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Should Postprandial Hyperglycaemia in Prediabetic and Type 2 Diabetic Patients be Treated?

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Abstract

Numerous prospective studies support the concept of postprandial glycaemia (PPG) as a risk factor for cardiovascular diseases (CVDs) in individuals with impaired glucose tolerance (IGT). A meta-analysis has demonstrated an exponential relationship between 2-hour postchallenge glucose levels and the incidence of CVD. This relationship is stronger than those observed with fasting glycaemia or glycosylated haemoglobin (HbA_{1c}), and persists after adjustment for other vascular risk factors. Although there are fewer data available for the diabetic population, those that are available also support PPG as a risk factor for CVD. Treating PPG with acarbose is associated with a reduction in cardiovascular events in both patients with IGT and diabetes mellitus. Acarbose also reduces the progression of intima-media thickness (IMT), which is a surrogate endpoint for atherosclerosis. It has been suggested that the beneficial effect could be related to an improvement in postprandial hyperglycaemia and associated atherogenic factors – oxidative stress, endothelial dysfunction and procoagulation factors – and to an improvement in other cardiovascular risk factors such as systolic blood pressure (by decreasing water and salt absorption), postprandial hypertriglyceridaemia and insulin resistance. Treating PPG with glinides improves IMT as well as interleukin-6 and C-reactive protein levels, while treating PPG with rapid-acting insulin analogues is also associated with improvements in endothelial dysfunction. The Kumamoto study suggests that reduced PPG is strongly associated with reductions in retinopathy and nephropathy. Finally, decreasing PPG in patients with IGT reduces the progression of diabetes.

In conclusion, physicians should increase efforts to control PPG in order to further improve HbA_{1c}, and should also ensure close control of postprandial hyperglycaemic peaks so as to optimise patients' chances of avoiding cardiovascular complications. As for the prevention of CVD, further prospective intervention trials, powered to answer this question, are still required.

The relationship between moderate chronic hyperglycaemia, assessed by glycosylated haemoglobin A1c (HbA_{1c}), and microvascular complications has been clearly established in type 2 diabetes mellitus, and it has been shown that these complications may be prevented by good glycaemic control.[1] However, many questions remain unanswered about macrovascular complications. The

UKPDS (UK Prospective Diabetes Study) showed a linear relationship between HbA_{1c} values and the incidence of myocardial infarction;[2] intensive treatment for chronic hyperglycaemia resulted in a mean decrease in HbA_{1c} of 0.9% over the 10-year study period, leading to a 16% reduction in myocardial infarction, which was at the limit of statistical significance ($p = 0.052$). Adjustment of hypoglycaemic medication was only based on fasting glycaemia (FG) and not on postprandial glycaemia (PPG) in the UKPDS.[1]

There are also unanswered questions regarding the remarkable results of the Kumamoto study,[3] in which, unlike the UKPDS, patients followed a more intensive treatment regimen with an insulin injection before each meal and dosage adjustment based not only on FG and HbA_{1c} values but also on PPG with a target of <2.0 g/L. In this case, not only was there a significant reduction in microvascular complications, as during UKPDS, but also an improvement of almost 50% in macrovascular complications. This trend did not reach statistical significance as the sample size was very small in comparison with UKPDS (110 vs 3867 patients). Were these results a nonsignificant, random event or a real trend that the small sample size was unable to confirm? The same trend was observed in the DCCT (Diabetes Control and Complications Trial) and to the same extent (41% reduction in macrovascular complications).[4] The threshold of significance was not reached because of the small number of cardiovascular events, as could be expected in this young population. Once again, preprandial insulin doses were adjusted to achieve PPG values <1.80 g/L.[4]

No large-scale interventional studies have as yet been conducted with the primary objective of reducing cardiovascular complications by treatment specifically aimed at reducing PPG values. However, numerous experimental studies have demonstrated the potential atherogenic role of postprandial glycaemic peaks. Numerous epidemiological studies have also demonstrated the link between postprandial hyperglycaemia and cardiovascular morbidity and mortality, and other interventional studies have suggested the value of a therapeutic strategy focusing not only on the control of global hyperglycaemia and FG but also on the specific control of PPG values. Both these aspects are discussed in this article.

