Plasma Glucose Levels Throughout the Day and HbA_{1c} Interrelationships in Type 2 Diabetes

Implications for treatment and monitoring of metabolic control

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OBJECTIVE — To evaluate the extent of plasma glucose excursions with meals, the relations between plasma glucose levels at different times of the day, and the relations between the latter and HbA_{1c} in non–insulin-treated type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS — Daily glucose profiles were assessed in non–insulin-treated type 2 diabetic patients. Outpatients at the diabetes clinic ($n = 371$; one daily plasma glucose profile) and at home ($n = 30$; five daily blood glucose profiles over 1 month) as well as inpatients ($n = 455$; profile of plasma glucose on the day of admission) were examined. Subjects had plasma/blood glucose assessment before and 2–3 h after breakfast, lunch, and dinner. HbA_{1c} was also measured.

RESULTS — After the meals many subjects had glucose levels >8.9 mmol/l (160 mg/dl) and/or glucose excursions >2.2 mmol/l (40 mg/dl). This was also often found when HbA_{1c} was satisfactory (<7%). The coefficients of simple correlation among plasma/blood glucose at different times of the day ranged from 0.52 to 0.88. Correlations between HbA_{1c} and plasma/blood glucose at different times of the day ranged from 0.44 to 0.67. The strongest correlation was between HbA_{1c} and mean daily glucose ($r = 0.57–0.69$). Multiple regression analyses showed that premeal but not postmeal plasma/blood glucose levels were independent predictors of HbA_{1c}.

CONCLUSIONS — These results suggest that *1*) the majority of non–insulin-treated type 2 diabetic patients have exaggerated plasma/blood glucose excursions with meals, and many of them have higher-than-recommended glucose concentrations 2 h after the meals; *2*) plasma/blood glucose levels throughout the day are not as strongly interrelated as one might believe; and *3*) HbA_{1c} is more related to preprandial than postprandial plasma/blood glucose levels. These findings have potential implications for treatment and monitoring of metabolic control in type 2 diabetes.

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The U.K. Prospective Diabetes Study (UKPDS) demonstrated that aiming at a normalization of fasting plasma glucose levels (<6.1 mmol/l, <110 mg/dl) in type 2 diabetes resulted in 1% lower levels of HbA_{1c} and a reduction in the risk of chronic complications of the disease (1). However, in the UKPDS the incidence of microangiopathic complications was markedly reduced by intensive treatment, whereas the incidence of macroangiopathic complications was not significantly decreased (1).

At variance with the Diabetes Control and Complications Trial (DCCT) (2), the UKPDS was not designed to control blood glucose levels all throughout the day. Therapeutic decisions were made according to fasting glucose levels, probably assuming that good control in the fasting state would have been associated with good control throughout the day. However, this was not verified. In particular, it might be hypothesized that nonfasting plasma glucose levels were not adequately controlled in the UKPDS, thus yielding only marginal effects on macrovascular diseases. In other words, it might be hypothesized that a regimen of treatment aimed at controlling blood glucose levels also in the nonfasting state could have resulted in fasting glucose levels and HbA_{1c} values lower than those observed, and that it could have hence resulted in a lower incidence of chronic diabetes complications. It is reasonable to assume that this may be the case. However, our knowledge of blood glucose variations throughout the day in treated type 2 diabetes, the relations between glucose levels at different times of the day, and the relations between the latter and HbA_{1c} is limited (3–5). In particular, the following questions need to be addressed: *1*) How frequently do diabetic patients experience broad glucose excursions with meals? *2*) How much does fasting plasma glucose influence subsequent glucose levels during the day? *3*) How strongly are plasma glucose levels at different times of the day interrelated? and *4*) Is HbA_{1c} influenced more strongly by fasting or nonfasting plasma glucose? The answers to these questions seem to be crucial for *1*) understanding whether diabetes care planning should focus on both fasting and nonfast-

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Abbreviations: DCCT, Diabetes Control and Complications Trial; 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.

ing (e.g., postprandial) glucose levels or whether it can de-emphasize nonfasting glucose levels, and for 2) establishing the potential role of drugs aimed at blunting postprandial plasma glucose excursions.

