Target for Glycemic Control

Concentrating on glucose

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It is commonly admitted that the glycemic control of patients with type 2 diabetes proceeds from a complex "alchemy" in which the respective contributions of both fasting and postprandial glucose are still a subject of debate (1). A1C, which remains the gold standard for assessing glucose homeostasis, is an integration of both fasting and postprandial glucose variations over a 3-month period (2). From a mathematical point of view, the theory can be formulated as follows (3):

$$[\text{A1C}]^{0-3\ \text{months}} = {}_0\int^{3\ \text{months}} \text{FPG}\ (t)\ dt + {}_0\int^{3\ \text{months}} \text{PPG}\ (t)\ dt$$

where FPG (t) and PPG (t) are the time courses of fasting and postprandial glucose, respectively.

As a consequence, the glycemic control of patients with type 2 diabetes can be schematically depicted by the "glucose triad," whose components are as follows: A1C, fasting, and postprandial glucose levels. At present, and even though the debate remains wide open, it seems that the best assessment of glycemic control is provided by the determination of the three above-mentioned components. Most recommendations that have been published by medical organizations in different countries take into account the three parameters, even though the position statements differ around the world, but also within the same country (4).

IMPORTANCE OF THE FOUR-POINT DIURNAL GLYCEMIC PROFILE

A tool for integrating the different periods of daytime

Whereas many physicians continue to emphasize fasting glucose and A1C to guide management of diabetes, observational studies have indicated that glucose testing at postprandial and postabsorptive time points could play an important role (5,6). For instance, lessons from physiology tell us that humans spend half of their lives in postprandial states (7,8). The postprandial state, with respect to glucose, is defined as a 4-h period that immediately follows ingestion of a meal (7). During this period, dietary carbohydrates are progressively hydrolyzed through several sequential enzymatic actions. Even though the insulin response rapidly reduces the postprandial glucose excursion with a return to baseline levels within <2 h, the overall period of absorption has approximately a 4-h duration that corresponds to the postprandial state. The postabsorptive state consists of a 6-h period that follows the postprandial period. During this time interval, glucose concentrations remain within a normal range in nondiabetic individuals through the breakdown of the glycogen (glycogenolysis) stored during the postprandial period. The "real" fasting state commences only at the end of the postabsorptive period (~10–12 h after the beginning of the last meal intake). During the fasting state, plasma glucose is maintained at a near-normal level by the gluconeogenesis: glucose derived from lactate, alanine, and glycerol. Therefore, it appears that in a nondiabetic patient who takes three meals per day at relatively fixed hours, the 24-h period of the day can be divided into three periods corresponding to fasting, postprandial, and postabsorptive states. The postprandial period (4 h each) is equal to 12 h and covers a full half-day period of time (Fig. 1) (8). The real fasting period is only limited to a 3- to 4-h period of time at the end of the night. Furthermore, taking into account the overlap between the postprandial and postabsorptive periods, it can be asserted that all the remaining parts of daytime correspond to postabsorptive states (Fig. 1). Although the postprandial glucose excursions are usually higher and last for longer, with greater variability, in patients with diabetes compared with those in healthy individuals (9), these three periods remain present in patients with diabetes. Therefore, the ideal regimen for assessing blood glucose variations over daytime should include one or several time points of self-monitoring of blood glucose within each of these three periods (10). Accordingly, for the last few years, we have been advised to use the four-point glycemic profile as an investigative tool for the monitoring of blood glucose in patients with type 2 diabetes (5,6). The prebreakfast glucose is a reflection of the real fasting state, the mid-morning and the 2-h postlunch values can be considered to reflect postprandial periods, and finally the 5-h postlunch glucose (extended postlunch value) is a marker of a postabsorptive period (7,8). It is obvious that, in non–insulin-using type 2 diabetic patients, such a four-point glycemic profile should not be regularly performed every day. For that reason, in these patients, we have limited the use of self-monitoring of blood glucose to once a day, but we recommend to rotate glucose testing at the different times of the day over a 4-day period to have a broader picture of the glucose fluctuations over daytime (10).