1. Relationship between Postprandial Glycaemia (PPG) Values and Cardiovascular Diseases: Epidemiological Data

Numerous prospective studies have been carried out in populations that have excluded known diabetic individuals but included either healthy or 'dysglycaemic' individuals with moderate fasting hyperglycaemia or impaired glucose tolerance (IGT), or individuals meeting the criteria for diabetes but with hitherto unrecognised moderate hyperglycaemia. These studies did not take PPG values into account, only glycaemia after a glucose challenge, usually 2 hours after 75g of glucose (2hPG). Although a glucose challenge test is not equivalent to a meal containing carbohydrates, lipids and protein, a strong correlation has been demonstrated ($r > 0.90$) between peak glycaemia values after a mixed meal and after an oral glucose loading dose.[5]

Twenty-nine studies were published between 1979 and 1995. These studies were reviewed by Coutinho et al.[6] and 20 were included in a meta-analysis which included 95 783 subjects, followed on average for 12.4 years, to obtain a total of 1 923 231 patient-years presenting 3707 cardiovascular events, including 3074 deaths. An exponential relationship was demonstrated between the incidence of cardiovascular events and FG or 2hPG. This relationship was stronger with 2hPG; if diabetic subjects diagnosed on inclusion with FG >7.8 or 2hPG ≥11.1 mmol/L were excluded, the relationship no longer reached the threshold of significance for FG ($p = 0.056$) but remained highly significant for 2hPG ($p = 0.00064$). These conclusions have certain limits as most studies only included men who were middle aged on inclusion (18 of 20 studies). As no individual data were available, no adjustment could be made for other cardiovascular risk factors. However, the significant link with cardiovascular events was still observed in only 5 of the 14 studies that

Table I. Relative risk of cardiovascular (CV) or coronary heart disease (CHD) mortality in patients with elevated postprandial glucose levels: results from seven population-based studies

Study	Population; age (y)	Duration of follow-up (y)	Relative risk
Hoorn Study[8]	2363 Dutch males and females; 50–75	8	CV mortality: 3.3 in patients with 2hPG ≥11.1 mmol/L vs normoglycaemic patients
Shaw et al.[9]	9179 males and females from Mauritius, Fiji and Nauru; >20	5–12	CV mortality: 2.6 in patients with 2hPG ≥11.1 mmol/L vs normoglycaemic patients
Honolulu Heart Program[11]	8006 Japanese American males; 45–68	23	CHD mortality: 2.01 in patients with 1hPG ≥11.1 mmol/L vs normoglycaemic patients
Rancho Bernado Study[12]	1704 males and females; 50–89	7	CV mortality: 2.6 in women with 2hPG ≥11.1 mmol/L vs normoglycaemic women
Cardiovascular Health Study[13]	4515 American males and females; >65	8	CV mortality: 1.22 in glucose intolerant vs normoglycaemic patients
Chicago Heart Association Detection Project in Industry Study[14]	11 554 White and 666 Black males; 35–64	22	CV mortality: 1.18 in White males with 2hPG ≥11.1 mmol/L vs normoglycaemic White males

hPG = hours post-glucose challenge.

made this adjustment, (2 with FG and 3 with post-challenge glycaemia); this discrepancy may be due to the limited number of subjects. This problem of sample size can be avoided by meta-analysis such as the DECODE (Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe) study,[7] which confirms the strong relationship between PPG and cardiovascular disease (CVD) [see later in this section].

Since 1995, several major studies have been published that clarify and modulate these findings (table I). The Hoorn Study[8] followed Dutch men and women for 8 years. After adjustment for standard vascular risk factors, the relative risk (RR) of cardiovascular mortality was 3.3 in patients with 2hPG ≥11.1 mmol/L compared with normoglycaemic subjects. Similar results were observed in radically different populations and environments. In one study, more than 9000 Mauritians, Fijians and Nauruans[9] were followed for 5–12 years. The RR of death from cardiovascular causes was 2.3 for men and 2.6 for women with 2hPG ≥11.1 mmol/L but normal FG compared with normoglycaemic subjects. The Funagata Diabetes Study[10] followed a Japanese population for 7 years. The RR of death from cardiovascular causes was 2.22 in subjects with IGT compared with normally tolerant subjects. Similar results were found in >8000 Japanese individuals living in the US[11] who were followed for 23 years. The RR of coronary heart disease mortality in patients with 2hPG >11 mmol/L was 2.01 compared with normoglycaemic subjects. In the Rancho Bernado Study,[12] subjects with FG <7 mmol/L were followed for 7 years. The RR of death from cardiovascular causes was 2.6 in women with 2hPG ≥11.1 mmol/L but this link was not found in men. During the Cardiovascular Health Study the RR for cardiovascular disease was lower but remained significant: 1.22 in participants with IGT versus those with normal tolerance.[13] In the Chicago Heart Association Detection Project in Industry Study, there was a small but significant risk of death from cardiovascular causes in White men presenting with glycaemia >11.1 mmol/L after a glucose challenge (RR = 1.18) compared with subjects with values ≤8.9 mmol/L after this challenge.[14] A similar trend was seen in Black men but this did not reach statistical significance, probably because of the limited number of subjects. These data are summarised in table I.