The aims of the present study were to evaluate the extent of plasma/blood glucose excursions after meals, to explore the relations among plasma/blood glucose levels at different times of the day, and to examine the relations between HbA_{1c} and plasma/blood glucose levels at different times of the day in a large sample of non–insulin-treated type 2 diabetic subjects. We addressed these points by examining daily plasma/blood glucose profiles in large samples of both outpatients and inpatients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Outpatients at the diabetes clinic. We screened type 2 diabetic patients regularly attending the hospital diabetes clinic of Montecchio Maggiore, which is located 50 km east of Verona and serves a population of ~300,000 people. Among them we selected those (~3,000) with no insulin treatment; no changes in diet, treatment or lifestyle within the 3 months before the study; no concomitant chronic diseases or recent acute illness; and a willingness to return to the clinic five times in 1 day to measure plasma glucose. Subjects with diabetes diagnosis within the previous 6 months were excluded.

A total of 371 patients (211 men and 160 women) satisfied the inclusion criteria and accepted to participate. The mean age was 60.3 ± 9.7 years, the duration of diabetes averaged 7.8 ± 5.8 years, and BMI was 28.5 ± 4.38 kg/m^2. Treatment consisted of diet only in 7.9% of subjects, metformin in 6.2%, sulfonylureas in 58.3%, and a combination of both drugs in 27.6%. The protocol was approved by the institutional ethical committee, and all subjects gave their informed consent.

Outpatients at home. A total of 30 type 2 diabetic patients with the same clinical features described above were selected among those regularly attending the hospital diabetes clinic of Desenzano, a town of ~22,000 people 40 km west of Verona. These patients were requested to monitor blood glucose at home. The mean age was 60.3 ± 10.3 years, the duration of diabetes averaged 8.3 ± 7.3 years, and BMI was 28.6 ± 5.9 kg/m^2. Treatment consisted of diet only in 20.7% of subjects, metformin in 10.3%, sulfonylureas in 27.6%, and a combination of both drugs in 41.4%.

Inpatients. We scrutinized the medical records of all patients with type 2 diabetes admitted as inpatients to the Division of Endocrinology and Metabolic Diseases of the University of Verona because of poor metabolic control or for screening or staging of chronic diabetes complications in the years 1987–2000. Patients were selected who met the following criteria: *1*) no diabetes diagnosis within the previous 6 months; *2*) admission in the morning after an overnight fast; *3*) no change in diabetes treatment in the first day of their stay in the hospital; *4*) no insulin treatment before admission or the first day after admission; *5*) no changes in diet, treatment, or lifestyle within the 3 months before the admission; and 6) no concomitant chronic diseases or recent acute illness.

A total of 455 patients (229 men and 226 women) satisfied the inclusion criteria. The mean age was 58.9 ± 11.5 years, the duration of diabetes averaged 8.0 ± 6.8 years, and BMI was 32.2 ± 8.23 kg/m^2. Treatment consisted of diet only in 12.2% of subjects, metformin in 5.3%, sulfonylureas in 49.7%, and a combination of both drugs in 32.8%.

Plasma glucose profiles

Outpatients at the diabetes clinic. Each patient was requested to come to the diabetes clinic in the morning (7:30–8:30 A.M.) after a 10- to 14-h overnight fast. At that time venous blood was withdrawn to measure plasma glucose and HbA_{1c}. Subjects were then asked to return to the clinic to measure plasma glucose ~2 h after breakfast (9:30–10:30 A.M.), before lunch (12:00–1:00 P.M.), ~2 h after lunch (2:00–3:00 P.M.), and before dinner (6:00–7:00 P.M.). Because the diabetes clinic is an outpatient clinic and is thus closed overnight, it was not possible to measure plasma glucose after dinner. Patients were asked to follow their usual treatment and eat their usual diet on the day of the study.

Outpatients at home. Each patient was asked to perform home blood glucose monitoring on 5 nonconsecutive days during a period of 1 month. In particular, they were requested to assess blood glucose in the morning just before breakfast (7:00–8:30 A.M.), after a 10- to 14-h overnight fast, ~2 h after breakfast (9:00–10:30 A.M.), just before lunch (12:00–1:00 P.M.), ~2 h after lunch (2:00–3:00 P.M.), just before dinner (7:00–8:00 P.M.), and 2 h after dinner (9:00–10:00 P.M.). In the middle of the month, HbA_{1c} was assessed. Patients were asked to follow their usual treatment and eat their usual diet during the month.

Inpatients. Plasma glucose was measured before breakfast (7:00–8:30 A.M.), before lunch (11:30–12:00 P.M.), ~3 h after lunch (2:30–3:00), before dinner (6:00–6:30 P.M.), and ~2 h after dinner (8:00–8:30 P.M.). On admission, HbA_{1c} was also assessed. All subjects consumed an isocaloric diet on the day of the admission to the hospital.