A tool for establishing the contributions of fasting and postprandial glucose to overall hyperglycemia in patients with type 2 diabetes

In recent years, new data have provided further information for the ongoing debate over whether A1C, fasting glucose, and postprandial glucose contribute equally or not to the overall hyperglycemia in type 2 diabetes (6,11–14). A few years ago, in non–insulin-treated type 2 diabetic patients, we found that postlunch and extended postlunch

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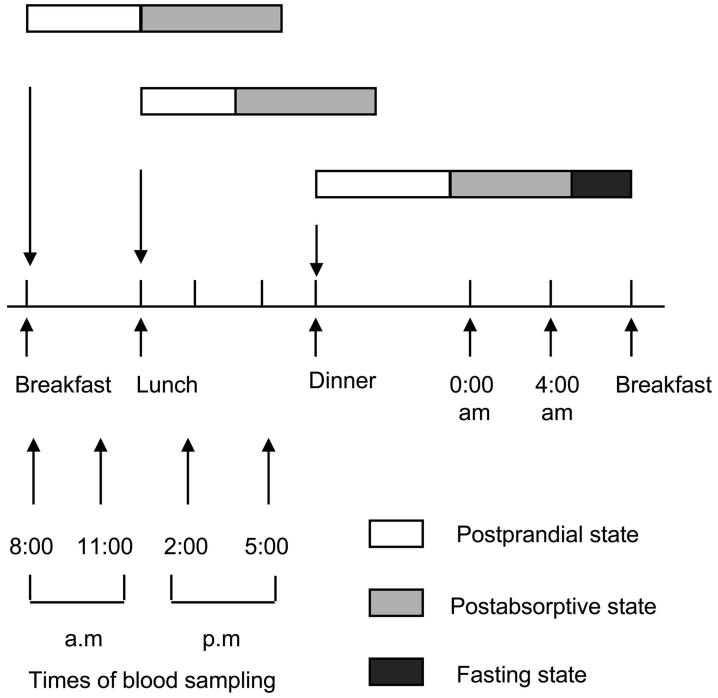

Figure 1—*Duration of the postprandial, postabsorptive, and fasting states. The postprandial and the postabsorptive states last for 4 and 6 h, respectively. Therefore, the cumulative duration of postprandial state is ~12 h, which is equivalent to a full half-day period of time, and the "real" fasting state is limited to a 3-h time interval at the end of the night.*

plasma glucose values correlated better with overall glycemic control as estimated from A1C than did prebreakfast and prelunch glucose levels (12). In the same type of patients, Bonora et al. (13) reported that preprandial plasma glucose concentrations were related to A1C more strongly than postprandial concentrations. In an analysis of a dataset collected in the Diabetes Control and Complications Trial, Rohlfing et al. (14) reported that better correlation with A1C was obtained for postlunch and mean daily glucose concentrations. These study-to-study discrepancies are certainly confounding information for clinical practice. By contrast, from a scientific point of view, these differences are not surprising, since it is well known that the multiple regression analysis used for studying the relationship between A1C and glucose values at different times is an unstable model when explanatory variables, i.e., the glucose values in the present example, are intercorrelated. To provide a correct answer, we used a different methodology that consisted of calculating two incremental areas under a four-point diurnal glycemic profile from 8:00 A.M. to 5:00 P.M., with two intermediary time points at 11:00 A.M. and 2:00 P.M. (6). The first incremental area was calculated above a baseline level equal to the fasting plasma glucose value and was therefore considered a reflection of the postprandial responses to breakfast and lunch. The second one was calculated above a baseline level equal to 6.1 mmol/l (110 mg/dl), reflecting the increases in both fasting and postprandial plasma glucose. The baseline value of 6.1 mmol/l was chosen because this threshold had been defined as the upper limit of normal plasma glucose at fasting or preprandial times by the American Diabetes Association up to 2003 (15) i.e., before the revision for the 2004 recommendations (16). Therefore, the difference of the two preceding areas can be considered an assessment of the increment in fasting plasma glucose values. Using this model of calculation, we have shown that regardless of the quality of the diabetic control, postprandial glucose made a substantial contribution to the overall hyperglycemia. However, when patients were divided into five groups, according to the quintiles of A1C, we found that postprandial glucose levels made the highest contribution (70%) in the lower quintile (A1C <7.3%), i.e., in patients with well-controlled to moderately controlled diabetes (6). By contrast, fasting hyperglycemia appeared as the main contributor to the overall diurnal hyperglycemia in patients with poorly controlled disease (A1C ≥9.3%). For all patients who had A1C levels ranging between 7.3 and 9.3%, the contributions of fasting and postprandial hyperglycemia were approximately equivalent. These results seem to conciliate the controversial data that were observed in the literature and it can be concluded that the respective contributions of fasting and postprandial can be depicted by a continuous spectrum from fairly to poorly controlled patients with type 2 diabetes.

