Postprandial glycaemia: a plea for the frequent use of delta postprandial glycaemia in the treatment of diabetic patients

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SUMMARY
Postprandial hyperglycaemia is a phenomenon often neglected by patients as well as doctors. While patients only voluntarily measure morning and preprandial capillary glycaemia, physicians do not encourage the measurement of anything further. The specific role of postprandial hyperglycaemia in the determination of late diabetes complications, such as micro- and macroangiopathy, remains controversial. It is however undeniable that the postprandial glycaemic excursion plays an important role in total hyperglycaemia reflected by an increase in glycated haemoglobin. The postprandial glycaemia measurement or, more appropriately, the postprandial glycaemic excursion (the difference between postprandial and preprandial glycaemia, also called the postprandial delta glycaemia), is important to measure and there are specific tools to correct it when abnormal. Postprandial delta glycaemia should lie between 30 and 50 mg/dl. It is thus suggested to measure it not necessarily on a daily basis, but when it is expected that the glycaemic couple, or "pre-postprandial couple", is high. The specific tools for treatment of postprandial hyperglycaemia can be dietetic (carbohydrate quantity reduction or ingestion of fiber-rich and/or low glycaemic index foods) or medi- cal. Among the specific medicinal treatments are the alpha-glucosidase-inhibitors (which can be used for both type 1 and type 2 diabetic patients), glinides and fast-acting insulins. Rather than first treating fasting and interprandial hyperglycaemia, as has been commonly done by physicians, the authors recommend the simultaneous treatment of pre-, inter- and postprandial hyperglycaemia. The opti- mal time at which to evaluate postprandial glycaemia is approximately 1 h and 15 minutes for type 1 and type 2 diabetic patients.

Key-words: Postprandial hyperglycaemia · Postprandial glycaemic excursion · Postprandial delta glycaemia · Glycated haemoglobin · Self-blood glucose monitoring · Glycaemic index · Rapid-acting analogs · Slow-acting analogs · Glinides · Alpha-glucosidase-inhibitors.

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Résumé
Repenser l’utilisation des glycémies post-prandiales des diabétiques ; pour un calcul du delta glycémique post-prandial
L’hyperglycémie post-prandiale est un phénomène trop souvent négligé par les patients aussi bien que par les médecins, les premiers pratiquant plus volontiers la mesure de la glycaémie capillaire au réveil et avant les repas, les seconds ne réclamant aucune autre information. Même si son rôle spécifique dans le déterminisme des complications tardives du diabète, micro- et macroangiopathiques, reste un sujet controversé, il est incontestable que l’excursion glycémique post-prandiale joue un rôle important dans l’hyperglycémie globale et l’élévation de l’hémoglobine glyquée. La mesure de la glycaémie post-prandiale ou, de façon plus adaptée, de l’excursion glycémique post-prandiale, différence entre la glycé- mie post-prandiale et la glycaémie pré-prandiale (delta glycémique post-prandial), est un élément d’autant plus important à mesurer qu’il existe des moyens spécifiques de le corriger. Ce delta glycémique post-prandial doit être compris entre 0,30 et 0,50 g/l et impose donc de mesurer, à une fréquence qui n’est pas nécessairement quotidienne mais élevée, des couples de glycaémie, "couple pré-post prandial". Les moyens spécifiques de corriger l’hyperglycémie post-prandiale peuvent être diététiques (diminution de la quantité de glucides absorbés, absorption d’un aliment riche en fibres et/ou à index glycémique bas) ou médicamenteux. Parmi les moyens médi- camenteux spécifiques, on retient d’une part les inhibiteurs des alphaglucosidases qui peuvent être utilisés aussi bien chez les dia- bétiques de type 2 que chez les diabétiques de type 1, les glinides, les insulines analogues ultrarapides. Plutôt que de s’attaquer à la nor- malisation de la glycaémie à jeun et inter-prandiale avant de corriger « éventuellement » les glycémies post-prandiales, les auteurs recommandent la lutte simultanée et immédiate sur ces deux fronts, glycaémie à jeun et inter-prandiale, et glycaémie post-prandiale. Le moment optimal pour évaluer le pic glycémique post-prandial se situe autour de 1 h 15 pour les diabétiques de type 1 et de type 2.