The Paris Prospective Study,[15] conducted in 7018 men aged between 44 and 55 years, was re-

cently re-assessed after a 17-year follow-up period. In individuals with baseline FG values <6.1 mmol/L, the hazard ratio (HR) for death from all causes was 1.92 if 2hPG values were between 7.8 and 11.1 mmol/L, and 4.29 if the value was >11.1 mmol/L (although the latter subjects were a minority comprising only 0.6% of the sample population). In contrast, this difference was no longer present in subjects with FG values ≥7 mmol/L and the HR was always slightly higher than 2 whatever the postchallenge glycaemia value. However, this concerned the risk of death from all causes and cancer accounted for many fatalities. The link was much smaller or even non-existent if only deaths from cardiovascular causes were considered.

What are the respective contributions of FG and PPG to the cardiovascular risk? This question was evaluated by the Framingham Offspring Study[16] in 3370 subjects without known diabetes, aged from 26 to 82 years (mean 54 years) who were followed for 4 years, during which time 118 cardiovascular events occurred. After adjustment for other vascular risk factors, FG, PPG and HbA_{1c} values were analysed separately and all were found to be significantly correlated with the onset of cardiovascular events. Pooled data showed that only 2hPG was predictive of cardiovascular risk, with an RR of 1.42 per 2.1 mmol/L increment in the model including FG, and an RR of 1.23 in the model including HbA_{1c}. The major role of PPG was confirmed by DECODE,[7] which grouped together ten prospective European studies totalling 22 514 subjects aged 30–89 years, with a median follow-up of 8.8 years. Multivariate analysis showed that the addition of FG values did not significantly improve results obtained with 2hPG, which alone was predictive of the cardiovascular risk; patients with 2hPG ≥11.1 mmol/L had an HR of 1.56 for death of coronary origin and 1.29 for death from stroke.

Thus, in healthy or moderately hyperglycaemic patients without previously known overt diabetes, hyperglycaemia following a glucose challenge was a cardiovascular risk factor, independent of other risk factors and FG levels. As hyperglycaemia after a glucose challenge is strongly correlated with the postprandial glucose peak,[5] the glycaemic peak after meals may be considered to be a major cardiovascular risk factor during daily life, which is independent of other 'traditional' risk factors and should be taken into account in any preventive strategy.

2. The Relationship between PPG and Cardiovascular Complications in Diabetes Mellitus

Fewer data are available on the relationship between PPG and cardiovascular risk in known, treated diabetic patients. The Diabetes Intervention Study[17] was the first study to investigate PPG 1 hour after a meal (in this case, breakfast), rather than glycaemia after a glucose challenge. In 1139 newly diagnosed type 2 diabetic subjects, followed for 11 years, those with PPG >10 mmol/L at inclusion had a 40% greater risk of myocardial infarction than those with values ≤8 mmol/L. Multivariate analysis showed that PPG values 1 hour after breakfast were predictive of death, whatever the cause. A total of 1745 Pima Indians aged 15–88 years with a history of diabetes of 2.5 ± 4.6 years duration were followed for an average of 10.6 years.[18] Independent of other risk factors, 2hPG values were correlated with the onset of CVD and the risk increased 20% with each 5.6 mmol/L increment. In contrast, multivariate analysis on 229 Finnish diabetic individuals[19] aged 65–74 years and followed for 3.5 years showed that neither FG nor PPG were linked to coronary events. The only predictive factors were the duration of diabetes and HbA_{1c} values, with an odds ratio (OR) of 4.3 for death of coronary origin if the initial HbA_{1c} value was >7%. These discrepancies could be due to the small number of subjects in this study. In contrast, for the cohort of 1121 type 2 diabetic subjects followed for 52 months in the Verona study, FG and glycaemia after breakfast or lunch were both predictive of cardiovascular events after adjustment for other risk factors.[20]

These limited data show that PPG may be an important predictive factor for cardiovascular risk in type 2 diabetes and is probably more relevant than FG. However, the relative role of these two parameters has not yet been established.