Analytical determinations

In both outpatients at the diabetes clinic and inpatients, venous blood was centrifuged within 1 h after withdrawal, and plasma was used for the immediate assessment of plasma glucose (glucooxidase method). HbA_{1c} was measured by high performance liquid chromatography (reference range in nondiabetic subjects was 3.5–5.5%). Home blood glucose monitoring was performed with the same glucose meter in all patients (Euroflash; Lifescan Italia, Milan, Italy).

Statistics

Standard procedures were used to calculate the means, SD, SEM, and simple correlation coefficients. Analysis of variance, χ^2 tests, and multiple linear regression analysis were also used. In the latter, all preprandial and postprandial plasma glucose levels were included as explanatory variables of HbA_{1c}. The cutoff point for good metabolic control was 7% for HbA_{1c} (6), 6.6 mmol/l (120 mg/dl) for fasting glucose (6,7), and 8.9 mmol/l (160 mg/dl) for postprandial glucose (7). Accordingly, an increase >2.2 mmol/l (40 mg/dl) in glucose levels 2 h after the meal was regarded as exaggerated.

RESULTS

Glucose profiles in outpatients

Plasma glucose averaged 8.8 ± 1.9 mmol/l in the fasting state (before breakfast), 2 h after breakfast it was 10.2 ± 3.0 mmol/l, and before lunch it averaged 8.1 ± 2.8 mmol/l. The corresponding values 2 h after lunch and before dinner were 10.0 ± 3.2 and 7.6 ± 2.8 mmol/l, respectively. Thus, the increase in plasma glu-

cose after breakfast and lunch was quite consistent, and plasma glucose returned to premeal levels under both circumstances. In the late afternoon (before dinner), plasma glucose was significantly lower than in the early afternoon (after lunch).

Most subjects had a plasma glucose level >6.7 mmol/l (120 mg/dl) before the meals: 78.7% of them before breakfast, 65.2% before lunch, and 57.1% before dinner. Most subjects had a plasma glucose level >8.9 mmol/l (160 mg/dl) after the meals: 60.9% of them after breakfast, 61.2% after lunch, and 77.1% after breakfast and/or lunch. Among subjects with fasting glucose levels <6.7 mmol/l (n = 79), 29.1% had plasma glucose levels >8.9 mmol/l after breakfast, 30.4% after lunch, and 48.1% after breakfast and/or lunch.

The average absolute increase in plasma glucose after breakfast and lunch were 2.07 ± 2.34 and 1.87 ± 2.54 mmol/l, respectively. The frequency of distribution of plasma glucose change after breakfast and lunch showed that 2 h after breakfast the excursion of plasma glucose was >2.2 mmol/l (40 mg/dl) in 41.0% of the subjects. The corresponding figure after lunch was 41.2%. In total, 67.4% of the subjects showed an exaggerated increase of plasma glucose (>2.2 mmol/l) after breakfast and/or lunch.

Data collected in the 30 outpatients who performed home blood glucose monitoring were similar to those from the outpatients examined at the diabetes clinic. Blood glucose levels averaged 7.9 ± 1.6 mmol/l (prebreakfast), 9.4 ± 2.3 mmol/l (postbreakfast), 7.4 ± 2.2 mmol/l (prelunch), 9.2 ± 2.7 mmol/l (postlunch), 7.3 ± 1.7 mmol/l (predinner), and 9.9 ± 2.1 mmol/l (postdinner). Most of these subjects had blood glucose levels >8.9 mmol/l after meals and/or an exaggerated blood glucose increase (>2.2 mmol/l) after the meals on a few or several occasions. In particular, 49.3% of the patients had postprandial blood glucose readings >8.9 mmol/l in >50% of the determinations, and 79.0% of the patients had an exaggerated postprandial blood glucose increase in >30% of the determinations.

Glucose profiles in inpatients

In the fasting state (before breakfast), plasma glucose averaged 10.1 ± 3.4 mmol/l, and before lunch it was 10.7 ± 4.1 mmol/l. The corresponding values 3 h after lunch, before dinner, and 2 h after dinner were 11.7 ± 4.6, 9.1 ± 4.0, and 11.2 ± 4.2 mmol/l, respectively.

Among subjects with fasting glucose levels <6.7 mmol/l (n = 54), 41.5% had plasma glucose levels >8.9 mmol/l after lunch, 40.9% after dinner, and 80.0% after lunch and/or dinner.