Mots-clés : Hyperglycémie post-prandiale · Excursion glycémique post-prandiale · Delta glycémique post-prandial · Hémoglobine glyquée · Auto-surveillance glycémique · Index glycémique · Analogues rapides · Analogues lents · Glinides · Inhibiteurs des alphaglucosidases.

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Introduction

The objectives of this article are:
1) To demonstrate that the calculation of postprandial excursion, also called delta postprandial glycaemia, provides a more useful value than the simple examination of absolute postprandial glycaemic value.
2) To provide support for determination of an average daily glycaemic profile to make better-informed therapeutic decisions for type 1 and type 2 diabetic patients.
3) To demonstrate the need for simultaneous treatment of both fasting/interprandial and postprandial hyperglycaemia.

Postprandial glycaemia and postprandial glycaemia excursion

In this article, we define the postprandial glycaemic excursion as the increase in glycaemia immediately following a meal, particularly those meals which contain starchy foods. This rise in glycaemia occurs 10 to 20 minutes following the beginning of ingestion, increases between 45 minutes and 2 hours post-meal, and returns to basal values from 2 to 5 hours. This definition differs from that utilized by Louis Monnier who distinguishes the post-absorptive hyperglycaemia, called postprandial glycaemia here, and the post-absorptive phase as the period following the return to basal glycaemia. To clarify the significant difference between the absolute value of postprandial glycaemia and the delta postprandial glycaemia [1], let us examine two different scenarios. Consider a patient with postprandial glycaemia of 225 mg/dl. Is this level too high? Alternatively, consider another patient with postprandial glycaemia of 150 mg/dl. Is this level normal? The answers to these questions are not as obvious as they appear at first.

These scenarios might be explained as follows: in the first case, if the preprandial glycaemia was 200 mg/dl and the postprandial glycaemia was 225 mg/dl, we can conclude that the patient was globally hyperglycaemic, but that the post-prandial delta variation was quite narrow; thus, efforts should be made only to correct basal, pre-prandial blood glucose control and not specifically the post-prandial state.

In the second example, 150 mg/dl could be considered as normal or only slightly high, at the first glance. If we now consider that this scenario could apply to a woman with gestational diabetes or an insulin-treated type 2 diabetic patient, the appreciation could be different: if the preprandial glycaemia was 80 mg/dl, the delta glycaemia would be 70 mg/dl, i.e. undoubtedly too high. Thus this might lead to the prescription of insulin therapy in the case of the pre-gnant woman or modification of the existing insulin therapy and/or oral drugs for the type 2 diabetic patient.

From the above, we can conclude that a postprandial glycaemia measure is more significant when compared to the immediate preprandial value, permitting the determination of a delta postprandial excursion. The delta post-prandial glycaemia is considered normal when, most frequently, between 30 and 50 mg/dl.

In addition, it also appears important that a patient’s nychthemeral variation of glycaemic profile be well described, since glycaemic excursion can vary between breakfast, lunch, dinner and snacks. These profiles can be obtained by glycaemic continuous subcutaneous glucose control (GCSM) over a period of 3 days, or simply by self-monitoring. Apart during pregnancy, patient compliance can often be difficult, if it means taking 6-8 glucose measures per day. It may be preferable for the patient to pay special attention to one meal time per week. For instance, week one the patient might take measures related only to breakfast, lunch during week 2, and dinner during week 3. From these data it would therefore be possible to calculate an average of the postprandial delta glycaemia after each individual meal time.

Differences that may exist for postprandial delta glycaemia measures at each meal time can originate from several factors, including the nature and quantity of carbohydrate consumed, whether the patient is taking some form of anti-diabetic treatment, whether the patient’s glucose is well managed, and the severity of his diabetes. In early stage diabetes, the rise in glycaemia is most prominent after breakfast and dinner, whereas with more advanced diabetes where the patient has severe endogenous insulin secretion deficit, the meal times are all similarly affected.

When to measure postprandial glycaemia?

The time to measure postprandial glycaemia is not absolutely codified. Personal unpublished data using continuous recordings of glycaemia show that the maximum glycaemic peaks are variable, from one day to another and from one patient to another. This peak most often occurs between one and two hours after the starting of the meal: the mean peaking time is 72 minutes, i.e. roughly 1 hour and 15 minutes, which value may serve as the best compromise.

