How should postprandial glycemia be treated?

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SUMMARY
In an attempt to prevent the complications of type 2 diabetes, particular attention should be paid to controlling postprandial glycemia (PPG): on the one hand, it contributes substantially to the HbA1c level in moderately controlled patients, on the other hand, the postprandial glucose peak induces oxidative stress and endothelial dysfunction, the first step toward accelerated atherogenesis. Metformin, glitazones, and insulin secretagogues have an additive effect on fasting blood glucose (FBG), and a significant impact on PPG. Alpha-glucosidase inhibitors can reduce PPG by a mean 0.50 g/l, no matter what the insulin resistance or insulinopenia status or the other diabetes treatments already in use. After evolving for several years and the failure of oral antidiabetics to normalize fasting blood glucose, long-acting (slow-acting) insulin analogues, well titrated, can reach this goal. They will have no effect on PPG other than a simple level effect. At this stage, rather than overtreating high fasting blood glucose concentrations, systematic PPG exploration should be the rule so as to better define PPG treatment: the advantages of alpha-glucosidase inhibitors and the role of GLP-1 analogs should be defined, the use of a rapid-acting insulin analog before the meal causing the highest postprandial blood glucose excursions, even systematically at all three meals, should be considered, or inhaled insulin.

As natural life expectancy is on the rise, these active strategies designed to normalize the daily glycemic profile, necessary in a strict strategy to prevent the complications of diabetes, will need to be discussed for an increasing number of patients with type 2 diabetes.

Key-words: Type 2 diabetes mellitus · Postprandial glycemia · Metformin · Thiazolidinediones · Sulfonylureas · Alpha-glucosidase inhibitors · Insulin.

REGUMÉ
Comment traiter la glycémie postprandiale ?
Dans une stratégie de prévention des complications du diabète de type 2, une attention particulière devrait être portée à la maîtrise des glycémies postprandiales (GPP) : d’une part, elle contribue de façon importante au niveau d’HbA1c, chez les patients modérément déséquilibrés, d’autre part, le pic hyperglycémique postprandial induit stress oxydatif et dysfonction endothéliale, première étape vers une athérogenèse accélérée. La metformine, les glitazones et les sécrétagogues insuliniques ont un effet additif sur les glycémies à jeun (GAJ), et un impact significatif sur les GPP. Les inhibiteurs des alpha-glucosidases permettent de réduire de 0,50 g/l en moyenne les GPP, quel que soit l’état d’insulinorésistance ou d’insulinopénie, ou les autres traitements du diabète déjà utilisés. Après plusieurs années d’évolution et l’échec des antidiabétiques oraux à normaliser la GAJ, les analogues de l’insuline de longue durée d’action (« lente »), bien titrés, atteindront ce but. Ils seront sans effet sur les GPP, autre qu’un simple effet de niveau. À ce stade, plutôt que de « surtraiter » la GAJ, une exploration systématique des GPP devrait être de règle, afin d’en mieux définir leur traitement : intérêt des inhibiteurs des alpha-glucosidases à envisager, rôle des analogues du GLP-1 à définir, ou utilisation d’un analogue rapide de l’insuline avant le repas le plus hyperglycémiant, voire systématiquement lors des trois repas, ou encore d’insuline inhalée par voie pulmonaire.

L’espérance de vie naturelle s’allongeant, ces stratégies actives de normalisation du profil glycémique nycthéméral, nécessaires dans le cadre d’une stratégie stricte de prévention des complications du diabète, devraient être discutées pour un nombre de plus en plus grand de patients atteints de diabète de type 2.