3. PPG, Atherosclerosis and Diabetes

The relationship between PPG and atherosclerosis may be evaluated before cardiovascular events occur by measuring the carotid intima-media thickness (IMT); this parameter has been shown to be a good predictor of myocardial infarction and stroke.[21] Thus, IMT was measured in 582 normoglycaemic, glucose-intolerant or type 2 diabetic patients.[22] Multivariate analysis showed that the only glycaemic parameter associated with abnormal IMT findings was 2hPG; there was no significant correlation between HbA_{1c} or FG values. When 2hPG was >7.8 mmol/L, the OR for an increased IMT was 1.88.[22] At a more advanced stage, carotid stenosis >50% was looked for in 628 subjects who were normoglycaemic (987), glucose-intolerant (169) or had undiagnosed diabetes (106), as well as 66 known diabetic patients treated with insulin or oral antidiabetics.[23] The prevalence of carotid stenosis ranged from 2.8% to 9.4%, depending on the group. Multivariate analysis showed that HbA_{1c} and 2hPG values were significantly associated with a risk of severe carotid stenosis, with an OR of 1.29 for each 1% increment in HbA_{1c} values and 1.09 for each 1 mmol/L increment in 2hPG. In the Bruneck Study,[24] 826 patients underwent a Doppler ultrasound examination of the carotid arteries before and after 5 years of follow-up. Five years after inclusion, the incidence of carotid stenosis was nearly 3-fold higher in patients with IGT than in those who were normoglycaemic at baseline.

In conclusion, hyperglycaemia observed after meals or a glucose challenge is a much better and more independent marker of accelerated atherogenesis than FG. It is associated with early atherosclerosis, which is easily measurable in the carotid artery and frequently leads to coronary or cerebral events. This has been clearly demonstrated in patients with IGT and is also observed in patients with type 2 diabetes.

4. Impact of the Treatment of PPG on Cardiovascular Complications

This demonstration of a link between PPG values and cardiovascular complications does not imply a causal relationship or that medication targeting PPG will reduce the incidence of cardiovascular events. In this context, data have been obtained using drugs that have the principal effect of lowering PPG values: α-glucosidase inhibitors, glinides and insulin or its rapid-acting analogues. Most clinical data come from studies using α-glucosidase inhibitors and, in particular, acarbose.

4.1 α-Glucosidase Inhibitors

As carbohydrates can only be absorbed by the digestive system in the form of monosaccharides, they must undergo two successive enzymatic digestions. They are first split by amylases into bi-, tri- or oligosaccharides, and then by glucosidases into monosaccharides in the jejunal brush border membrane. Inhibition of α-glucosidase by drugs such as acarbose, miglitol or voglibose causes a more gradual and delayed absorption of carbohydrates in the small intestine, which reduces the height of the postprandial glycaemic peak.[25,26] This phenomenon is amplified by the slower gastric emptying of a mixed meal and prolonged secretion of glucagon-like peptide 1 (GLP-1) induced by α-glucosidase inhibitors. Several studies have demonstrated a significant rise in circulating GLP-1 levels after a test meal combined with acarbose 100mg, compared with placebo, in healthy volunteers[27-29] and in patients with poorly controlled type 2 diabetes.[30] One study gave heterogeneous results in subjects aged >65 years,[31] while another was negative in a small series of ten diabetic subjects.[32] When an elevation of GLP-1 was observed, this was sustained for at least 6 hours after the meal,[30] possibly because of the delayed and prolonged contact of disaccharides with endocrine cells in the distal ileum.[29] Delays were also seen in gastric emptying measured using an isotopic method or using the absorption of paracetamol (acetaminophen) as a marker. This slowing appears to be correlated with an increase in circulating GLP-1 levels.[27] Similar results were obtained with miglitol[33] and voglibose.[34]

The hypoglycaemic effects of this therapeutic class in type 2 diabetes have been widely investigated, mainly with acarbose. The review by

