FOR DEBATE

Should diabetic patients be asked to test their blood glucose 90 to 120 minutes after the beginning of their meals?

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SUMMARY

There are three distinct objectives in reducing the post-prandial blood glucose peaks: 1st to reduce the risk of foetal macrosomia in pregnancy, 2nd to reduce cardiovascular morti-mortality, 3rd to lower the HbA1c. With 6–7 glycaemic controls per day and fractionning their meals, motivated women with gestational diabetes reach this goal. But there is no data today directly proving that post-prandial glycaemia is specifically related to the development of micro and macrovascular complications. So to reduce the cardiovascular risk, there are more arguments in favour of lowering HbA1c or prescribing statins than in prescribing a hypoglycaemic drug acting selectively on post-prandial glycaemia. Lastly, to reduce HbA1c near to the goal of 7%, the most important is to reduce the preprandial glycaemia below 1.20 g/l. The patients must be required to monitor their post-prandial glycaemia 2 hours after the beginning of the meal only when the aim is to lower the HbA1c below 7% or 6.5%, for example during pregnancy, or in case of discrepancy between glycaemia at 8 a.m. and 7 p.m. (below 1.20 g/l and HbA1c, above 7%). In other cases, in type 2 diabetes, two glycaemias per day, fasting and vesperal, seems sufficient.

Key-words: Post-prandial hyperglycaemia · Pregnancy · Cardiovascular risk · Fasting glycaemia · Glycated haemoglobin · Self-blood glucose control.

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RÉSUMÉ

Il y a trois raisons de vouloir réduire l’hyperglycémie post-prandiale : réduire le risque de macrosomie au cours d’une grossesse, réduire le risque cardiovasculaire, diminuer l’HbA1c. En réalisant 6 à 7 contrôles par jour et en fractionnant leur alimentation, les femmes motivées atteintes d’un diabète gestationnel atteignent cet objectif. Mais il n’y a en revanche pas de preuve aujourd’hui que la réduction de la glycémie post-prandiale diminue spécifiquement le développement des complications micro et macrovasculaires. Pour réduire le risque cardio-vasculaire, il y a beaucoup plus d’arguments pour diminuer l’HbA1c ou prescrire une statine que pour prescrire un médicament hypoglycémiant qui agit sélectivement sur la glycémie post-prandiale. Enfin, pour ramener l’HbA1c vers l’objectif de 7 %, le plus important est de ramener la glycémie pré-prandiale au-dessous de 1,20 g/l. On ne doit demander aux patients de mesurer leur glycémie post-prandiale 2 heures après le début du repas, seulement lorsque le but est de diminuer l’HbA1c au-dessous de 7 ou 6,5 %, par exemple au cours de la grossesse, ou en cas de discordance entre la glycémie à 8 heures et la glycémie à 19 heures (au-dessous d’1,20 g/l) et l’HbA1c (au-dessus de 7 %). Dans les autres cas, au cours du diabète de type 2, deux glycémies par jour, la glycémie à jeun et la glycémie avant le dîner nous semblent suffisantes.

Mots-clés : Hyperglycémie post-prandiale · Grossesse · Risque cardio-vasculaire · Glycémie à jeun · Hémoglobine glyquée · Auto-surveillance glycémique.

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Whatever the pathophysiological importance of postprandial metabolic phenomena, one can only ask patients to test their postprandial blood glucose 90 to 120 minutes after the beginning of the meal if they can really expect to reap a proven benefit from it. There are three distinct objectives in reducing the postprandial blood glucose peak, i.e. the difference between postprandial and preprandial blood glucose (the delta blood glucose): first, to reduce the risk of foetal macrosomia in pregnancy; second, to reduce cardiovascular morbi-mortality, independent of lowering of preprandial glycaemias; third, to lower HbA1c and in the same way to diminish the risk of micro- and macroangiopathy.

To reduce the risk of macrosomia

A rational pathophysiology has been well established here. We know that maternal hyperglycaemia induces foetal hyperglycaemia which is responsible for foetal hyperinsulinism. It is this hyperinsulinism which causes asymmetric macrosomia, and is a source of potential complications [1].

Clinical studies have confirmed the importance of postprandial hyperglycaemia in this setting. A study by De Veciana et al [2], undertaken in 66 women with gestational diabetes mellitus randomized in two groups, one benefiting from a fasting glycaemia control, and the other a postprandial glycaemia control, showed a reduction in macrosomia: 3.4 vs. 3.8 kg (P=0.01) in the group benefiting from therapeutic supervision of postprandial glycaemia.

Nevertheless, rather unexpectedly, Langer et al [3], in a randomized study of 400 women with gestational diabetes mellitus, demonstrated that glyburide produced identical results to those of intensive insulin therapy. Postprandial glycaemias were no different (1.13 vs. 1.12 g/l) and incidence of macrosomia was identical (23% vs. 13%).