The frequency of distribution of plasma glucose change after lunch and dinner showed that 3 h after lunch the excursion of plasma glucose was >2.2 mmol/l (40 mg/dl) in 32.8% of the subjects. The corresponding figure after dinner was 45.6%. In total, 64.6% of the subjects showed an exaggerated increase in plasma glucose (>2.2 mmol/l) after lunch and/or dinner.

HbA_{1c}

HbA_{1c} averaged 6.6 ± 1.5% in outpatients examined at the diabetes clinic. We found that 65% of these patients had values <7.0%. Among the latter, 68.3% had plasma glucose levels >8.9 mmol/l after breakfast and/or lunch. In outpatients who performed home blood glucose monitoring, HbA_{1c} averaged 7.0 ± 1.2%. Virtually all of these patients with an HbA_{1c} value <7% showed blood glucose values after breakfast, lunch, or dinner that were >8.9 mmol/l on a few or several occasions.

The mean HbA_{1c} in inpatients was 8.4 ± 2.4%. We found that 30.1% of these patients had a value <7%. Among them, 92.4% had plasma glucose levels >8.9 mmol/l after lunch and/or dinner.

Correlations

Table 1 reports simple correlations among plasma/blood glucose levels at different times of the day in both outpatients and inpatients. All of the correlations were highly significant, but most of them were not particularly strong. Coefficients of correlation ranged from 0.52 to 0.88 and were quite consistent in outpatients examined at the clinic, outpatients who performed home blood glucose monitoring, and inpatients. However, stronger correlations were generally found in outpatients who performed home blood glucose monitoring. In these subjects, mean glucose levels at different times of the days (i.e., mean prebreakfast, mean postbreakfast, etc.) were used to compute correlations.

Table 2 presents the simple correlations we found between HbA_{1c} and plasma/blood glucose levels at different times of the day. The coefficients of correlation were quite similar, ranging from 0.44 to 0.64, and were not particularly strong. The correlations between mean daily plasma/blood glucose and HbA_{1c} were stronger. The correlations between HbA_{1c}

Table 1—*Simple correlations between plasma glucose levels at different times of the day in patients with non–insulin-treated type 2 diabetes*

	Outpatients		
	Clinic	Home*	Inpatients
n	371	30	455
Fasting vs. postbreakfast	0.631	0.653	ND
Fasting vs. prelunch	0.625	0.659	0.759
Fasting vs. postlunch	0.592	0.676	0.612
Fasting vs. predinner	0.531	0.542	0.560
Fasting vs. postdinner	ND	0.688	0.545
Postbreakfast vs. prelunch	0.713	0.737	ND
Postbreakfast vs. postlunch	0.534	0.722	ND
Postbreakfast vs. predinner	0.524	0.626	ND
Postbreakfast vs. postdinner	ND	0.688	ND
Prelunch vs. postlunch	0.648	0.884	0.735
Prelunch vs. predinner	0.615	0.754	0.661
Prelunch vs. postdinner	ND	0.679	0.623
Postlunch vs. predinner	0.671	0.701	0.775
Postlunch vs. postdinner	ND	0.746	0.638
Predinner vs. postdinner	ND	0.564	0.641

$P < 0.01$–0.001 for all correlations. *In these patients the correlations were computed with the means of five glucose determinations per each time of the day.

Table 2—*Simple correlations between HbA_{1c} and plasma glucose levels at different times of the day in patients with non–insulin-treated type 2 diabetes*

	Outpatients		
	Clinic	Home	Inpatients
n	371	30	455
HbA_{1c} vs. prebreakfast PG	0.483*	0.580*	0.646*
HbA_{1c} vs. postbreakfast PG	0.445*	0.568†	ND
HbA_{1c} vs. prelunch PG	0.496*	0.673*	0.630*
HbA_{1c} vs. postlunch PG	0.477*	0.580*	0.550*
HbA_{1c} vs. predinner PG	0.491*	0.674*	0.620*
HbA_{1c} vs. postdinner	ND	0.495†	0.528*
HbA_{1c} vs. mean daily PG	0.574*	0.685*	0.694*
HbA_{1c} vs. Δ PG prepost breakfast	0.180‡	0.225	ND
HbA_{1c} vs. Δ PG prepost lunch	0.055	0.042	0.003
HbA_{1c} vs. Δ PG prepost dinner	ND	−0.040	0.090‡

*$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$. PG, plasma glucose.

and plasma/blood glucose changes with meals were weak, if present at all.