A tool for simplifying the recommendations: the trilogy of "sevens"

By analyzing and comparing the recommendations in 13 countries, the authors of the AGREE study concluded that despite disparities in guidelines around the world, there exists a high degree of international consensus—when the recommendations are limited to both A1C and fasting glucose concentrations (4). At present, two levels of A1C are usually recognized as threshold values for satisfactory diabetic control: 7% for the American Diabetes Association (17) and 6.5% for the American College of Endocrinologists (18) and the International Diabetes Federation (19). In terms of fasting glucose, recommended goals are set within a 70–130 mg/dl (3.9–7.2 mmol/l) range for the American Diabetes Association (17) and at <110 mg/dl (6.1 mmol/l) and 100 mg/dl (5.5 mmol/l) for the American College of Endocrinologists (18) and the International Diabetes Federation (19), respectively. For postprandial glucose threshold values, large discrepancies are observed. For the American Diabetes Association, the postprandial glycemic threshold value has been set at 180 mg/dl (17). This value corresponds to the upper limit that was chosen in patients who were allocated to the intensively treated group of the DCCT (20). For the American College of Endocrinologists (18) and the International Diabetes Federation (19), the recommendation is to maintain postprandial glucose values below 140 mg/dl. The selection of this value was mainly based on the fact that 140 mg/dl is the cutoff value for defining the impaired glucose tolerance at the second hour of an oral glucose tolerance test.

The variability in the recommendations results in difficulties for diabetes management. Trying to struggle with the jumble of recommendations and values is obviously more complicated for health care providers than memorizing a single

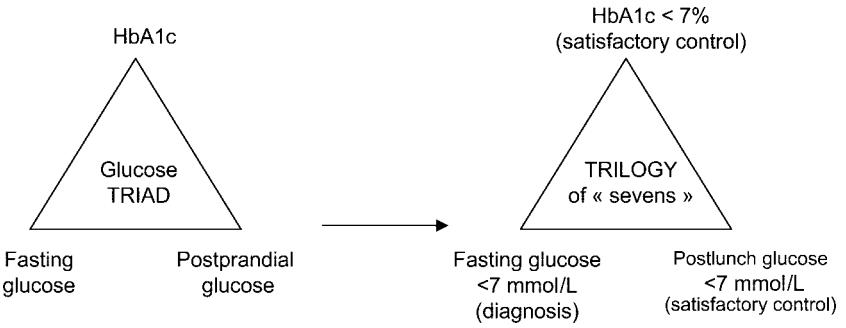

Figure 2—*How to translate the "glucose triad" into the trilogy of "sevens."*

number. As a consequence, the targets should be as simple as possible. An answer to this problem can be obtained from data that we have previously published (21).

By analyzing the four-point diurnal glucose profiles in 480 non–insulin-using type 2 diabetic patients, we tested the performance of plasma glucose at each time point to detect a cutoff value that defines the quality of patients' diabetic control as estimated from A1C levels. The tests were performed at a 7% threshold of A1C, a value less than this level being considered as a reference for good or satisfactory diabetic control (17). Sensitivities and specificities for predicting the quality of diabetic control were calculated at different levels of plasma glucose using step-by-step increments of plasma glucose from low to high values.