Mots-clés : Diabète de type 2 · Glycémie postprandiale · Metformine · Thiazolidinediones · Sulfonylurées · Inhibiteurs des alpha-glucosidases · Insuline.
Following information from studies such as the UKPDS (United Kingdom Prospective Diabetes Study), it is now universally admitted that to prevent the complications of type 2 diabetes requires good overall glucose control, which is defined by an HbA1c level lower than 7% or less than 6.5%, depending on the guidelines. Many other parameters should also be taken into account, particularly for macrovascular complications: high blood pressure, dyslipidemia, smoking, etc. However, the HbA1c level is only the sum of fasting blood glucose (FBG) and postprandial glycaemia (PPG) and therefore gives an overall assessment that may be inadequate. The ideal would undoubtedly be to aim for a normalization of the patient’s glycemic profile: FBG is regularly taken into account because it is used to adapt daily pharmacological treatment. The same should be done for PPG for two reasons:

- in patients presenting type 2 diabetes who are treated with oral antidiabetic drugs (OADs), PPG is an even more important component of HbA1c when the latter is not too high. PPG accounts for 70% of residual chronic hyperglycaemia when HbA1c is less than 7.3% [1];
- whatever the HbA1c level, poorly controlled postprandial glucose peaks, even brief with little impact on HbA1c, create an endothelial dysfunction that is known to be the first step toward an accelerated atherogenic process. There are now several epidemiological arguments and a few arguments from therapeutic interventions that prove this [2].

This article attempts to describe the different therapeutic tools now available to control PPG. We will successively describe the treatments targeting basal hyperglycaemia, then the sulfonylureas (SU), and finally the treatments targeting postprandial hyperglycaemia.

**Treatments targeting basal (fasting) glycaemia**

Three classes of medications target basal (fasting) glycaemia. They are reputed to have almost no effect on PPG [3], other than a simple lowering through a level effect: metformin, thiazolidinediones (TZDs) or glitazones, and long-acting insulins, also called slow-acting insulins.

**Metformin**

Metformin, a drug that is recommended in first-line treatment when diet and physical activity are not enough to maintain the HbA1c level at or below 6%, improves insulin resistance mainly by decreasing hepatic glucose production. The gain in terms of HbA1c level can be 1-2%, resulting from reduced fasting glucose levels. Metformin is reputed to be without effects other than a level effect on PPG [4]. Actually, in a pharmacodynamics study, a single prandial dose of 1,700 or 2,550 mg of metformin significantly reduced PPG by 0.19 and 0.31 g/l compared to placebo. After administering several doses (850 mg t.i.d. for 5 days), hyperglycaemia dropped significantly compared to placebo, by 0.31 g/l fasting but by double that in postprandial measures (0.60 g/l) [5]. There is a linear relation between how much PPG decreases and the FBG level. In clinical practice, it may be that metformin has an effect on PPG nearly as great as the effect of acarbose, a specific treatment for postprandial hyperglycaemia. After randomization, the ESSEN II Study compared the respective efficacy of 850 mg b.i.d./day of metformin and 100 mg t.i.d./day of acarbose vs placebo in 96 poorly controlled type 2 diabetics. After 24 weeks of treatment, the drop in PPG in both treatment groups was significantly greater than in those who received placebo, but was not different between the two groups (–0.40 g/l for acarbose and –0.35 g/l for metformin). The reduction in fasting glucose levels and HbA1c levels was identical in the two treatment groups [6]. In a similar study, metformin was compared to repaglinide, a drug that is also reputed to act mainly on PPG. The study was conducted in 112 type 2 diabetics in whom dietary treatment alone had failed (HbA1c > 7%) and randomized to receive either metformin (1,500-2,500 mg/day) or repaglinide (2-4 mg/day). After 1 year of treatment, PPG improvement was double that obtained for fasting glucose in the two groups (respectively, 1.2 mmol/l and 0.6 mmol/l in the metformin group, and 1.6 mmol/l and 0.8 mmol/l in the repaglinide group). The improvement was slightly but significantly higher for repaglinide (p<0.05), but overall the gain on the HbA1c level was not different between the two groups [7].