When we performed multiple regression analyses, premeal but not postmeal plasma glucose levels were independent predictors of HbA_{1c} in both outpatients and inpatients. Plasma glucose levels before the meals showed quite similar standardized regression coefficients with HbA_{1c} in the multiple regression analyses. These coefficients of correlation were substantially lower for the outpatients (prebreakfast 0.225, prelunch 0.204, predinner 0.246; $P < 0.001$ each) and inpatients (prebreakfast 0.330, prelunch 0.156, predinner 0.327; $P < 0.001$ each) compared with those yielded with the univariate analyses. Prebreakfast, prelunch, and predinner plasma glucose levels explained 32.5% of the HbA_{1c} variability in outpatients and 51.1% of the HbA_{1c} variability in inpatients.

Glucose profiles according to diabetes treatment

When we examined plasma glucose profiles in subjects belonging to different categories of treatment, we found that patients treated with sulfonylureas (alone or in combination with metformin) showed the highest plasma glucose values either before or after meals and the greatest plasma glucose excursions after meals. In Table 3 we present data from outpatients examined at the diabetes clinic. Similar data were observed in inpatients. Subjects undergoing these modes of treatment had a longer duration of diabetes.

CONCLUSIONS—The main results of the present study are that *1*) the majority of non–insulin-treated type 2 diabetic patients have higher-than-recommended plasma/blood glucose levels and/or exaggerated glucose excursions after meals; *2*) high postprandial plasma/blood glucose levels were also often found when long-term glucose control was satisfactory (HbA_{1c} <7.0%); *3*) plasma/blood glucose levels throughout the day are not as strongly interrelated as one might believe; and *4*) HbA_{1c} is more related to preprandial than postprandial plasma/blood glucose levels.

These findings have potential implications from two different perspectives. First, they indicate that many diabetic patients with apparently good metabolic control, as inferred from HbA_{1c} levels <7% or by fasting glucose values <6.6 mmol/l (<120 mg/dl), indeed have high glucose levels after meals and/or exaggerated glucose excursions with the meals, reaching unexpectedly high plasma glucose levels. In these subjects, one might consider the use of medications that are particularly effective in blunting postprandial glucose excursions. Second, they indicate that monitoring of glucose control and evaluation of the efficacy of treatment cannot be restricted to fasting glucose and/or HbA_{1c}. Indeed, both fasting glucose and HbA_{1c} are poor indicators of glucose levels at other times of the day, especially those occurring in the postprandial state. In particular, preprandial glucose levels and HbA_{1c} do not provide any accurate information on postprandial glucose peaks. Thus, if one aims at controlling plasma glucose not only in the fasting state but throughout the day to achieve better long-term metabolic control (HbA_{1c}) and minimize the risk of chronic diabetic complications, glucose monitoring cannot be limited to fasting or preprandial glucose. This might seem rather obvious, but it is not substantiated by many reports. On the other hand, our data are in agreement with findings that monitoring and correcting fasting glucose solely ameliorates HbA_{1c} only partially, as in the UKPDS (1), whereas monitoring and correcting glucose levels all throughout the day results in a greater reduction of HbA_{1c}, as in the DCCT (2) or the Kumamoto Study (8). In fact, the difference in HbA_{1c} in patients undergoing conven-

Table 3—*Main clinical features and glucose parameters according to treatment in 371 outpatients with non–insulin-treated type 2 diabetes*

	Diet	MET	SU	MET + SU	*P*
Sex (% men)	79	65	54	54	0.06
Age (years)	60 ± 2.0	57 ± 1.4	62 ± 0.7	59 ± 0.9	0.08
Duration of diabetes (years)	5.3 ± 1.2	6.7 ± 1.1	7.7 ± 0.4	9.4 ± 0.6	0.009
BMI (kg/m^2)	29.0 ± 0.9	29.7 ± 0.8	27.8 ± 0.3	29.5 ± 0.5	0.005
HbA_{1c} (%)	5.8 ± 0.2	6.0 ± 0.3	6.4 ± 0.1	7.2 ± 0.2	<0.0001
Prebreakfast PG (mmol/l)	6.5 ± 0.2	7.8 ± 0.3	7.8 ± 0.1	8.9 ± 0.2	<0.001
Postbreakfast PG (mmol/l)	7.9 ± 0.5	8.9 ± 0.5	9.9 ± 0.2	11.5 ± 0.3	<0.001
Prelunch PG (mmol/l)	7.7 ± 0.4	6.9 ± 0.3	7.8 ± 0.2	9.4 ± 0.3	<0.001
Postlunch PG (mmol/l)	8.1 ± 0.4	8.6 ± 0.5	9.7 ± 0.2	11.3 ± 0.3	<0.001
Predinner PG (mmol/l)	6.1 ± 0.2	6.9 ± 0.3	7.3 ± 0.2	8.7 ± 0.3	<0.001
Δ PG breakfast (mmol/l)	1.3 ± 0.4	1.1 ± 0.3	2.1 ± 0.2	2.6 ± 0.3	0.009
Δ PG lunch (mmol/l)	1.4 ± 0.3	1.6 ± 0.4	1.9 ± 0.2	1.9 ± 0.3	0.719

