. For instance, a postlunch glycemic level <150 mg/dl and an extended postlunch glycemic level <125 mg/dl might be recommended as therapeutic objectives for patients to self-monitor blood glucose. We also suggest that measurement of postlunch PG and extended postlunch PG could serve as a relatively good alternative when measurements of HbA_{1c} are unreliable or unavailable. The latter situation still occurs in many parts of the world. Nonetheless, measurement of HbA_{1c}, when done properly, has a ≤2% coefficient variation within specimen duplicates or between duplicate runs (23), whereas PG usually has a greater variability. However, we must reemphasize that our study was designed to mimic as closely as possible the current clinical practice of a general practitioner, rather than that of a specialist working in a research environment. Therefore, no ward condition was used to ascertain the precise timing of blood sampling for PG measurement. Patients were asked to keep their normal living and eating habits and to visit their usual laboratory for blood sampling every 3 h from 8:00 A.M. to 5:00 P.M. Hence, our results may be useful for common clinical practice.

From our study data, we conclude that extended postlunch PG better reflects the overall glycemic control of type 2 diabetic patients than does FPG. As a result, we suggest that studies of the efficacy of an antidiabetic treatment should include either extended postlunch PG or a glycemic profile in addition to or in place of FPG and that the treatment of patients with type 2 diabetes should be directed not only at normalizing FPG necessarily, but also at normalizing extended postlunch PG. When no reliable method for measuring HbA_{1c} is available, measurement of postlunch PG or extended postlunch PG can be a good additional substitute in evaluating the mean glycemic control of an individual.

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