**Thiazolidinediones**

Thiazolidinediones (TZDs) reduce insulin resistance by improving peripheral utilization of glucose and reducing neoglucogenesis and lipolysis. In monotherapy, rosiglitazone or pioglitazone, at maximal doses, reduces FBG by 0.62-0.76 g/l and HbA1c level by 1.5-1.6% [8]. This class of drugs has no specific added effect on PPG other than a simple level effect [3]. In a study comparing troglitazone (a TZD now taken off the market) and metformin as monotherapy, the PPG reduction following a test meal after 3 months of treatment was 50% higher than the decrease obtained for FBG, identical for both treatments: respectively, 0.87 g/l and 0.58 g/l for troglitazone and 0.83 g/l and 0.54 g/l for metformin [9]. In a large study investigating 1,199 type 2 diabetic patients with poorly controlled diabetes, comparing pioglitazone and metformin administered in monotherapy over 1 year, the improvement in the HbA1c level was identical for the two treatments (–1.4% and –1.5%, respectively), with a slight advantage for pioglitazone on FBG and PPG. An oral glucose tolerance test (OGTT) was performed at the beginning and at the end of the study to 382 patients, equally distributed into the two groups. The area under the insulin curve (AUC0-3h), was identical at the beginning of the study (348 vs 362 mg.h/dl). After 1 year of treatment, the decrease in the AUCp was twice greater in the pioglitazone group (–90 mg.h/dl) than in the metformin group (–41 mg.h/dl; p < 0.001) [10]. The same effect was reported in similar
studies (the Quartet studies) with better results with pioglitazone than with glimepiride, with pioglitazone combined with SUs compared to metformin combined with SUs, or with pioglitazone combined with metformin compared to a combination of glimepiride and metformin [11].

Therefore, it seems that drugs aimed to treat insulin resistance, metformin and TZD, which are believed to have no effect on PPG, in fact lower PPG in absolute value more than they lower fasting glucose levels. This effect seems to be of the same magnitude or slightly less than the effect observed with the other classes of drugs that are believed to be active on PPG, such as alpha-glucosidases inhibitors (AGI) or glinides.

Long-acting (slow-acting) insulins

The only pharmacological class that acts only on basal glycemia, with only a level effect on PPG, is long-acting (or slow) insulins. This has been demonstrated with the insulin glargine: the LAPTOP study compared an injection of insulin glargine in the morning + OAD with an injection morning and evening of premixed 30/70 insulin, in patients whose the associated therapy of metformin and a sulfonylurea had failed.

In this study, in addition to the OADs (mean, glimepiride 3.4 mg/day and metformin 1,900 mg/day), 177 patients received insulin glargine in the morning (mean, 28 UI/day). After 24 weeks of treatment, fasting glucose levels decreased from 1.71 g/l to 1.15 g/l, a mean decrease of 0.56 g/l. The mean decrease in PPG 2 h after the three meals, measured during two consecutive 24-h glycemic cycles, was never higher than this mean decrease in fasting blood glucose [12].

Sulfonylureas

Sulfonylureas (SUs) bind to SUR-1 membrane receptors of β-pancreatic cells and thus stimulate the secretion of insulin in fasting periods as well as during meals. In monotherapy, they increase the HbA1c level by 1.0%–1.9% compared to placebo [13]. They have a clear effect on fasting blood glucose and a more powerful effect in absolute value compared to placebo [13]. They have a clear effect on fasting blood glucose levels with metformin monotherapy, substituting metformin with glimepiride significantly improves PPG (−0.22 g/l, p = 0.029); however, the improvement is not significant for FBG. In cases of failure with metformin, the best strategy seems to be to combine the two classes of drugs [15].

Treatments targeting postprandial glycemia

Four drug classes act specifically on PPG: alpha-glucosidase inhibitors (AGIs), glinides, rapid-acting insulins, and glucagon-like peptide-1 (GLP-1). However, before pharmacology, the first factor influencing PPG is the amount of glucides in the meal. Modelization of the hyperglycemic effect of carbohydrates is well known in type 1 diabetes [16, 17]. Postprandial hyperglycemia can be calculated using the following formula: PPG = FBG + 2.40 × carbohydrates (g)/weight (kg). Proteins and fats should undoubtedly also be taken into account. The most frequently suggested basis for estimation considers that 60% of proteins and 10% fats will be transformed into glucose after digestion [18]. One should also take into account the indirect effect of proteins on glucose levels, via the stimulation of glucagon secretion [19]. This type of simulation has yet to be elaborated in type 2 diabetes, but it is now admitted that the carbohydrate-calorie reduction remains the foremost means to reduce postprandial glucose excursion.