It is therefore possible to reduce macrosomia during gestational diabetes mellitus. To do so, it is necessary to obtain preprandial glycaemia of less than 0.9 g/l and glycaemia of less than 1.20 g/l two hours after the beginning of meals. The women in question should be asked to do 6-7 glycaemic controls per day, to fraction their meals by reducing their glucose intake to 40% of total calorie intake and to drastically reduce their glucose intake at breakfast time to 10-15 grams. By doing this, in our experience, the macrosomic rate can be reduced to that of the non-diabetic population, i.e. around 10%. However, despite an intensification of the treatment and a “near-normalisation” of HbA1c, it is not possible (in insulin-dependent diabetes mellitus) to reduce the macrosomic rate to less than 30%. Clearly, in spite of the motivation of these women and intensive insulin therapy, glycaemic fluctuations are inherent in the treatment of type 1 diabetes [4]. To conclude, it does not seem reasonable to expect all type 2 diabetic patients to be submitted to comparable therapeutic constraints as those presenting gestational diabetes, and it is illusory to fix such a drastic objective on type 1 diabetics. Let us recall that DCCT had for objective the normalisation of HbA1c in the “intensive treatment” group and that this objective could not be reached, despite a high rate of severe hypoglycaemia. But is it worthwhile lowering postprandial hyperglycaemia to reduce cardiovascular morbi-mortality?

To reduce cardiovascular morbi-mortality

The second reason for reducing postprandial hyperglycaemia would be to diminish cardiovascular morbi-mortality, independent of a lowering of preprandial glycaemias. Let us overview the arguments justifying a reduction in delta glycaemia (postprandial glycaemia minus preprandial glycaemia). They are threefold: epidemiological, pathophysiological and factual.

Epidemiological aspects

The epidemiological arguments arise mainly in non-diabetic or pre-diabetic patients, whose glycaemia at the second hour of OGGT is better correlated to cardiovascular morbi-mortality than fasting glycaemia, as the study by DECODE shows [5] and a meta-analysis of 20 studies including 95,780 individuals (94% men) followed up, on average, for 12.4 years [6]. However, note that correlation does not equal causality. Hyperglycaemia at the second hour of OGGT or postprandial hyperglycaemia can only be accompanied by postprandial hyperlipemia or insulin-resistance, initiating an excess of cardiovascular morbi-mortality [7]. Above all, this correlation is no longer discovered in diabetic patients.

Clearly, the DIS study [8] had shown a correlation between glycaemic control one hour after a “normal” breakfast and the cardiovascular morbi-mortality observed during an 11-year follow-up, but it was not the objective of the study and in a multivariated study, cholesterol was not predictive of cardiovascular morbi-mortality. More precisely, the difference in data for inclusion between the survivors and the deceased patients was the following: for fasting glycaemia: 7.3 mmol/l vs. 7.5 mmol/l NS, for cholesterol: 5.7 mmol/l vs. 5.9 mmol/l N.S. and for postprandial glycaemia: 8.4 mmol/l vs. 8.9 mmol/l (P<0.01). Conversely, Balkau et al [9], referring to the Paris Prospective Study, conclude: “The two hours plasma glucose was not associated with early mortality in men with a diabetes mellitus (according to fasting plasma glucose), in contrast to men with impaired or normal fasting glucose”.

Pathophysiological arguments

Conversely, the pathophysiological arguments accumulate, showing that postprandial hyperglycaemia and hypertriglyceridaemia are responsible for an oxidative stress provoking an endothelial dysfunction, well documented by
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Ceriello [10]. Nevertheless, if this endothelial dysfunction can be corrected with hypoglycaemic medication acting principally on the postprandial glycaemia, like acarbose [11,12] or on fasting and postprandial plasma glucose, like gliclazide [13], even more interestingly, it is the statins and sartans which have proved their efficiency in two studies undertaken by Ceriello’s team [14,15].

Factual arguments

Even if the pathophysiological arguments do seem convincing, factual medicine still lacks evidence for the moment. We know that during the DCCT-EDIC study, cardiovascular morbi-mortality was reduced by 42% in the group which had benefited from intensive insulin therapy during the six years of the DCCT, despite an HbA1c which remained identical in the control group during the 11 years (EDIC) of the post-DCCT follow-up [16]. The nychthemeral profile of the patients during the DCCT study does not appear to show a big difference in delta glycaemia (postprandial glycaemia minus preprandial glycaemia) between the two groups. Everything seems to indicate that the endothelium had retained memory of the difference in mean glycaemia, i.e. of HbA1c.