Sequential or simultaneous treatment of fasting, or preprandial, and postprandial hyperglycaemia

Many arguments support simultaneous treatment of fasting, or preprandial, and postprandial hyperglycaemia. Among these arguments are:
1) The contribution of postprandial glycaemia in the nychthemeral hyperglycaemia of the diabetic patient has been estimated to be approximately 40% [2-5] (figure 1). Figure 1 shows glycaemic profiles obtained in 12 controls and 60 type 2 diabetic subjects. The superposition of the 2 profiles is interrupted at 3 distinct points:
HbA1c, i.e. about 1% HbA1c in absolute value. An excursion can account for 40% to the abnormal rise in -S2 = area under the curve of interprandial hyperglycaemia, -S3 = area under the curve of strictly prandial hyperglycaemia. We notice that the contribution of prandial hyperglycaemia (S3) to total abnormal hyperglycaemia (S2+S3) is approximately 40%. However this contribution would be different in a patient with fasting glycaemia of 250 mg/dl versus one with 150 mg/dl. In these two examples, the contribution of prandial hyperglycaemia to total hyperglycaemia would vary between 25 and 60%, respectively. An average contribution of 40% is thus assumed as has been supported by J. Brandt-Miller et al. as well as others [2-5].

- We estimate that the abnormal postprandial glycaemic excursion can account for 40% to the abnormal rise in HbA1c, i.e. about 1% HbA1c in absolute value.

2) At least two studies, DIS [6] and STOP NIDDM [7], have demonstrated that abnormal postprandial hyperglycaemia has deleterious effects which can be alleviated by correcting postprandial hyperglycaemia.

3) We have many tools at our disposal to correct postprandial hyperglycaemia, which will be detailed later in this article.

4) Nevertheless, the most important point supporting the simultaneous treatment of pre- and postprandial glycaemia is as follows:

It is believed by many physicians that what is paramount in the treatment of diabetes is normalization of fasting glycaemia. Although improvement of preprandial glycaemia is often accompanied by a similar reduction in postprandial glycaemia, delta postprandial glycaemia remain unchanged. For example, let us examine a patient who has a preprandial glycaemia of 200 mg/dl and postprandial glycaemia of 260 mg/dl. Decreasing the preprandial glycaemia from 200 mg/dl to 150 mg/dl will be accompanied by a similar fall in postprandial glycaemia from 260 mg/dl to 210 mg/dl, giving an “apparent” improvement in this patient’s postprandial glycaemia. However, if we refer to our previous discussion of delta postprandial glycaemia and its importance, this parameter is left unchanged by merely treating fasting glycaemia; delta postprandial glycaemia would remain 60 mg/dl, a level considered as pathologic. This case is commonly observed in patients being given basal insulin treatment, where increased basal insulin improves fasting glycaemia, but not the delta postprandial glycaemia. This situation becomes even more complex when drugs known to alter insulin secretion are introduced. While sulphonylureas may reduce postprandial glycaemia, the same is not true for delta postprandial glycaemia [8].

It should be noticed from what we’ve discussed thus far, that the determinants of the pre- and postprandial glycaemia may be independent and thus should be treated distinctly, when possible. In figure 2 [9] we see the reproducibility of glycaemic excursions in different populations after being presented with identical meals. Glycaemic excursions for those patients with controlled versus uncontrolled glycaemia are surprisingly similar despite very different fasting glycaemias of 110 mg/dl and 200 mg/dl, respectively. Based upon these data, the glycaemic index of the meal can be evaluated. Moreover, this index does not appear to depend on the patient’s glycaemic control.

1) The idea that pre- and postprandial glycaemia are independent entities is not always true:

- As suggested above, insulin secretagogues can improve not only interprandial, but also postprandial glycaemia.

- It has been shown that long-term improvement of postprandial glycaemia can in fact also improve fasting glycaemia.
mia. This has been demonstrated with metformin treatment [10], acarbose treatment [5] preprandial humalog without basal insulin treatment in obese patients [4], altered fiber intake [11], and with a low glycaemic index diet [12-14]. The specific effect of the thiazolidinediones on the postprandial glycaemia, however, is not well known.