Alpha-glucosidase inhibitors

AGIs act specifically on PPG by slowing down the digestion of oligosaccharides, thus leveling off the prandial glycemic peak. This phenomenon is amplified by the slowing down of gastric emptying and the increase and prolongation of GLP-1 secretion.

Effects of AGIs on blood glucose control

The glucose-lowering effect in type 2 diabetes of the AGIs has been widely studied, mainly with acarbose. Lebovitz’s 1998 review [20], compiled 13 randomized, double-blinded studies, totaling 1,094 patients who were treated either with placebo or acarbose (100 mg t.i.d./day in nine studies, 150-900 mg/day for the other studies). The majority of these studies lasted 24 weeks, and from 16 to 104 weeks for the others. Overall, these studies reported a mean PPG reduction of 0.54 ± 0.16 g/l. The effect on FBG was more modest, but significant (0.24 ± 0.07 g/l). The mechanism of action remains uncertain: it could be related to the improvement demonstrated in insulin resistance, induced by improved postprandial metabolism [21–23]. The increase and prolongation of GLP-1 secretion could also be involved [24]. The overall effect on chronic hyperglycemia is a mean reduction of the HbA1c level of 0.90 ± 0.25%. Other studies have confirmed these results: Fischer et al. [25] included 495 patients, randomized into five arms (placebo, 25, 50, 100, and 200 mg acarbose t.i.d.) and treated for 24 weeks, showed a dose-effect relation with a 11–22% PPG reduction, for a decrease of 0.42–1.09% in the HbA1c level. A recent meta-analysis provided similar results (drop in glucose levels 1 h after glucose load of 0.42 g/l, i.e. very slightly better than sulfonylureas, and of 0.20 g/l in FBG) [26].

When oral monotherapy fails, adding acarbose as a bitherapy provides a similar improvement as when acarbose is administered in monotherapy. The results of 14 randomized studies showed a mean reduction of the HbA1c level of 0.89% compared to placebo when acarbose is combined with metformin, 0.88% when it is combined with SUs, and 0.54% when it is combined with insulin. This gain is essentially the...
result of reducing PPG: a mean of 0.51 g/l when combined with metformin, 0.54 g/l in combination with SU, and 0.48 g/l in combination with insulin [2].

**Impact of acarbose treatment on the progression of atherosclerosis and the incidence of cardiovascular complications**

We have available data for patients with impaired glucose tolerance and patients presenting with an established diabetes.

The progression in carotid intima/media thickness (IMT) was measured in a subgroup of patients in the STOP-NIDDM (Study TO Prevent Non-Insulin Dependent Diabetes Mellitus) [27]. In this study, 56 patients with impaired glucose tolerance received acarbose and 59 received a placebo. After 3.9 years, the increase in carotid IMT was significantly lower (0.02 ± 0.07 mm) in patients in the acarbose group compared to those in the placebo group (0.05 ± 0.06 mm, p = 0.027). Annual progression of carotid IMT was also lowered by approximately 50% and brought within the mean ranges observed in nondiabetic subjects. This improvement remained significant after multivariate analysis integrating sex, BMI (body mass index) variations, heart rate, and HDL-cholesterol and total cholesterol levels.

The STOP-NIDDM study was initially designed to demonstrate in patients with impaired glucose tolerance, and treated with acarbose vs placebo, a reduced progression toward established type 2 diabetes, which in fact was shown in this study [28]. However, this study also created the surprise by showing a considerable decrease in cardiovascular events [29]. The study investigated 1,368 patients presenting 2 h after a 75 g-oral glucose load, a plasma glucose level between 1.40 g/l and 2 g/l, and FBG between 1 g/l and 1.40 g/l. After randomization, they were treated with either placebo or acarbose (mean dose, 194 mg/day for 3.3 years), taken before each meal. Of these patients initially classified as having impaired glucose tolerance, 135 had initial FBG between 1.26 g/l and 1.40 g/l, and were therefore classified later as “diabetic” due to the changes in the international norms adopted 2 years after the beginning of the study. However, this terminology problem changed nothing in terms of results: patients treated with acarbose showed a significant reduction of 49% in cardiovascular events, all causes combined, with an absolute risk reduced by 2.5%. The effect was more pronounced for myocardial infarction, for which the relative risk decreased by 91% and the absolute risk by 2.9%. Therefore, treating 34 patients for the study duration (3.3 years) prevent one myocardial infarction.

