Self-monitoring of blood glucose in diabetic patients: from the least common denominator to the greatest common multiple

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SUMMARY

Self-monitoring of blood glucose (SMBG) is recognized as necessary in insulin-treated diabetic patients. There is less evidence for the regular use of SMBG in non-insulin-using type 2 diabetic patients. The rationale for an appropriate regimen of SMBG might be to have at least one time-point of monitoring included within each of the 3 periods of daytime i.e. fasting, postprandial and postabsorptive periods. Interventional trials have indicated that a 4-to 5-point daily profile represents an optimal regimen for SMBG in type 1 diabetic patients with satisfactory diabetic control. This type of SMBG includes 4 daily glucose determinations (3 before each meal and one at bedtime) and one weekly monitoring at 3:00 am. However additional determinations should be made within postprandial states, particularly when rapid insulin analogues or pump-treatments are used. In non-insulin-using type 2 diabetic patients, studies of diurnal glycemic profiles have indicated that postprandial glucose is an important contributor to HbA1c and that mid-morning hyperglycemia is the “weakest link” of metabolic control. Therefore mid-morning glucose testing should be recommended when HbA1c levels are not correctly controlled. Furthermore, extended postlunch determinations at 5:00 pm can be helpful for checking both the quality and safety of diabetic control in such patients. The frequency and timing of SMBG depend both on the type (1 or 2) of diabetes and should be a compromise between optimal and minimal regimens.

Key-words: SMBG · Type 1 and type 2 diabetes.

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RÉSUMÉ

Auto-surveillance glycémique chez le patient diabétique : du plus petit commun dénominateur au plus grand commun multiple

L’auto-surveillance de la glycémie est indispensable chez les diabétiques insulinés. Son utilisation régulière est moins évidente chez les diabétiques de type 2 non insulinés. Une surveillance glycémique rationnelle devrait comporter au moins une mesure glycémique sur chacune des 3 périodes de la journée : jeûne, periodes post-prandiale et post-absorptive. Les études d’intervention ont montré que le schéma optimal pour l’auto-surveillance du diabète de type 1 bien équilibré comportait 4 à 5 glycémies quotidiennes (3 avant chaque repas et une au coucher) et une hebdomadaire à 3 : 00 am. Toutefois d’autres déterminations devraient être proposées pendant les périodes post-prandiales, notamment dans le cadre de traitements par analogues rapides de l’insuline ou par pompes. Chez les diabétiques de type 2 non insulinés, l’étude des profils glycémiques diurnes a montré que la glycémie post-prandiale est un déterminant important de l’HbA1c et que l’hyperglycémie de milieu de matinée est le « maillon faible » du contrôle métabolique. C’est pourquoi un contrôle glycémique devrait être recommandé pendant cette période chaque fois que l’HbA1c n’est pas suffisamment contrôlée. Enfin, des mesures de la glycémie pendant la période post-absorptive qui suit le déjeuner (5 : 00 pm) peuvent contribuer à une meilleure évaluation de la qualité et de la sécurité du contrôle diabétique chez ces patients. La fréquence et les heures de l’auto-surveillance glycémique dépendent du type (1 ou 2) de diabète et devraient être un compromis entre un régime optimal et un régime minimal.

Mots-clés : Auto-surveillance glycémique · Diabètes de type 1 et 2.

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The last ADA's recommendations on Self-Monitoring of Blood Glucose (SMBG) have stated that this technique is a component of effective therapy and that its allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved [1]. These general recommendations imply that SMBG is a useful tool for: (i) preventing hypoglycemia, and (ii) adjusting medications, dietary treatments and physical activities. However the recommendations remain loosely defined when specific situations are considered. For instance, many questions remain to be solved in terms of timing and frequency of SMBG. At present time, SMBG is recognized as necessary in insulin-treated diabetic patients. From the experience of the DCCT's investigators [2] it has been stated that SMBG is recommended 3 or more times daily in type 1 diabetic patients, this attitude being extended to pregnant women treated with insulin [3, 4, 5]. There is less evidence for the regular use of SMBG in type 2 diabetic patients especially in those who are not using insulin treatments [1, 6, 7, 8]. At present time it is difficult to know whether SMBG can be considered optional, recommended or mandatory in non-insulin-using type 2 diabetic patients and the last ADA's recommendations are summarized by a short evasive sentence: "The optimal frequency and timing of SMBG in type 2 diabetic patients is not known but should be sufficient to facilitate reaching glucose goals". As a result several important questions remain to be solved. One of them is to find whether it exists a common rationale for SMBG in type 1 and type 2 diabetic patients. As a consequence another question is whether an optimal or minimal regimen for SMBG can be defined in each type of diabetes.