No study of morbi-mortality in type 2 diabetes mellitus is available. We only dispose of surrogate outcomes such as carotid intima-media thickness. Indeed, Hanefeld et al. [17] have demonstrated the existence of a stronger correlation of the intima-media thickness with plasma glucose at 2 hours from OGTT than with fasting plasma glucose (OR=1.9 vs. OR=1.3), but there again, correlation does not equal causality. More conclusively, a randomised study [18] comparing repaglinide with glyburide in 175 type 2 diabetics, for a year, showed a greater decrease in the intima-media thickness in the patients treated with glinide compared to those treated with glyburide (52% vs 18%), whereas decrease in HbA1c was identical (0.9%) and postprandial glycaemia was significantly more reduced with repaglinide than with glyburide (1.50 vs. 1.80 g/l). However, the results appear so spectacular that confirmation through other studies is needed, and in particular, proof in a cardiovascular morbi-mortality study.

Such a cardiovascular morbi-mortality study has been undertaken in pre-diabetic subjects (Stop NIDDM) [19]. This study involved 1,400 patients with impaired glucose tolerance, administered with 100 mg of acarbose vs placebo over a 3-year period. Cardiovascular incidents were spectacularly reduced by 53%, but here again it is difficult to conclude, since morbi-mortality was not a major end-point, but only a secondary criterion of judgement. Moreover, rates of drop-out and exclusion from the study were very high (37% and 14%, respectively). Furthermore, interpretation of the results remains uncertain, since postprandial plasma glucose concentrations were not assessed and where, by contrast, a marked decrease in arterial blood pressure was observed. Finally, this study was the source of a public controversy regarding the reliability of data [20].

In conclusion, one can say like the group of experts (RJ Heine, B Balkau, A Ceriello, S Del Prato, ES Horton and MR Taskinen) “There is no data directly supporting the hypothesis that postprandial plasma glucose is related to the development of micro- and macrovascular complications” [21]. Pending evidence which is likely to be contributed by studies on morbi-mortality demonstrating the necessity to diminish the delta plasma glucose, to decrease the cardiovascular risk in diabetics, it is important today to lower the HbA1c levels with, for one point less of HbA1c, around 15% less myocardial infarctions in 5 to 10 years. If postprandial hyperglycaemia is considered as a marker of cardiovascular risk, it is not necessarily a factor and there are more arguments today in favour of prescribing a statin rather than an antidiabetic oral agent acting selectively on postprandial glycaemia. We can recall the results of the Kumamoto study [22], which showed the absence of development of microangiopathy for 8 years, and a 50% decrease in cardiovascular incidents in patients with HbA1c less than 6.5%, fasting plasma glucose less than 1.10 g/l, and postprandial blood glucose 2 hours after the meal less than 1.80 g/l.

To decrease HbA1c

The third objective: to reduce postprandial hyperglycaemia to decrease HbA1c, and in doing so, to reduce the risk of micro- and macroangiopathy. In this context, it is necessary to distinguish between type 1 diabetes and type 2 diabetes.

Type 1 diabetes

In type 1 diabetes, reference is the DCCT model [23], in which patients should control capillary glucose at least 4 times a day (a control before each meal and a control at bedtime). During functional insulin therapy, the patients are requested to undertake therapeutic correctives by measuring their blood glucose before each meal and, if necessary, after meals. The time of the measurement depends on the therapeutic corrective proposed. If an extra rapid insulin injection is required, patients will be asked to measure their blood glucose 3 to 4 hours after meals to prevent a crossover of insulin, a source of hypoglycaemia. If, on the other hand, it is necessary to modify the quantity or quality of carbohydrates intake, notably by decreasing food with a high glucose index, in favour of food with a low glucose index, it is logical to ask for a glucose control 90 to 120 minutes after the beginning of the meal. One can wonder if this constraint is really justified outside pregnancy, since it would seem unreasonable to ask diabetic patients to measure their blood glucose before the meal, ½ to 2 hours after and 3 to 4 hours later, in all, 9 measurements a day!
Type 2 diabetes

In type 2 diabetes, glucose self-monitoring is not systematic. In our view, it appears justified every time the HbA1c goal is not reached and each time the patient considers that self-monitoring of controls helps him to reach his objective. The aim, to prevent micro- and macrovascular complications, is, in fact, dual. The ideal objective, particularly for the prevention of macroangiopathy is an HbA1c of less than 6.5%. An acceptable objective, particularly for the prevention of microangiopathy is an HbA1c of less than 7%. We should note that following the preliminary results in the Ecodia 2 study, 30% of French diabetics have an HbA1c of less than 6.5% and 50% have an HbA1c of less than 7%.

– How often, and at what hour, should self-monitoring of blood glucose be recommended?