The MERIA meta-analysis [30] reviewed seven studies investigating type 2 diabetes, treated in double-blind after randomization, with acarbose or placebo. There were at least 50 patients per study, treated for a minimum of 52 weeks. The patients’ mean age was 61 years and they had known diabetes for a mean of 6.4 years (acarbose) and 7.0 years (placebo). Cardiovascular events were individualized among the adverse events reported during these studies according to the COSTART terminology. This meta-analysis was based on 2,180 patients treated for a mean of 1.9 years. The results obtained were quite close to those observed during the STOP-NIDDM study: there were 35% fewer cardiovascular events in patients treated with acarbose compared to those receiving placebo (p < 0.0061). The absolute risk was reduced by 3.3% and 30 patients had to be treated for the study duration (1.9 years) to prevent one cardiovascular event. As in the STOP-NIDDM study, the results were particularly good for myocardial infarction, reduced by 64% in patients treated with acarbose compared to those receiving placebo. However, one study’s results were not in agreement: this was an ancillary study of the UKPDS, conducted at the end of the UKPDS, investigating a subgroup of the patients of the UKPDS cohort. Acarbose was proposed late in the UKPDS – a mean of 8 years after their inclusion in the UKPDS – to the 3,309 patients who were still in the study; 40% of them refused or could not be included. The others, 1,946 patients, in addition to all the other treatments, received either a placebo or acarbose (before the three meals) for an additional 3 years. These patients had had diabetes for a slightly longer duration than those in the MERIA meta-analysis and 38% of them received insulin. At the end of the study, the intent-to-treat analysis showed only a 0.2% reduction in the HbA1c level. The results on cardiovascular event incidence have not yet been published, but apparently, there was no significant difference. It must be noted that at the end of the 3 additional years, patient compliance was disastrous: only 39% of patients in the acarbose group were still taking the drug. Digestive tolerance was not the main cause of this poor compliance, but rather the lack of motivation after such a long study, as evidenced by the fact that in the placebo group, 42% of the patients were no longer taking their medication. This explains the disappointing results of this study.

**Glinides**

Unlike the SUs that act throughout the day and night, glinides are insulin secretagogues acting mainly during prandial periods. Repaglinide seems to have a slightly better effect on PPG than glibenclamide (glyburide), but it has less effect on FBG. There is one intervention study available conducted with these two drugs that has evaluated the impact of a specific reduction in PPG on the progression of atheroma estimated based on carotid IMT [31], conducted in 175 drug-naive type 2 diabetics. After randomization, these patients were treated with either repaglinide or glibenclamide. After 1 year of treatment, the postprandial glucose peak, initially identical in the two groups (2.24 g/l and 2.31 g/l, respectively) was significantly lower in the repaglinide group (– 0.24 g/l; p < 0.001). Inversely, the initially near identical FBG (1.59 g/l and 1.63 g/l, respectively) was significantly less reduced in the repaglinide group (– 0.24 g/l) than in the glibenclamide group (– 0.32 g/l; p < 0.001). Consequently, overall the HbA1c level improved nearly identically (– 0.9% and – 0.8%, respectively).
particular for IL-6 [34] and CRP [35]. On the other hand, CRP, whose atherogenic role is also clearly substantiated, in part prevents the development of atheroma.

The postprandial glucose peak, and to a lesser degree with the decrease in the HbA1c level and CRP concentration. It is true that this study does not have the weight of the preceding studies testing acarbose discussed above, in that it did not measure clinical cardiovascular events. However, acarbose is an intermediary substitution criterion whose relation to cardiovascular complications, particularly coronary complications, has been validated [32]. The gain in IMT in this study, reflects of atheromatous macroangiopathy, seems closely related for the most part to improvement of the postprandial glucose peak and its impact on improvement of pro-inflammatory factors [33] whose atherogenic role is also clearly substantiated, in particular for IL-6 [34] and CRP [35].