In this view lessons from physiology of intestinal carbohydrate absorption and of glucose metabolism over daytime can be hepful.

Rationale for SMBG: lessons from the study of daytime periods by taking meals as reference

The postprandial state, with respect to glucose, is defined as a 4-h period that immediately follows ingestion of a meal. During this period, dietary carbohydrates (mainly starch and to a lesser extent, oligosaccharides and disaccharides) are progressively hydrolyzed through several sequential enzymatic actions. The monosaccharides (mainly glucose units) that are released are absorbed by the intestine, entered the portal stream and, finally are delivered into the systemic circulation within a few minutes after eating. As a result a rapid rise in blood glucose concentration is observed. Even though the glucose absorption decreases progressively with time the overall period of absorption has approximately a 4-h duration which corresponds to the postprandial period. The postabsorptive state corresponds to a 6-h period which follows the postprandial state. During this period blood glucose concentrations remain within a normal range in non diabetic patients. The rate of removal of glucose from the circulation is compensated by the hepatic glucose output, which is mainly derived from the breakdown (glycogenolysis) of the glycogen stored during the preceding postprandial period.

The "real" fasting state starts only at the end of the postabsorptive period (i.e. approximately 10-12 h after the beginning of the last meal intake). During the fasting state, blood glucose levels are maintained at a nearly normal steady state in non diabetic individuals. This stabilization is due to the fact that the glucose production shifts progressively from glycogenolysis to gluconeogenesis (i.e. glucose derived from lactate, alanine and glycerol) as the duration of the fasting state is prolonged.

Therefore it appears that in a non diabetic patient who takes three meals per day at relatively fixed hours, the overall nycthemeral period can be divided into 3 periods corresponding to fasting, postprandial and postabsorptive states. The postprandial period (4h each) is equal to 12 h and covers a full half-day period of time: from 8:00 am to 4:00 pm and from 7:00 (dinner time) to 11:00 pm *(Fig 1)*.

The "real" fasting period is only limited to a short period of time at the end of the night (from 5:00 am to 8:00 am). 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: from 4:00 pm to 7:00 pm and from 11:00 pm to 5:00 am *(Fig 1)*.

Although postprandial blood glucose rises are usually higher, longer and more generally have a greater variability in diabetic patients than in non diabetic individuals, these 3 periods remain present in diabetic patients. Therefore the ideal regimen to assess blood glucose variations over daytime should at least include one time-point of monitoring within each of these 3 periods *(Fig 2)*. This rationale might be the basis for a minimal SMBG in insulin-treated diabetic patients. However since this protocol includes at least 3 glucose testing per day it is difficult to recommend it in non-insulin-using type 2 diabetic patients who are generally poorly motivated. Furthermore there is no evidence that in such patients frequent daily self-monitoring would be hepful for achieving better diabetic control. Therefore the "least common denominator" i.e. the minimal regimen for SMBG is not probably the same in type 1 and type 2 diabetic patients.

From the "least common denominator" (minimal regimen of SMBG) to the "greatest common multiple" (maximal regimen of SMBG) in diabetic patients

Type 1 diabetic patients

Lessons from such interventional trials as the DCCT indicate that a 4- to 5-point profile represents an optimal regi-