A theoretical answer can be provided to this question, according to L. Monnier [24]. In the non diabetic individual, the day is divided into 6 distinct periods: postprandial: from 8 to 12 am, from 12 am to 4 pm, and from 7 to 11 pm; post-absorptive: from 4 to 7 pm, and from 11 pm to 5 am; at the end of the night, from 5 to 8 am, the increase in hepatic production of glucose is mainly secondary to hepatic neoglucogenesis.

In reality, if this segmentation is equally true for the stable diabetic, with an HbA1c less than 7%, it is not the case in poorly stabilized diabetic patient with an HbA1c more than 7%. In fact, we observe a gradual loss of “metabolic flexibility”, and an increase in neoglucogenesis, not only at the end of the night, but also persisting at the postprandial period after breakfast [25]. The postprandial glycogenolysis is insufficiently curbed and can last as long as 5 to 6 hours or longer after meals [26], then the postprandial glucose clearance diminishes [27]. Finally, the preprandial glycaemia depends on the preceding meal and is, in a way, a delayed postprandial glycaemia. It is easy to demonstrate this by observing that in patients after 2 days of hospitalisation and a balanced diet, and before any change in treatment fasting glycaemia more often improves dramatically.

It is therefore only necessary to distinguish the preprandial from the postprandial target, if diabetes is well controlled (with an HbA1c less than or equal to 7%), and if one expects an improved result, especially as all oral antidiabetic agents act on preprandial glycaemia and on early postprandial glycaemia. The study by Monnier et al [28] assesses the contribution to preprandial glycaemias above 1.1 g/l and the increase in the postprandial area under curves of glycaemia in the determination of the HbA1c above 6%. When HbA1c is at 7%, 70% of delta of HbA1c (6-1 point) corresponds to postprandial glycaemia and 30% to preprandial glycaemia. Inversely, when HbA1c is around 10%, 70% of delta of the HbA1c (10-6 = 4 points) corresponds to the increase in preprandial glycaemia and only 30% to the increase in postprandial glycaemia.

Schematically, we can calculate that by reducing fasting blood glucose to less than 1.10 g/l, we can gain 0.3 to 0.5 points for an HbA1c at 7%, 1 point for an HbA1c at 8%, 2 points for an HbA1c at 9%, and 3 points for an HbA1c at 10%. In this way, HbA1c can be reduced to around 7%. Nevertheless, by eliminating postprandial hyperglycaemia, 1 point of HbA1c can, in theory, be gained whatever the level of HbA1c. But actually, postprandial hyperglycaemia is not eliminated, but rather decreased, so that we can hope to gain 0.5-0.7 points of HbA1c, as demonstrated with acarbose in the UKPDS study [29].

– In practice, what is the minimal frequency of relevant glycaemia self-monitoring for a type 2 diabetic patient on metformine and with an HbA1c in excess of 6.5%?

In our view, 2 capillary glucose determinations per day are sufficient: fasting glycaemia and evening glycaemia around 6 to 7 pm.

Raised fasting plasma glucose is due to lack in insulin. It justifies therapeutic action with a bitherapy if HbA1c is above 6.5% and then a tritherapy or recourse to “bedtime” insulin if HbA1c becomes higher than 7 or 7.5%, or if fasting plasma glucose is above 1.60 or 1.80 g/l, despite an HbA1c below 7%.

Monitoring of the evening capillary glucose around 6 to 7 pm ensures absence of hypoglycaemia. Its importance is confirmed by the rule of the three 7s proclaimed by Monnier: a glycaemia of 7 mmol/l at 7 p.m. means a predictable HbA1c of 7% [30].

When can patients be asked to monitor their capillary glycaemia more frequently?

In our view, in two situations:

– When there is a discrepancy between glycaemias at 8 a.m. and 7 p.m. and the HbA1c after having confirmed the validity of the capillary glyaemic and the HbA1c results. In our experience, in 53 type 2 diabetic patients, seen consecutively, and “declaring” a fasting glycaemia and a before dinner glycaemia of less than 1.20 g/l, 39 had an HbA1c of less than or equal to 7% and 1 had an HbA1c of 7.1%;

– Finally, in case of “bedtime” insulin failure, defined by an HbA1c of more than 7.5% or 8%, despite a fasting glycaemia of less than 1.20 g/l or very high delayed doses of insulin, above 0.7 units/kg, it would be wise to add a rapid analogue before one of the meals, according to an appraisal of the nycthemeral glycaemic status.

Conclusion

In conclusion, when the objective is to switch from 6.5% to 6%, during pregnancy, for example, or even from 7% to 6.5% in a type 2 diabetic patient, under bi or tritherapy, then the patient must be requested to monitor his postprandial glycaemias 2 hours after the beginning of the meal. If, however, the objective is to bring the HbA1c to around 7%, then the priority is preprandial glycaemias (fasting in the
morning and before dinner in the evening) which are, in fact, only delayed postprandial glycaemias.

**References**