Rapid-acting insulins

Rapid-acting insulins remain the absolute weapon in prandial glucose control after failure of oral therapies. They also provide an indirect benefit on FBG. For example, 25 patients presenting with type 2 diabetes and with SU monotherapy failure were randomized, in a crossover design study, either to the rapid-acting insulin analog lispro before each meal or to continuation of their previous SU treatment. Insulin titration was not strict in this study because after 4 months of treatment with insulin lispro, PPG, which was initially of 3.30 g/l with SUs alone, had indeed decreased, but remained at 2.58 g/l after insulin lispro. Nevertheless, this PPG improvement of 0.80 g/l was accompanied by a FBG improvement of 0.44 g/l and a 1.9% decrease in the HbA1c level, which was lowered from 9.0% to 7.1% [36]. Another investigation studied 16 obese type 2 diabetics (mean BMI, 31 kg/m²), treated with two injections of NPH insulin or two injections of premixed insulin after OAD failure. They were randomized to either continue this treatment, intensifying it if possible, or to receive triple therapy consisting of metformin and/or a SU, a GLP-1 analog, exenatide, or a GLP-1 agonist, vildagliptin (a dipeptidyl-peptidase 4 inhibitor), after 1 year of treatment, significantly improved PPG by 0.40 g/l compared to placebo. It also improved FBG by 0.16 g/l. The overall result was a 1.0% improvement in the HbA1c level [38]. In another investigation studying patients with insufficient glucose control using monotherapy or a bitherapy with metformin and/or a SU, a GLP-1 analog, exenatide, at a dose of 0.08 µg/kg/day in two or three subcutaneous injections, after 4 weeks of treatment resulted in a PPG improvement of 0.47-0.69 g/l depending on the times and number of injections, compared to placebo [39]. In the meantime, FBG was only lowered insignificantly (0.02-0.11 g/l). Finally, another study compared exenatide and insulin glargine in 551 patients for whom a bitherapy combining metformin and a SU had failed (mean HbA1c, 8.3%). Adding two daily 10-µg injections of exenatide (without glucose self-monitoring blood glucose being necessary) to the OAD was compared to adding an injection of insulin glargine, which required titrating the dose according to self-monitoring blood glucose, especially in the morning, until patients reached a FBG level under 1.0 g/l. After 26 weeks of treatment, the reduction obtained in the HbA1c level was identical in both groups (1.11%). Daily blood glucose profiles showed that the glucose levels were identical in the two groups: from 1.84 g/l at T0 to 1.46 g/l after exenatide, and from 1.82 g/l to 1.44 g/l after insulin glargine. However, the benefit of exenatide was obtained mostly by a normalization of PPG, with FBG only decreasing by 0.22 g/l, whereas insulin glargine acted by decreasing FBG to values close to normal, leaving postprandial blood glucose excursion unchanged [40]. GLP-1 agonists or analogs therefore appeared to be excellent treatments for PPG, provided that insulin secretion persisted. After OAD failure, the alternative could very well not be choosing between a GLP-1 analog or glargine insulin but rather combining these two treatments, given their complementary mode of action, at least if normalization of the blood glucose profile and not simply improvement of HbA1c is sought.