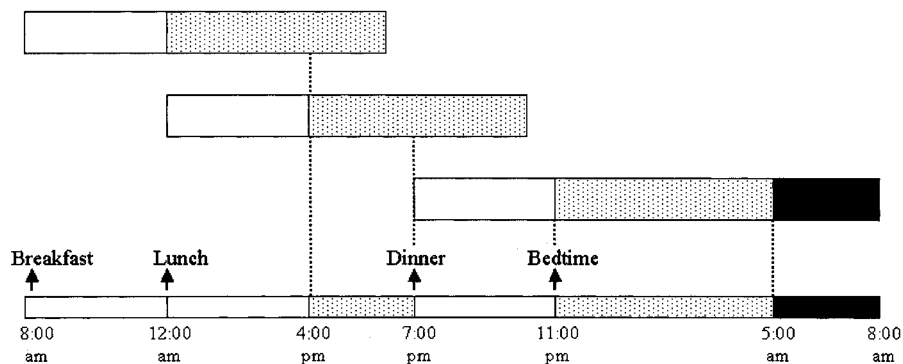

Figure 1
Periods of daytime by taking mealtimes as reference. Considering that the postprandial (white areas) and postabsorptive (grey areas) states following a given meal last 4 and 6 hours respectively, the cumulative duration of postprandial states is approximately equal to 12 h. The "real" fasting state (black area) is limited to a 3-h time interval at the end of the night. In an individual who eats 3 times a day and considering the overlap between postprandial and postabsorptive periods, the postabsorptive state covers 2 periods: from 4:00 pm to 7:00 pm and from 11:00 pm to 5:00 am.

men for SMBG in relatively stable type 1 diabetic patients [2]. The patients in the intensive-therapy group were required to test their blood glucose daily before each meal and at bedtime. A weekly determination was required at 3:00 am and postprandial testing was counselled occasionally. The treatment goals were to achieve a near normal diabetic control: fasting and prepandial glucose between 70 and 120 mg/dl, postprandial glycemia less than 180 mg/dl and glucose values at 3:00 am of 65 mg/dl or above. In the conventionally-treated group no precise timing and goals were defined, the patients being counselled to test urine or blood 3 or 4 times daily [11]. In the intensively-treated group a significant and persistent improvement in diabetic control was obtained compared with the conventional group, the difference in terms of HbA1c being approximately equal to 2%. Furthermore significant differences in development and progression of long-term microvascular complications of diabetes were observed between the 2 groups [2]. As a consequence, this 4- to 5-point daily profile of SMBG seems to offer the better compromise between the benefits and the constraints for diabetic patients and therefore it can be considered as the least common denominator for type 1 diabetic patients *(Fig 3)*. However it must be noted that the main failure of this monitoring program is that it does not include any marker of the "real" postprandial state. Such periods should be normally monitored after each meal when: (i) insulin treatment are initiated; (ii) profound adjustments of insulin doses are required; and (iii) rapid insulin analogues or pump treatments are used. Therefore the testing of postprandial periods leads to a 8-point daily glucose monitoring *(Fig 3)*. For instance it has been demonstrated that such programs of SMBG are of particular interest for adjusting the doses of rapid insulin analogues and therefore for reducing the postprandial excursions in type 1 diabetic patients who are treated with a combined insulin therapy: a single injection of basal NPH at bedtime and 3 bolus of fast-acting insulin analogues administred thrice a day, immediately before meals [12]. However it should be noted that such SMBG regimens remain poorly realistic in the long-term because the patient's constraints are usually too high. For that reason

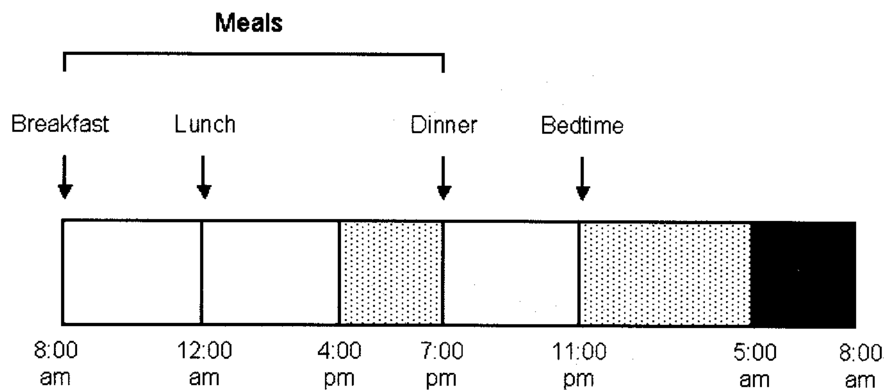

Figure 2
An "ideal regimen" for SMBG should provide at least one glucose testing within each period of daytime i.e. within fasting (black area), postprandial (white areas) and postabsorptive (grey areas) periods.