Data are means ± SEM. *P* values were derived from analysis of variance or χ^2. MET, metformin; PG, plasma glucose; SU, sulphonylureas.

tional and intensive treatment was ~1% in the UKPDS and ~2% in the DCCT and the Kumamoto Study.

The results of our study suggest that glucose levels in the postbreakfast, prelunch, postlunch, predinner, and postdinner states are not merely a drift of fasting (prebreakfast) glucose but are the result of the ability of the pancreatic β-cells to respond to glucose stimulation and the ability of peripheral tissues to dispose of glucose after meals. As a consequence, the control of glucose levels throughout the day can be pursued only with specific interventions targeting both fasting and nonfasting glucose levels. For example, our data strongly suggest that the majority of patients with type 2 diabetes might have an insulin secretion after meals that is insufficient to keep circulating glucose within the desired range. This insufficiency is probably the main factor responsible for exaggerated plasma/blood glucose excursions after meals. These subjects might benefit from the use of drugs capable of improving the abnormal insulin response to glucose or restoring the normal response.

We found that HbA_{1c} was better correlated to preprandial than postprandial glucose levels. In addition, preprandial but not postprandial glucose levels were independent predictors of HbA_{1c} in multivariate analyses. These findings are likely explained by the fact that more hours are spent in the interprandial and nocturnal periods than in the postprandial phases. As a consequence, average daily blood glucose, the main determinant of the extent of the hemoglobin glycation process, is a function more of interprandial and nocturnal glucose levels than of glucose spikes after meals. Thus, the assessment of HbA_{1c} is poorly informative of the degree of postprandial glucose control. On the other hand, the mean daily glucose level was the strongest correlate of HbA_{1c}, confirming that the glycation process is a function of the average exposure to high glucose.

The finding that preprandial glucose levels were related to HbA_{1c} more strongly than postprandial glucose levels is at variance with the results reported by Avignon et al. (3). However, this finding is consistent with the conclusions reached by a panel of experts designated by the American Diabetes Association to review the available data on postprandial glucose (9). In addition, this finding is consistent with data from the National Health and Nutrition Examination Survey (NHANES) III documenting that HbA_{1c} was higher in subjects with fasting but not postchallenge hyperglycemia compared with subjects with isolated postchallenge hyperglycemia (10). Furthermore, most, although not all (11), clinical studies that were based on the use of medications targeting postprandial glucose, but which neglected the short-term effect of these drugs and their failure to increase or provide basal insulin levels, yielded a reduction of postprandial glucose but did not substantially change HbA_{1c} (12–15).

Recent studies suggested that postprandial glucose levels might exert a stronger deleterious effect on the cardiovascular system than fasting glucose levels (16). Interestingly, when treatment of diabetes was aimed solely at the normalization of fasting glucose, as in the UKPDS, the results on macroangiopathy were limited (1). Our finding that HbA_{1c} is essentially dependent on preprandial glucose levels might explain why the reduction of HbA_{1c} had only a marginal effect on cardiovascular disease when only fasting plasma/blood glucose was controlled, as in the UKPDS (1) or the Veteran Administration Cooperative Study (17). On the other hand, when postprandial glucose was also controlled, as in the Kumamoto Study (8) or the Diabetes Mellitus and Insulin Glucose Infusion in Myocardial Infarction (DIGAMI) Study (18), a better cardiovascular outcome was observed. Furthermore, there are numerous observational studies carried out in diabetic subjects or in the general population documenting that postchallenge hyperglycemia and, by extrapolation, postprandial hyperglycemia are associated with increased cardiovascular risk (19–22). In addition, several experimental data support the idea that postprandial glucose peaks are harmful for the arterial wall (23–26). In this regard, it is noteworthy that other molecules with proatherogenic properties are elevated in the postprandial state (27).