The most important result of this study was that a value of 7 mmol/l measured at 2 h after lunch appeared to be the optimal threshold value for predicting treatment success defined by high specificity (≥90%) A1C levels of <7%. By considering first that the criteria for the diagnosis of diabetes is a fasting plasma glucose level ≥7 mmol/l and second that 7% has, for a number of years, been the American Diabetes Association's A1C threshold value for satisfactory diabetic control (17), we suggest that these two number "sevens" can be joined by an additional postprandial "seven" to complete the series. As a consequence, the "glucose triad" could be translated for clinical purpose into the trilogy of "sevens" (Fig. 2) that integrates a cluster of measures, including diagnosis (≥7 mmol/l glucose at fasting), interventional threshold values for completing treatment: A1C goals <7% and postprandial glucose targets <7 mmol/l at 2-h after lunch. This "seven" rule is certainly easier to remember than many recommendations that have been made around the world (3).

However, all these recommendations should be revisited on the basis of the new perspectives raised by the analysis of the results obtained in the three main controlled trials that were recently published: the ACCORD (22), ADVANCE (23), and VADT Diabetes (24) trials. As the ADVANCE results (23) indicate a small but incremental benefit in microvascular outcomes with A1C levels as close as possible to normal, it is suggested that, for patients in whom the treatment is not at risk of hypoglycemic episodes or other adverse effects, the general goal can be <7% (25). Such patients include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. By contrast, the results of the ACCORD study (22) seem to indicate that less stringent goals than the general target of <7% may be more appropriate in patients treated with such hypoglycemic agents as sulfonylureas and/or insulin that are at risk of producing severe hypoglycemic events. More flexible recommendations should also be applied to patients who have a limited life expectancy or who exhibit advanced micro- or macrovascular complications (25). As a consequence, the question is to know whether a future reevaluation of the fasting and postprandial targets will not become necessary in patients exhibiting an increased risk for adverse events. Such changes should take into account the new data on the correlation between A1C and average glucose levels (26). The relationship indicates that a 6% A1C level is equivalent to a 126 mg/dl mean glucose concentration and that each 1% increment of A1C corresponds to a 29 mg/dl increase in mean glucose concentration. However, these correlations remain unable to provide a measure of glycemic variability and/or hypoglycemia (27).

IMPORTANCE OF CONTINUOUS GLUCOSE MONITORING SYSTEMS

A tool for improving our knowledge on the pathophysiology of type 2 diabetes

Type 2 diabetes is a disease characterized by three main abnormalities (28): *1*) a defect of β-cell function (29,30), *2*) a state of insulin resistance (31), and *3*) an overproduction of glucose by the liver (32). Despite that currently available oral hypoglycemic agents are able to target deficiencies in either the endogenous insulin secretion or the insulin sensitivity at different target sites, the attainment of satisfactory diabetes control becomes more and more difficult the longer the duration of the disease (9).

By analyzing continuous glucose patterns over 24 h, we recently demonstrated that the deterioration of glucose homeostasis can be approximated to a three-step process (9). The first step corresponds to a loss in postprandial control that occurs in patients with A1C levels between 6.5 and 6.9% and with mean diabetes duration of 4.4 years. As mentioned above, the second step is characterized by a deterioration of the glycemic control during the pre- and postbreakfast periods in patients who exhibit A1C levels between 7 and 7.9% and who have mean diabetes duration of 8.4 years. The final step in the deterioration of diabetic control occurs generally beyond the end of the first decade of diabetes duration and is represented by a chronic sustained basal hyperglycemia over both nocturnal and interprandial periods and excess postprandial glycemia. In conclusion, the natural history of the worsening of dysglycemia in type 2 diabetes is marked by an early loss of prandial glycemic control that precedes a deterioration of basal hyperglycemia. This deterioration progresses from a period corresponding to a short time interval limited to the end of the overnight fast up to an extended period that covers the nocturnal and interprandial periods considered as a whole (9). The prebreakfast glucose deterioration that occurs at the end of the overnight fast is known as the "dawn phenomenon" (33) and is mainly explained by the circadian variation of the hepatic glucose production that starts to rise in the evening and reaches a peak toward the end of the nocturnal period (32). These abnormal high glucose excursions that are observed after breakfast can be