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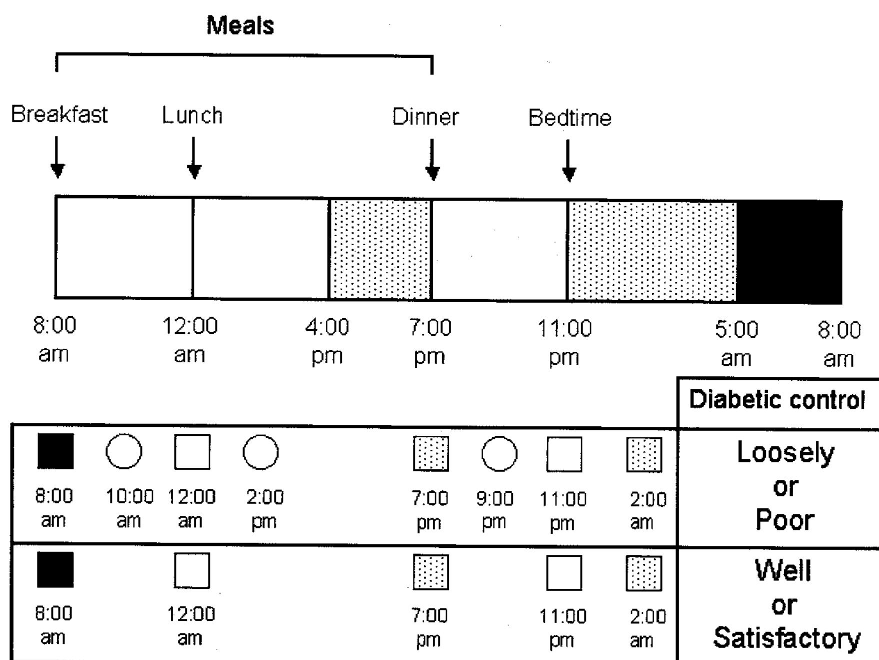

Figure 3
Proposals for SMBG in type 1 diabetic patients.
■ Testing at fasting.
○ Testing during the postprandial period: 2 h after meal.
□ Testing during the late postprandial period: 4h after meal.
▒ Testing during the postabsorptive period.

this type of SMBG can be considered as the maximal regimen in terms of frequency of blood glucose testing and can therefore be namely entitled as the "greatest common multiple", an option which is only recommended at initiation of new insulin regimens or more generally in brittle conditions of diabetic control.

Type 2 diabetic patients

Although recent publication have indicated that SMBG in combination with a structured counselling program can produce positive effects on the diabetic control of non-insulin-treated type 2 diabetic patients [13], the efficacy of SMBG in type 2 patients still remains a question of debate [6]. For instance it has never been clearly demonstrated that lifestyle changes especially better adherence to dietary recommendations and excercice advices might be promoted by SMBG [14]. For that reason recommendations for management of non-insulin-using type 2 diabetic patients are mainly based on HbA1c determinations [1, 15]. Fasting or more generally preprandial blood glucose values are also used as therapeutic targets in several interventional studies such as the UKPDS [16]. The most recent ADA's recommendations [1] have stated that: (i) HbA1c levels should be maintained below 7%; (ii) preprandial plasma glucose should be within a range of 90-130 mg/dl and (iii) peak postprandial plasma glucose should be kept below 180 mg/dl (10 mmol/l). However, fasting glycemia and HbA1c suffer from several limitations for several reasons: (i) HbA1c is a reflection of both fasting and postprandial glycemia [17-19], (ii) postprandial glycemic excursions play an important role in the overall metabolic control of type 2 diabetic patients [21-24], (iii) HbA1c does not provide any information on hypoglycemic episodes [25] and (iv) variations in HbA1c occur after a delay of several weeks [25]. SMBG is certainly of interest in patients at risk of hypoglycemia or in those exhibiting exaggerated postprandial glycemic excursions [26] and more generally in all patients requiring rapid therapeutic adjustments. However for a majority of non-insulin-using type 2 diabetic patients it is difficult to recommend a frequent daily SMBG and it is, even, not easy to know whether self-monitoring should be optional or recommended. Lessons from studies of diurnal glycemic profiles over daytime can help to give an answer to the above-mentioned questions.