Lebovitz[35] in 1998 collated data from 13 randomised double-blind studies that included a total of 1094 patients treated with placebo or acarbose (100mg three times daily in nine studies, 150–900 mg/day in the others). Most of these studies were for 24 weeks and the others ranged from 16 to 104 weeks. Overall, the mean reduction in PPG values was 0.54 ± 0.16 g/L. There was a smaller but significant effect on FG (0.24 ± 0.07 g/L). The mechanism of this effect is unclear but it may be linked with the demonstrated improvement[36-39] in insulin resistance caused by the improvement in PPG. Increased and prolonged GLP-1 secretion may also be involved.[30] The overall effect on chronic hyperglycaemia was a mean reduction in HbA_{1c} values of 0.90 ± 0.25%. The French National Agency for Health Accreditation and Evaluation (ANAES) report is based on these findings.[40] The French Health Products Safety Agency (AFSSAPS) report[41] also reached the conclusion of a mean reduction in PPG of 0.54 g/L. Other studies have subsequently confirmed these results. The study by Fischer et al.[42] involving 495 patients in five treatment arms (placebo or acarbose 25, 50, 100 or 200mg three times daily), over a 24-week period demonstrated a dose-response relationship with an 11–22% reduction in PPG values, producing a 0.42–1.09% reduction in HbA_{1c} levels. An equivalent therapeutic benefit was observed with miglitol, with reductions in PPG, FG and HbA_{1c} values of 0.46 g/L, 0.21 g/L and 0.81%, respectively (mean reductions for five randomised studies).[35] Voglibose, which is marketed in Asia, seems to have similar, although slightly less pronounced, effects to acarbose.[43]

If oral monotherapy fails to lower PGG levels, two-agent combinations that include acarbose induce an equivalent improvement in PGG values to that observed when this agent is administered alone. Results of 14 randomised, placebo-controlled studies demonstrated mean reductions in HbA_{1c} of 0.89%, 0.88% and 0.54% when acarbose was added on in patients whose type 2 diabetes is insufficiently controlled with metformin,[35,44,45] sulfonylureas[35,46,47] and insulin,[35] respectively. These gains were mainly achieved by a reduction in PPG values with mean reductions of 0.51, 0.54 and 0.48 g/L with metformin, sulfonylureas and insulin, respectively.

4.1.1 Impact of Treatment with Acarbose on Atherosclerosis and Incidence of Cardiovascular Complications

Data are available in patients with IGT and in those with confirmed diabetes. The progression of IMT was measured in a subgroup of patients enrolled in the STOP-NIDDM (Non-Insulin Dependent Diabetes Mellitus) study;[48] 56 glucose-intolerant patients were given acarbose and 59 received a placebo. After 3.9 years, the progression of IMT (0.02 ± 0.07mm) was significantly lower in the acarbose group than in the controls (0.05 ± 0.06mm; $p = 0.027$). The annual progression of IMT values was reduced by approximately 50% and returned to the mean values observed in non-diabetic individuals. This improvement in IMT values remained significant after multivariate analysis integrating sex and variations in body mass index (BMI), heart rate, high-density lipoprotein-cholesterol and total cholesterol.

The STOP-NIDDM study was initially designed to demonstrate a reduction in progression to confirmed type 2 diabetes in IGT patients treated with acarbose versus placebo, and this objective was attained.[49] However, this study unexpectedly demonstrated a considerable reduction in cardiovascular events.[50] The study was conducted in 1368 patients presenting with a 2hPG of 1.40–2 g/L and a FG of 1–1.40 g/L. The patients were randomised to treatment with either placebo or acarbose before each meal (on average, 194 mg/day for 3.3 years). 135 of these initially 'IGT' patients had baseline FG values of between 1.26 and 1.40 g/L and were, thus, subsequently classified as 'diabetic' because of changes to international standards that occurred 2 years after the start of the study. However, this change in terminology did not affect the results; patients treated with acarbose benefited from a significant 49% reduction in all-cause cardiovascular events and a 2.5% reduction in the absolute risk. The effect was more marked for myocardial infarction, where the RR fell by 91% and the absolute risk by

Table II. Reduction in relative risk (RRR) or absolute relative risk (ARR) and number of patients who must be treated during the study to prevent one event in the STOP-NIDDM (Non-Insulin Dependent Diabetes Mellitus) study and MeRIA (Meta-analysis of Risk Improvement under Acarbose) meta-analysis

Study	No. pts	Follow-up	Cardiovascular event			Myocardial infarction		
		(years)	RRR	ARR	NNT	RRR	ARR	NNT
MeRIA[51]	2180	1.10	35%	3.3	30	64%	1.32	75
STOP-NIDDM[50]	1368	3.3	49%	2.5	40	91%	2.9	34

NNT = number needed to treat.

2.9%. Therefore, it was necessary to treat 34 patients for the period of the study (3.3 years) to avoid one myocardial infarction (table II).