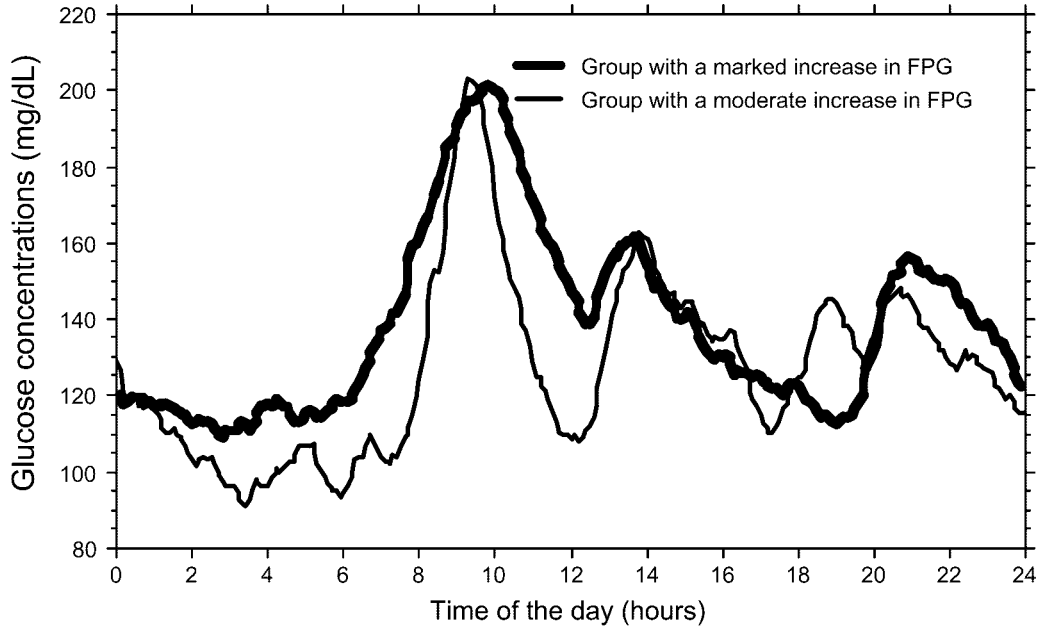

Figure 3—*The 24-h recordings from the continuous glucose monitoring system in non–insulin-using type 2 diabetic patients with A1C between 7 and 8%. The patients were divided into two subgroups according to whether plasma glucose at fasting was higher* (n = *25) or lower* (n = *7) than 126 mg/dl (7 mmol/l).*

depicted as an "extended dawn phenomenon," which is due to the remnant effect of the hepatic glucose overproduction during the morning period in combination with the dietary intake of carbohydrates at breakfast. The "dawn" and the "extended dawn" phenomena are two main causes of failure in the diabetic control of many patients with type 2 diabetes, especially those who have A1C levels ranging from 7 to 8% and who are already treated with maximal doses of oral hypoglycemic agents. Such observations help us to understand why type 2 diabetes, a relentless progressive disease, requires advances from monotherapy with oral antidiabetic agents to combination therapy using multiple oral agents and finally insulin replacement without undue delay (34).

A tool for choosing between insulin regimens in patients suffering from severe insulin deficiency