**Targeted treatment of postprandial hyperglycaemia**

As mentioned above, there are specific methods to correct postprandial hyperglycaemia. These methods are typically dietetics [15]. The modulation of carbohydrate intake is an effective tool to attenuate postprandial hyperglycaemia. These modulations may include decreasing the overall daily carbohydrate caloric intake, differing the carbohydrate caloric contribution to a snack or other meal in which postprandial glycaemia is usually low, ingesting carbohydrates only when glycaemia is typically low, or decreasing carbohydrate caloric intake when glycaemia is typically high (e.g. breakfast). Gut absorption of food with a low capacity to induce hyperglycaemia, either because it is rich in fiber or has a low glycaemic index, is also an effective tool to control abnormal postprandial hyperglycaemia [3,9,11-14].

Postprandial hyperglycaemia can be treated pharmacologically as well. Several drugs have proven effective in reducing postprandial hyperglycaemia:

- **Acarbose** is usually a first step in treatment. Initially, acarbose is given in a single dose of 50 mg per day with the meal inducing the greatest degree of hyperglycaemia (e.g. breakfast) for at least 3 weeks. This dose is then increased to 100 mg for 3 weeks if control of postprandial glycaemia has not been achieved. If glycaemic control has not been achieved yet, subsequent addition of acarbose to the treatment regimen is introduced before other meal times with the following rules: 0 mg acarbose if the delta postprandial glycaemia lies between 30 and 50 mg/dl; 50 mg for 3 weeks then 100 mg (to minimize side effects) if the delta glycaemia exceeds this number. Subsequent treatment may be titrated to effect for the individual patient’s needs such as 100 mg before the morning meal, 0 mg at lunch, and 50 mg in the evening for example.

- **Repaglinide**, in 0.5 mg, 1 mg or 2 mg pills, is given in doses of up to 6 mg before each meal. Like acarbose treatment, dosing of repaglinide is increased gradually, for adaptation purposes and adjusted to achieve the best possible improvement in delta postprandial glycaemia of each given meal. In contrast to acarbose, however, times between dose changes should not exceed a few days, due to the drug’s very rapid mode of action.

- **Rapid-acting insulin therapies** such as aspart, lispro and the soon-to-be introduced glulisine are specific tools to improve postprandial glycaemia. So appears to be the use of inhaled, pulmonary absorbed insulin. For treatment of preprandial glycaemia, only the long-acting insulins glargine and detemir appear to be effective in conjunction with metformin treatment which acts to decrease hepatic glucose output, thereby eliciting a preferential reduction in preprandial glycaemia.

- **Sulphonylureas** are more complex, having effects on preprandial rather than postprandial glycaemia. Thiazolidinediones, insulin sensitizing drugs, have similar effects. However, few data are currently available on the specific effects of both sulphonylureas and thiazolidinediones on postprandial blood glucose values.

**Change of insulin treatment: biphasic insulin multi-injections towards a basal-bolus injection**

Experiments demonstrate that the requirements of insulin for the type 1 and type 2 diabetic patients receiving insulin therapy are distributed in such a way that roughly half is needed for basal while the other half is needed for prandial insulin. Thus, a patient being given 48 units of insulin per day could have his insulin therapy divided into 24 units of the slow-acting insulin glargine or detemir and approximately 24 units of the rapid-acting insulin aspart or lispro. In this case, a typical initial prescription might be an injection of 8 units of rapid insulin before each of the three meals, then “tuned according to delta-postprandial BG assessments”. The amount of glargine or detemir to be injected is adjusted according to the blood glucose value observed in the morning when glargine or detemir is injected in the evening or according to the pre-dinner value when glargine or detemir is injected in the morning. We suggest that patients adjust glargine dosage in two-unit increments or decrements with five-day adjustment periods, in order to obtain a morning glycaemia between 80 and 110 mg/dl (for those patients using glargine in the evening).

Determination of the preprandial glycaemia before dinner (if injection is also given before dinner) makes it possible to determine the duration of action of glargine insulin or detemir given in a one injection a day. In a considerable number of cases (10 to 15%), glycaemia before dinner is significantly higher than in the morning, indicating that the injection of glargine/detemir does not work over the complete 24 hours. Glycaemia becomes high by 20 hours after, but significantly so by 24 hours after the last injection. This indicates an insufficient glargine/detemir dose. In practice, postponing the injection of slow-acting insulin from pre-dinner to late evening makes it possible to coincide its lack of action with dinner hour which will be covered by rapid-acting insulin. The rapid-acting insulin dose is modulated according to the delta postprandial glycaemia; the dose must be decreased if delta postprandial glycaemia...
is below 20 to 30 mg/dl and increased by 2 unit increments if the delta glycaemia is greater than 40 — 50 mg/dl.