The meta-analysis known as MeRIA (Meta-analysis of Risk Improvement under Acarbose)[51] was performed on seven studies involving patients with type 2 diabetes randomly assigned to double-blind treatment with acarbose 50–200mg three times daily or placebo. There were at least 50 patients in each study, treated for a minimum of 52 weeks. The average age of patients was 61 years with a known history of diabetes of 6.4 (acarbose) and 7.0 years (placebo). Cardiovascular events were separated from all other adverse events reported during these studies according to the COSTART terminology. This meta-analysis involved a total of 2180 patients treated for an average of 1.90 years and the results obtained were relatively similar to those observed during the STOP-NIDDM study (table II). There were 35% fewer cardiovascular events in patients treated with acarbose than in those receiving placebo ($p < 0.0061$). The absolute risk was reduced by 3.3%, meaning that it was necessary to treat 30 patients during the study period (1.9 years) to prevent one cardiovascular event. As in the STOP-NIDDM study, particularly good results were obtained for onset of myocardial infarction with a 64% reduction in patients treated with acarbose compared with the placebo group. These results were of the same order of magnitude as those observed in diabetic patients receiving secondary prevention with statins.[52,53] However, they were better than those of the UKPDS study, during which patients who had received 'intensive' therapy had a 16% lower risk of infarction than control subjects at the end of the treatment period (at the limit of significance, $p = 0.052$) and HbA_{1c} values were reduced by 0.9%.[1] In MeRIA, the risk of infarction was reduced by 64% and HbA_{1c} values by 0.6%.[16] However, during the UKPDS, the therapeutic strategy was based solely on FG values with a target of FG <6 mmol/L, and patients received either a sulfonylurea or an injection of ultralente or isophane insulin.[1] In contrast, acarbose acted principally on PPG values in MeRIA, with a mean reduction of 0.42 g/L and a slight reduction in FG values (−0.14 g/L). The remarkable reduction in coronary risk was in all probability due to an improvement in postprandial hyperglycaemia and associated atherogenic factors (oxidative stress, endothelial dysfunction, etc.), and to an improvement in other cardiovascular risk factors (systolic blood pressure [SBP], BMI, postprandial hypertriglyceridaemia, postprandial pro-coagulant factors). This is the only mechanism of action that may explain why similar results were obtained in the STOP-NIDDM study, which included only initially patients with IGT or patients with no or only slight fasting dysglycaemia.

One ancillary study of the UKPDS, which was performed after the main trial in part of the cohort, gave discordant results.[54] Acarbose was proposed at a late stage during the UKPDS to 3309 patients who were still in the study, on average 8 years after their inclusion; 40% refused or were ineligible for inclusion. The remaining 1946 patients received either placebo or acarbose 50–100mg three times daily before each of the three meals, in addition to their other medication, for a further 3 years. These patients had a slightly longer history of diabetes than those in MeRIA and 38% were receiving insulin. At the end of the study, intent-to-treat analysis demonstrated a reduction in HbA_{1c} values of only 0.2%. The results for the incidence of cardiovascular events have not as yet been published, although

apparently they did not demonstrate any significant difference. In fact, after 3 years of treatment, patient compliance was extremely poor and only 39% of patients in the acarbose group were still taking the medication. The main reason for this discontinuation was not gastrointestinal adverse effects, but rather lack of motivation after such a lengthy study, as 42% of the patients in the placebo group were not taking their medication either. Thus, it is easier to understand the disappointing results of this study.

4.1.2 Impact of Treatment with Acarbose on Vascular Risk Factors Other than Glycaemia

There was a 34% reduction in the incidence of new cases of hypertension (>140/90mm Hg) in patients treated with acarbose compared with placebo during the STOP-NIDDM study.[50] The MeRIA meta-analysis demonstrated a slight but significant reduction of 2mm Hg in SBP values in patients receiving acarbose.[51] Two mechanisms may be suggested: a reduction in endothelial dysfunction linked to the lowering of PPG values; and/or a reduction in postprandial water and salt absorption induced by acarbose, previously demonstrated in healthy volunteers.[55]

Other changes that may also contribute to reducing the cardiovascular risk have been demonstrated with acarbose. Postprandial increases in blood glucose levels are associated with an elevation in triglycerides. In patients with type 2 diabetes with normal fasting triglyceride values, serum triglyceride levels were doubled or tripled during the day, with a peak after dinner and at bedtime.[56] This postprandial hypertriglyceridaemia in diabetic individuals may play an important atherogenic role as it is closely correlated with carotid IMT values, as are PPG and low-density lipoprotein cholesterol values.[57] In addition to stabilised PPG values, adequate control of postprandial hypertriglyceridaemia may, therefore, be an important means for preventing macrovascular complications in diabetic individuals.[58] Acarbose acts on both parameters and induces a significant reduction in postprandial hypertriglyceridaemia, whether FG values are normal or elevated.[59,60] Acarbose also reduces the levels of postprandial remnants[59] and chylomicrons.[60]