Whether the putative detrimental effects of postprandial hyperglycemia are related to the absolute height of plasma glucose peak or the magnitude of plasma glucose excursion after the meal is currently hard to hypothesize. The first hypothesis seems to be more plausible, so that the same plasma glucose increase might be less deleterious when superimposed on a fair premeal glucose value. However, the alternative hypothesis cannot be ruled out a priori, and both hypotheses need to be addressed by specific studies. These studies should clarify whether HbA_{1c} is able to exhaustively represent hyperglycemia and all its harmful effects and whether postprandial hyperglycemia is an independent contributing factor in the pathogenesis of chronic diabetic complications.

The lack of strong correlations between HbA_{1c} and glucose levels in a single day is indirect proof that the plasma/blood glucose profile varies day by day, and that 5–6 determinations of plasma/blood glucose in a single day, although more informative than a sporadic fasting or random glucose determination, cannot adequately describe daily glucose profiles occurring within an 8- to 10-week period. Indeed, there is good evidence that several glucose determinations over a period of several weeks are better correlated to HbA_{1c} than a single or a few glucose determinations on a single day (28). Our data collected in patients who were asked to repeat the assessment of blood glucose profile several times at home over a period of 1 month are consistent with such a conclusion.

On average, metabolic control was satisfactory in most of our outpatients. This finding is consistent with data recently collected in ~20,000 type 2 patients examined in a multicenter observational Italian study. In this study, the mean duration was 8 years and the average HbA_{1c} was 7.0% (M. Velussi, personal communication). In this regard, Italian type 2 diabetic patients are at variance with English patients in the UKPDS, whose mean HbA_{1c} at 9 years since diagnosis was ~8% in the intensive-treatment group (1). The reasons for such differences are not obvious, but might include a greater attention to postprandial glucose. Nevertheless, HbA_{1c} was >7% in many subjects we examined. Moreover, most of them had glucose levels after the meals that were >8.9 mmol/l (160 mg/dl), the upper limit of postprandial glucose targets indicated by the European Diabetes Policy Group (7). Thus, a considerable proportion of non–insulin-treated type 2 diabetic patients, many of whom were showing a satisfactory HbA_{1c} level, indeed had poor glucose control after the meals. Because postprandial hyperglycemia is an independent risk factor of car-

diovascular disease in type 2 diabetes (16), the specific periodic assessment of postprandial glucose in type 2 diabetes, along with the measurement of fasting glucose and HbA_{1c}, seems to be warranted.

Patients treated with sulfonylureas (alone or in combination with metformin) showed poorer metabolic control and more marked glucose excursions with meals in comparison with patients treated with diet or metformin alone. The finding is not surprising if one takes into account that these patients had a longer duration of diabetes and, consequently, were in a more advanced stage of the disease. Indeed, the UKPDS clearly indicated that the natural history of type 2 diabetes is featured by a progressive worsening of glucose control (1). Nevertheless, our findings also clearly document that drugs currently used for the treatment of type 2 diabetes fail to achieve the goals of diabetes treatment in most cases.

Although they were asked to follow their usual diet on the day(s) of the study, it is possible that outpatients we examined at the diabetes clinic had complied better than usual with their diet. This could have lowered their postprandial glucose peaks and reduced the correlation of postprandial glucose with HbA_{1c}. However, we found consistent results in outpatients who assessed glucose profiles at home. In addition, we found that preprandial glucose values had stronger relations with HbA_{1c} than did postprandial values when we retrospectively examined glucose profiles in those patients who regularly performed home blood glucose monitoring and showed their glucose diary during the periodic visits at the Verona Diabetes Clinic (M.M., B.E., unpublished data). These subjects certainly had not watched their diet more closely.

In conclusion, glucose monitoring in type 2 diabetes seems to be more complex than previously thought, because fasting plasma glucose is a rather poor index of glucose levels throughout the day. HbA_{1c} seems to provide poor information on postprandial glucose levels, and it provides no information on glucose excursions with meals. Indeed, a remarkable proportion of type 2 diabetic patients have poor glucose control in the nonfasting state, mainly in the postprandial period, even when HbA_{1c} is satisfactory. These subjects might benefit from the use of medications specifically suited for providing a more physiological insulin profile after the meal. Thus, the exhaustive and comprehensive description of glucose levels throughout the day, given the risk they possibly carry, should rely on the monitoring not only of fasting glucose and/or HbA_{1c} levels but also glucose levels at other times of the day, especially in the postprandial period. Home blood glucose monitoring seems to be suited to accomplish this requirement. The control of postprandial glucose is likely useful in the achievement of lower HbA_{1c}. A more strict control of postprandial glucose might also result in a better outcome in type 2 diabetes. The results of intervention trials specifically designed to address this question are awaited.