The 4-point diurnal glycemic profile is based on the determination of plasma glucose by using an enzymatic method at 4-time points: 8:00 am (before breakfast), 11:00 am, 2:00 pm (2 hours after lunch) and 5:00 pm. In these conditions, the prebreakfast plasma glucose value at 8:00 am is considered to reflect a "real" fasting state, the 2-h postlunch value at 2:00 pm corresponds to a non questionable postprandial period, the 3-h postbreakfast value is con-

sidered as a compromise between a late postbreakfast and an early prelunch value, whereas the 5-h postlunch value (extended postlunch at 5:00 pm) is a marker of a postabsorptive period [10].

The first important finding is that postprandial glucose is an important contributor to HbA1c and a major player is moderately-controlled diabetes [24]. The relative contributions of postprandial and fasting hyperglycemia to the overall diurnal hyperglycemia were studied by calculating the incremental areas under the 4-point glycemic profile from 8:00 am to 5:00 pm. Three areas were calculated. The first one was calculated above a baseline level equal to the fasting plasma value and was therefore considered a reflection of the postprandial responses to breakfast and lunch. The second area 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. Therefore, the difference of the 2 preceding areas can be considered an assessment of the increment in fasting plasma glucose values. Using this mode of calculation we have shown that whatever was the quality of the diabetic control, postprandial glucose made a substantial contribution to the overall hyperglycemia. However when the patients were divided into five groups, according to the quintiles of HbA1c we found that postprandial glucose levels made the highest contributions, 70% in the lower quintile (HbA1c < 7.3%), in patients with well— to moderately— controlled diabetes. By contrast fasting blood glucose levels were the highest contributor to the overall hyperglycemia in patients with poorly-controlled disease. This finding claims that monitoring of postprandial glucose levels in type 2 diabetic patients is somewhat important in order to get a full picture of diabetic control since HbA1c can be considered as the sum of glycemic excursions during both fasting, postprandial periods and postabsorptive periods.

The second important finding is that mid-morning hyperglycemic excursions are the "weakest link" of diabetic control [23]. In non-insulin-using type 2 diabetic patients we have demonstrated that prelunch glucose concentrations at 11:00 am were significantly increased when compared with those observed at 8:00 am, 2:00 pm and 5:00 pm. This permanent failure was observed in all groups of type 2 diabetic patients, whatever the clinical (BMI), biological (HbA1c), therapeutic (diet alone, one-drug or combined antidiabetic treatments) and pathophysiological (residual β-cell function) status. Therefore mid-morning testing should be recommended for detecting such abnormalities and for correcting them with appropriate therapies.

The third important finding is that the extended postlunch glycemia (at 5:00 pm) can serve as a global assessment for both quality and safety of metabolic control in type 2 diabetic patients [27]. From the analysis of the 4-point diurnal profiles in 480 patients with type 2 diabetes it has been shown that extended postlunch glucose concentrations at 5:00 pm have a better sensitivity and specificity for predicting HbA1c < 7% than fasting glucose values. At 5:00 pm, the optimal cutpoint glucose value balancing high sensitivity (90.9%) and high specificity (81.1%) was found to be 7 mmol/l. This value is set at a lower level (6 mmol/l) when the calculation was applied to screen for treatment success in a given patient, i.e. to predict HbA1c < 7% with a specificity ≥ 90%. Therefore the observation of glucose values > 6 mmol/l at 5:00 pm raises the question whether the physician should accelerate the implementation of additional effective therapies even though the HbA1c levels remain less than 7%. Furthermore the extended postlunch value corresponds usually to one of the nadirs of daytime [28, 29], the others occuring usually in the late morning or over the early period of the night [30, 31]. When HbA1c levels were less than 7%, the extended postlunch glucose value was the lowest of the diurnal profile in 60% of the patients, and 17.5% of them were at risk of hypoglycemic episodes i.e. with glucose levels less than 80 mg/dl, at this moment of the day.