These concepts are exploited in functional insulin treatment [16-18], which we refer to more explicitly as ambulatory self-training with treatment of type 1 diabetes (AT1) [17]. In this educational strategy, it is suggested that patients determine the number of units of rapid-acting insulin necessary to prevent hyperglycaemia induced by ingestion of 10 g of carbohydrate [16-18], keeping the delta postprandial glycaemia between 30 and 50 mg/dl. This approach allows a wide range of food choice to diabetic patients of normal weight receiving insulin treatment [16-18].

**Does the prandial insulin amount have to remain constant from one day to another?**

The answer is no. On the contrary, prandial insulin dose must be modulated according to several parameters:

- First priority is the quantity of carbohydrate in the meal. The patient can be easily shown that there is a personal mathematical correlation between the quantity of carbohydrate in the meal and the quantity of insulin necessary to maintain normoglycaemia: x rapid-acting insulin units are necessary for x grams (10 or 20 g) of carbohydrate.
- The nature of ingested carbohydrate also plays an important role. This is the glycaemic index concept. Very simply, a smaller insulin dose will be required before a meal with low glycaemic index foods.
- The quantity of protein in the diet can also be of slight importance. One or two unit increases in insulin may be necessary when the protein ratio of the meal increases.
- Although seldom necessary, a decrease in rapid-acting insulin dose may be necessary if physical activity occurs just after the meal. Let us however emphasize the importance of treating preprandial hyperglycaemia; it is useful to add a small amount of fast-acting insulin (1-3 units) to those calculated to cover the planned meal. In other words, a “corrective” insulin dose is added to that of the “prospective dose”.
- In addition, we suggest that patients keep record of all instantaneous modifications in insulin therapy in their notebooks as well as write down “6 + 2 U” rather than merely “8 U”. This approach permits to emphasize that the preprandial insulin dosage is constant for similar meals, but that an additional correction may be needed to correct preprandial hyperglycaemia.

**Some additional theoretical considerations**

We discussed previously that postprandial hyperglycaemia represents an absolute increase in HbA1c of about 1%, the remaining 1 to 6% being due to interprandial hyperglycaemia. In other words, correcting interprandial hyperglycaemia accounts for 80-90% of the improvement to be made in patients with an HbA1c level of 12% when correcting postprandial hyperglycaemia may be the only way to decrease HbA1c level from 7.5% to 6.5% or below.

Another theoretical consideration is whether it is necessary to place the same pathogenic importance on postprandial and fasting hyperglycaemia. On one hand, postprandial hyperglycaemia, being more brief than the stable interprandial hyperglycaemia, may be less effective in the process of protein and HbA1c glycation. On the other hand, the most complex postprandial metabolic disturbances accompanying postprandial hyperglycaemia (hyperaminoacidemia, hyperlipidaemia, procoagulation state) may add their deleterious effects.

**Conclusions**

1. The determination of postprandial delta glycaemia as well as fasting glycaemia for all three meals is essential. This results in proposing that patients practice glycaemic cycles by making a minimum of four glycaemic measurements per day: one in the morning, one at night, and the two remaining ones in order to determine the delta postprandial excursion after breakfast or at lunch or dinner. One method could be to concentrate on week one for the breakfast, week two for lunch, and week three for dinner, and so on. Teaching patients to practice these pre- and postprandial “glycaemic couple” measurements, appears essential to us to achieve the goal of “normoglycaemia”.

2. The objective is to reduce the delta glycaemia to values between approximately 30 and 50 mg/dl.

3. It is imperative to try to improve, both as soon as possible and simultaneously, the fasting and postprandial glycaemia using treatment with long-acting oral antidiabetic drugs, the slow-acting insulins glargine/detemir, diet changes, and/or other appropriate medications. Inhibitors of alpha-glucosidases are drugs of choice for first-line treatment; subsequent treatment with repaglinide or nateglinide may be justified if the first-line treatment is insufficient.

4. Single doses of sulphonylureas, as well as thiazolidinediones, appear to have a combined action on fasting and postprandial glycaemia. Further studies in this area are necessary to better characterize these changes.

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