Insulin should be implemented as soon as oral hypoglycemic agents at maximal doses do not achieve satisfactory diabetic control (34). At present, there is little doubt that patients with a sustained level of A1C >8% should be treated with insulin. Because in these patients basal hyperglycemia is preponderant over prandial hyperglycemia, insulin regimens based on basal insulin should be preferred to prandial insulin at initiation of the insulin therapy. If the target cannot be achieved, premeal boluses of rapid insulin analogs should be added, especially before the meals that result in the more pronounced glycemic excursions. The problem is slightly more complex in those patients who exhibit A1C levels between 7 and 8%. In this situation, most patients are reluctant to being treated with insulin. Furthermore, despite recent publications of more stringent recommendations, many physicians delay insulin treatment until further deterioration in A1C occurs. The new recommendations (34) indicate that insulin treatment should be initiated as soon as A1C remains above 7%, with maximal doses of oral hypoglycemic agents combining insulin sensitizers (metformin + glitazone) with an insulin secretagogue. These recommendations are in agreement with our data, since the mean interval of time that separates the moment at which A1C levels reach 7 and 8% is ~4 years (9), a duration that is not negligible in terms of risk for development or progression of diabetic complications. At present, it is recommended to start insulin with one injection of a long-acting insulin analog before dinner or at bedtime (35). With such a regimen, the insulin action reaches a maximum over a period corresponding to the dawn and extended dawn phenomena, i.e., over a period that covers the end of the overnight fast and the postbreakfast period (9). In patients with A1C ranging between 7 and 8%, plasma glucose values over this time interval are usually more elevated than at any other period of daytime. However, this group of patients can be divided into two subsets according to whether prebreakfast glucose levels were lower or greater than 126 mg/dl (7 mmol/l). Most patients (more than two-thirds) had glucose patterns with both a "dawn" and "extended dawn" phenomena (Fig. 3) and should be treated with a single injection of long-acting insulin analog before dinner or at bedtime. In less than one-third, prebreakfast glucose values remained below 126 mg/dl (Fig. 3). In this latter subgroup of patients, the dawn phenomenon was absent. Nevertheless, these patients with near-normal glycemia before breakfast experience abnormal postbreakfast excursions, which result in sustained hyperglycemia over the entire morning period. To combat this glycemic profile, which is limited to the postbreakfast period, it is probably preferable to administer a small bolus of a rapid-acting insulin analog at prebreakfast than a long-acting insulin analog before dinner or at bedtime. Continuous glucose monitoring can be a useful tool for guiding the choice between these two insulin regimens. When this type of monitoring is not available, the clinician can use, as a surrogate, the glucose values at prebreakfast and at 2-h postbreakfast times. The observation of concomitant elevation of both pre- and postbreakfast glucose suggests that the basal hyperglycemia should be controlled

first and, as a consequence, that the insulin regimen should be initiated with either intermediate-acting insulin or a long-acting insulin analog. By contrast, an elevated postbreakfast level with a near-normal fasting glucose level indicates that a bolus of rapid insulin analog should be administered before breakfast to blunt the postbreakfast glucose excursions. Tailoring the insulin replacement rather than adopting standardized insulin strategies is a more logical approach to achieve satisfactory metabolic control.

WHY ARE BOTH GLUCOSE AND A1C DETERMINATIONS COMPLEMENTARY?

— In the present review, we have mainly developed the glucose side for targeting the glycemic control. However, it should be mentioned that both glucose and A1C determinations are important for the monitoring and management of patients with diabetes. For instance, A1C levels provide useful information on the respective contributions of postprandial and basal hyperglycemia to the overall hyperglycemia of patients with type 2 diabetes (6). Because postprandial glucose is a predominant contributor in patients with A1C levels ranging from 6.5 to 7.5%, it is more logical to implement treatment aimed at reducing postprandial excursions in such patients to achieve A1C levels below 6.5%. By contrast, in those patients who exhibit A1C levels above 7.5%, it has been demonstrated that the basal hyperglycemia becomes predominant, and therefore any treatment to improve diabetes control should be initiated by using medications that mainly act on fasting and interprandial glucose. For instance, the level of A1C should dictate the choice of an insulin secretagogue as second-line or third-line therapy, according to whether the patient is already treated with metformin alone or with combinations of metformin and glitazone. In patients who have an A1C >7.5%, it is more appropriate to select a sulfonylurea, which is more efficient than other insulin secretagogues on the fasting and more generally on the basal hyperglycemia. By contrast, in those patients who have A1C <7.5%, glucodependent insulinotropic agents such as glucagon-like peptide-1 analogs or dipeptidyl peptidase IV inhibitors would be a better choice, since these medications are mainly active on postmeal glucose excursions (36).

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