All these findings suggest strongly that SMBG is an important complementary tool for assessing the degree of diabetic control of type 2 diabetic patients even though HbA1c is unanimously considered as the "gold standard" in this type of patients. A 3-point glucose testing appears to be the most appropriate regimen in loosely or poorly controlled type 2 diabetic patients since this type of SMBG covers the main periods of daytime: fasting, postprandial and postabsorptive periods. A one-point glucose testing in the late afternoon seems to be sufficient when stable conditions of diabetic control are achieved *(Fig 4)*.

According to the title of this article: "from the least common denominator to the greatest common multiple", it can be concluded that SMBG is a necessary tool in the monitoring of both type 1 and 2 diabetic patients but should be modulated from maximal to minimal regimens. This modulation depends at least on two parameters: the type of diabetes mellitus, and the degree of stability of the disease.

In type 1 diabetic patients, the 8-point daily glucose monitoring, i.e the greatest common multiple, is necessary in brittle diabetes and in all conditions that require frequent adjustements of insulin doses. In more stable situations, the daily frequency of glucose monitoring can be limited to a 5-point profile that constitutes the least common denominator. In type 2 diabetic patients, the greatest common multiple is certainly achieved by a 3-point daily testing that should be used when treatment changes are needed, i.e. in all situations that correspond to insufficient diabetic control. In type 2 diabetic patients who are apparently well-controlled the one-point daily testing might be sufficient to confirm the adequacy of the diabetic control. In this case, such a regimen represents what we have called the least common denominator. In type 1 diabetic patients it is obvious that the 5- or the 8-point monitoring should be performed, as appropriate, every day of life. In type 2 diabetic patients there remains to know at which weekly frequency the one- or the 3-point

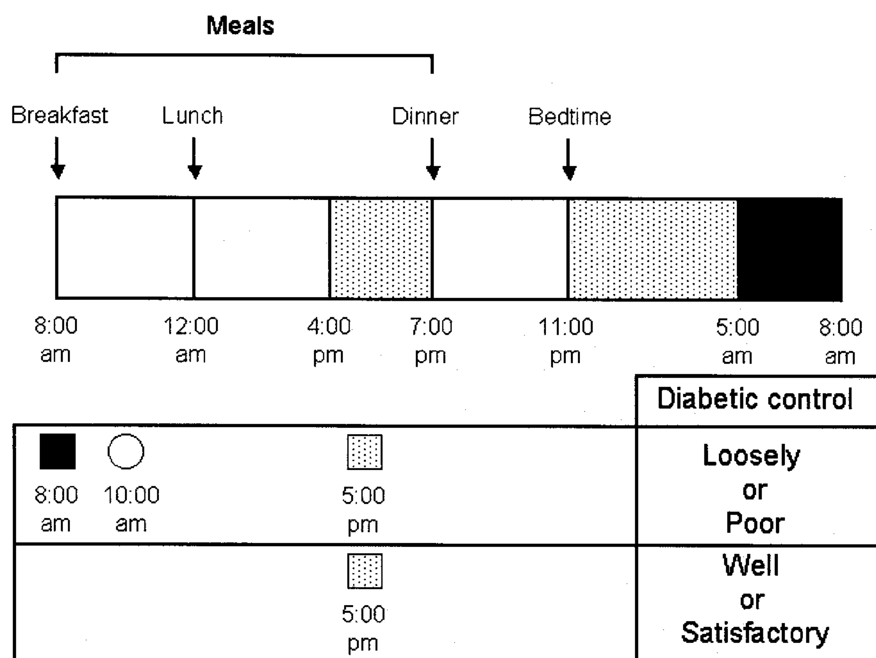

Figure 4
Proposals for SMBG in type 2 diabetic patients.
■ Testing at fasting.
○ Testing during the postprandial period: 2 h after meal.
Testing during the postabsorptive period.

monitoring should be applied. Once or twice a week might be sufficient in most patients, but such a proposal remains purely speculative in the absence of any study asserting this hypothesis. However, in order to maintain a weekly frequency of SMBG within reasonable limits, and in order to combine the advantages of the one- and 3-point profiles, we suggest first that one single control at either breakfast, mid-morning or extended postlunch times should be done every two days and second that the testing order should be arranged as a circular permutation.

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