Acarbose induces a significant reduction in postprandial procoagulant factors. After a test meal in 17 patients with type 2 diabetes, circulating levels of prothrombin fragments 1+2 and D-dimers rose significantly less with acarbose than with placebo.[61] After several months of treatment, acarbose lowered plasma insulin levels by 72% and proinsulin levels by 46.7% 2 hours after a test breakfast[62] and significantly increased insulin sensitivity, as measured using the clamp method.[36] Insulin sensitivity was also improved in glucose-intolerant individuals treated for 4 months with acarbose compared with placebo.[37] With acarbose, several other vascular risk factors as well as postprandial hyperglycaemia were reduced, and this probably impacts on the course of atherosclerosis and cardiovascular complications in patients with diabetes.

4.2 Glinides

Unlike sulfonylureas, which act throughout the daily 24-hour period, glinides are insulin secretagogues that are effective mainly during the postprandial period. The one interventional study conducted with glinides determined the impact of a specific reduction in PPG values on the course of atherosclerosis, as assessed by carotid IMT values.[63] A total of 175 previously untreated patients with type 2 diabetes were randomised to either repaglinide 1.5–12 mg/day or glibenclamide 5–20 mg/day. After 1 year, peak PPG values, which were initially equivalent in the two groups (2.24 and 2.31 g/L), were significantly lower in the repaglinide group (−0.70 g/L) than in the glibenclamide group (−0.51 g/L; $p < 0.001$). In contrast, the fall in FG values (initially 1.59 and 1.63 g/L, respectively) was significantly smaller in the repaglinide group (−0.24 g/L) than in the glibenclamide group (−0.32 g/L; $p < 0.01$). Consequently, overall HbA_{1c} values improved to an equivalent extent (−0.9% and −0.8% for initial mean values of 7.5% and 7.4%; p-value nonsignificant). Nevertheless, there was a significant reduction in carotid IMT in the repaglinide group ($p < 0.02$) when compared with the glibenclamide group, whose IMT values remained globally unchanged. There were no significant changes to

lipid or blood pressure parameters in either group. However, there were drops in interleukin-6 and C-reactive protein (CRP) levels that were more marked in the repaglinide group and correlated with the fall in PPG values. Finally, multivariate analysis showed that changes in IMT values were independently and principally linked to the course of postprandial hyperglycaemic peaks, and to a lesser extent to those of HbA_{1c} and CRP. Obviously, this study was not as wide ranging as the previous ones conducted with acarbose insofar as it did not measure clinical cardiovascular events. However, IMT values constitute an intermediate parameter that has a validated relationship to cardiovascular, and particularly coronary, complications.[21] The reduction during this study in IMT values, a marker of atheromatous macroangiopathy, appeared mainly to be related to the improvement in postprandial hyperglycaemic peaks and its impact on improving inflammatory factors,[64] the atherogenic role of which has also been clearly confirmed, particularly for interleukin-6[65] and CRP.[66]

4.3 Insulin and Rapid-Acting Insulin Analogues

To date, no studies have evaluated the impact of treating PPG in patients with type 2 diabetes with rapid-acting insulin analogues on cardiovascular morbidity and mortality or the course of atherosclerosis as measured by IMT values. However, two studies have measured its impact on postprandial endothelial dysfunction in patients with type 2 diabetes. Endothelial dysfunction occurs during the course of type 2 diabetes[67] and may be the first step in the constitution of atheromatous macroangiopathy and subsequent cardiovascular complications, at least in hypertensive patients.[68] Many experimental findings have indicated that hyperglycaemia plays an important role in the aetiology of endothelial dysfunction[69] and particularly postprandial hyperglycaemia.

Ceriello et al.[70] recently studied 23 patients with type 2 diabetes and 10 healthy controls matched for sex, age and BMI. The diabetic patients received 0.15 U/kg ordinary insulin or a rapid-acting insulin analogue (aspart) before two test meals containing 600 kcal (50% in the form of carbohydrates). PPG values were little modified in the healthy controls but were elevated in the diabetic patients. However, the area under the blood glucose concentration-time curve (AUC) was significantly lower when the diabetic patients were treated with the rapid-acting analogue, aspart ($p < 0.04$), than with ordinary insulin. Endothelial dysfunction was evaluated by measuring variations in the diameter and blood flow of the brachial artery after compression. The endothelial dysfunction assessed in this way was present at baseline in diabetic patients and worsened during the postprandial period in parallel with the hyperglycaemia. Endothelial dysfunction was improved by the administration of insulin before the test meal. A more marked improvement was obtained with the rapid-acting analogue than with ordinary insulin and the reduction in brachial blood flow was greater when patients were treated with ordinary insulin than with the aspart analogue. However, there was no correlation between the AUC for blood glucose values and variations in the brachial flow.[70]