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References

1. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
2. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
3. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822–1826, 1997
4. Soonthornpun S, Rattarasarn C, Leelawattana R, Setasuban W: Postprandial plasma glucose: a good index of glycemic control in type 2 diabetic patients having near-normal fasting glucose levels. *Diabetes Res Clin Pract* 46:23–27, 1999
5. Guillausseau PJ: Monitoring of metabolic control in patients with non-insulin-dependent diabetes mellitus on oral hypoglycemic agents: value of evening blood glucose determination. *Diabet Med* 14: 798–802, 1997
6. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 23 (Suppl. 1):S32–S42, 2000
7. European Diabetes Policy Group: A desktop guide to type 2 diabetes mellitus. *Diabet Med* 16:716–730, 1999
8. Shichiri M, Kishikawa H, Ohkubo Y, Wake N: Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 23 (Suppl. 2):B21–B29, 2000
9. American Diabetes Association: Postprandial blood glucose (Consensus Statement). *Diabetes Care* 24:775–778, 2001
10. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 20:1859–1862, 1997
11. Bastyr EJ 3rd, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE, for the IOEZ Study Group: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}. *Diabetes Care* 23: 1236–1241, 2000
12. Anderson JH Jr, Brunelle RL, Koivisto VA, Pfutzner A, Trautman ME, Vignati L, DiMarchi R, the Multicenter Insulin Lispro Study Group: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 46:265–270, 1997
13. Nielsen FS, Jorgensen LN, Ipsen M, Voldsgaard AI, Parving HH: Long-term comparison of insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen. *Diabetologia* 38:592–598, 1995
14. Ciofetta M, Lalli C, Del Sindaco P, Torlone E, Pampanelli S, Mauro L, Chiara DL, Brunetti P, Bolli GB: Contribution of postprandial versus interprandial blood glucose to HbA_{1c} in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care* 22:795–800, 1999
15. Wolffenbuttel BHR, Landgraf R, on behalf of the Dutch and German Repaglinide Study Group: A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care* 22:463–467, 1999
16. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J, the DIS Group: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year fol-

low-up. *Diabetologia* 39:1577–1583, 1996
17. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS, the VA CSDM Group: Cardiovascular events and correlates in the Veteran Affairs Diabetes Feasibility Trial: Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM). *Arch Intern Med* 157:181–188, 1997
18. Malmberg K, for the DIGAMI Study Group: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infraction in patients with diabetes mellitus. *BMJ* 314:1512–1515, 1997
19. Sievers ML, Bennett P, Nelson RG: Effect of glycemia on mortality in Pima Indians with type 2 diabetes. *Diabetes* 48:896–902, 1999
20. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ: Isolated post-challenge hyperglycemia confirmed as a risk factor for mortality. *Diabetologia* 42:1050–1054, 1999
21. De Vegt F, Dekker JM, Ruhe HG, Stehouwer CDA, Nijpels G, Bouter LM, Heine RJ: Hyperglycemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 42:926–931, 1999
22. The DECODE study group on behalf of the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-h diagnostic criteria. *Arch Intern Med* 161:397–404, 2001
23. Pirags V, Assert R, Haupt K, Schatz H, Pfeiffer A: Activation of human platelet protein kinase C-beta 2 in vivo in response to acute hyperglycemia. *Exp Clin Endocrinol Diabetes* 104:431–440, 1996
24. Giugliano D, Marfella R, Coppola L, Verrazzo G, Acampora R, Giunta R, Lucarelli C, D'Onofrio F: Vascular effects of acute hyperglycemia in humans are reversed by L-arginine: evidence for reduced availability of nitric oxide during hyperglycemia. *Circulation* 95:1783–1790, 1997
25. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy M-A, Simonson DC, Creager MA: Acute hyperglycemia attenuates endothelium-dependent vasodilatation in humans in vivo. *Circulation* 97:1695–1701, 1998
26. Marfella R, Esposito K, Giunta R, Coppola G, De Angelis L, Farzati B, Paolisso G, Giugliano D: Circulating adhesion molecules in humans: role of hyperglycemia and hyperinsulinemia. *Circulation* 101: 2247–2251, 2000
27. Ceriello A: The post-prandial state and cardiovascular disease: relevance to diabetes mellitus. *Diabetes Metab Res Rev* 16: 125–132, 2000
28. Brewer KW, Chase HP, Owen S, Garg SK: Slicing the pie: correlating HbA_{1c} values with average blood glucose values in a pie chart form. *Diabetes Care* 21:209–212, 1998