**GLP-1 antagonists or analogs**

GLP-1 antagonists or analogs increase insulin secretion induced by glucose, reduce hyperglucagonemia, and slow down gastric emptying. They have a direct effect mainly on PPG improvement. In type 2 diabetics who do not achieve sufficient glucose control with metformin, adding vildagliptin (a dipeptidyl-peptidase 4 inhibitor), after 1 year of treatment, significantly improved PPG by 0.40 g/l compared to placebo. It also improved FBG by 0.16 g/l. The overall result was a 1.0% improvement in the HbA1c level [38]. In another investigation studying patients with insufficient glucose control using monotherapy or a bitherapy with metformin and/or a SU, a GLP-1 analog, exenatide, at a dose of 0.08 µg/kg/day in two or three subcutaneous injections, after 4 weeks of treatment resulted in a PPG improvement of 0.47-0.69 g/l depending on the times and number of injections, compared to placebo [39]. In the meantime, FBG was only lowered insignificantly (0.02-0.11 g/l). Finally, another study compared exenatide and insulin glargine in 551 patients for whom a bitherapy combining metformin and a SU had failed (mean HbA1c, 8.3%). Adding two daily 10-µg injections of exenatide (without glucose self-monitoring blood glucose being necessary) to the OAD was compared to adding an injection of insulin glargine, which required titrating the dose according to self-monitoring blood glucose, especially in the morning, until patients reached a FBG level under 1.0 g/l. After 26 weeks of treatment, the reduction obtained in the HbA1c level was identical in both groups (1.11%). Daily blood glucose profiles showed that the glucose levels were identical in the two groups: from 1.84 g/l at T0 to 1.46 g/l after exenatide, and from 1.82 g/l to 1.44 g/l after insulin glargine. However, the benefit of exenatide was obtained mostly by a normalization of PPG, with FBG only decreasing by 0.22 g/l, whereas insulin glargine acted by decreasing FBG to values close to normal, leaving postprandial blood glucose excursion unchanged [40]. GLP-1 agonists or analogs therefore appeared to be excellent treatments for PPG, provided that insulin secretion persisted. After OAD failure, the alternative could very well not be choosing between a GLP-1 analog or glargine insulin but rather combining these two treatments, given their complementary mode of action, at least if normalization of the blood glucose profile and not simply improvement of HbA1c is sought.
Conclusion

Preventing complications is the major issue in treating diabetes. The HbA$_1c$ level remains the unavoidable key to good overall blood glucose control, but it is perhaps insufficient. Certain markers of oxidative stress, a determining step of vascular alterations, are perfectly correlated with daily rhythm glucose fluctuations whose acute postprandial glucose rise is the first cause in type 2 diabetes; but these markers are not correlated with the HbA$_1c$ level [41]. Particular attention should now be paid to these fluctuations [42]. In clinical practice, self-monitoring of blood glucose will make it possible to evaluate the impact of treatments on these daily fluctuations, in particular postprandial fluctuations.

A number of pharmacological agents are now available; their effects are additive not only on FBG, but also on PPG. Metformin, TZDs, and the SUs, all have a significant impact on PPG. A particular interest should again be given to AGIs; indeed, because of its mode of action, this class of drugs reduces PPG by a mean of 0.50 g/l whatever the insulin resistance or insulinopenia status is, or the other treatments already used. With OAD failure, when metformin, TZDs, and/or SUs become incapable of limiting the hepatic production of glucose and FBG increases, the logical and effective treatment is the long-acting (slow-acting) insulin analog, properly titered to normalize fasting morning glucose concentration. However, this strategy leaves PPG unchanged. It is for this very reason that as a general rule FBG should be “overtreated”. After OAD treatment failure, adding insulin glargine can provide a mean HbA$_1c$ level of 7% (and not 6%), provided that a mean FBG level of 1.0 g/l is achieved; for FBG at 1.20 g/l, the HbA$_1c$ level will be 7.4%, and for a mean FBG of 1.40 g/l, the HbA$_1c$ level will be 7.9% [43]. PPG should be systematically explored at this stage to discuss the therapeutic addition that may be necessary. The advantage of AGIs should be re-examined, and the place of GLP-1 analogs needs to be defined. If not, the rapid-acting insulin analogs (while waiting for the inhaled insulins to be marketed) should be discussed at an earlier stage, to provide a chance to prove the efficacy of a progressive “basal + 1” type of strategy, i.e., one injection of a rapid-acting insulin analog before the most hyperglycemic meal, then later two and then three injections when necessary. Studies to evaluate this strategy approach are in progress. Whatever strategy is chosen, the increasingly early age of onset of type 2 diabetes must be taken into account, given that the population’s life expectancy is lengthening: at 75 years of age, life expectancy in France is nearly 11 years for men and nearly 14 years for women (source: INSEE). We should therefore have even more ambitious metabolic objectives for our patients with type 2 diabetes.

References