Another study using insulin lispro before meals demonstrated an improvement in endothelial dysfunction values (measured using the same method as Ceriello et al.[70]) after 6 weeks of insulin therapy. This improvement appeared both in the baseline state and after a test meal. However, during this study, the test meal consisted entirely of lipids (80g saturated fats) and all postprandial lipid parameters were improved by insulin lispro. The improvement in endothelial dysfunction induced by this rapid-acting analogue was significantly amplified by combination with an antioxidant (vitamin C) compared with placebo.[71]

Thus, treatment of type 2 diabetes with a rapid-acting insulin analogue before meals improved postprandial endothelial dysfunction. This effect may be mediated by a reduction in the postprandial hyperglycaemic peak and also by the improved postprandial lipid levels.

5. Impact of the Treatment of PPG on Microvascular Complications

The UKPDS clearly demonstrated a link between chronic hyperglycaemia and microvascular complications in type 2 diabetes. A 1% reduction in HbA_{1c} values resulted in a 37% reduction in the risk of retinal disease.[2] However, this study did not consider PPG values and only used FG values to adjust treatment. In contrast, the Kumamoto study took both of these parameters into account when adjusting intensified insulin therapy during the 8 years of treatment.[3] This study demonstrated that PPG values were strongly associated with the onset of retinal and kidney disease (as were FG and HbA_{1c}).[3] This suggests that postprandial hyperglycaemia participates with fasting hyperglycaemia in diabetic microangiopathy and the microvascular complications specific to diabetes. The relative importance of this contribution increases when hyperglycaemia is moderate. When HbA_{1c} values are <7.3% in patients with type 2 diabetes treated with oral antidiabetic drugs, PPG contributes 70% to the residual excess of HbA_{1c}.[72] In these patients, treatment specifically targeting PPG, such as acarbose or a glinide, may logically be combined with treatment focused on controlling baseline hyperglycaemia.

6. Impact of Treating PPG and the Prevention of Type 2 Diabetes

Only one study on the prevention of type 2 diabetes, the STOP-NIDDM study, has specifically targeted the treatment of postprandial hyperglycaemia. Its primary aim was to demonstrate a reduction in progression towards confirmed type 2 diabetes by treating glucose-intolerant patients with moderate fasting hyperglycaemia (1.10–1.40 g/L) with acarbose. At an average daily dose of 194mg for 3.3 years, the rate of onset of diabetes was reduced by 25% compared with placebo.[49] This outcome is not specific to α-glucosidase inhibitors, as data suggesting or demonstrating a preventive effect on the occurrence of type 2 diabetes have been obtained with diet combined with exercise, metformin, thiazolidinediones, orlistat and ACE inhibitors.[73]

7. Discussion and Conclusions

Cardiovascular complications are responsible for 40–50% of deaths in patients with type 2 diabetes[74] and reduce life expectancy by 5–10 years, particularly for patients developing this disease at an early age.[75] Numerous experimental and epidemiological studies have shown that postprandial hyperglycaemia is involved in the onset of these cardiovascular complications in patients with IGT or type 2 diabetes.

PPG may be a marker of all the metabolic abnormalities combining to generate early and progressive atherosclerosis or an aetiopathogenic factor at the origin of these complications meaning that it must be normalised to prevent this risk. This hypothesis is supported by several interventional studies with glinides and insulin but above all with acarbose in patients with ITG or type 2 diabetes. However, final confirmation must be obtained by conducting broad-ranging, prospective studies with the primary objective of preventing cardiovascular complications by targeted treatment of postprandial hyperglycaemia. Until the results of such studies are available, clinicians must take currently available data into account in order to give their patients the best possible chance of preventing these cardiovascular complications through optimum control of PPG values. A wide range of medication now exists for which the main iatrogenic risk is hypoglycaemia; this risk is absent with α-glucosidase inhibitors because of their mechanism of action.

The main metabolic target of type 2 diabetes therapy is the strict control of chronic hyperglycaemia with HbA_{1c} values <6.5%.[40] However, as far as control of PPG values is concerned this objective no longer suffices as patients with ITG may have HbA_{1c} levels within a normal range and still have twice the cardiovascular risk of healthy individuals. In patients with type 2 diabetes, active treatment of baseline hyperglycaemia may produce satisfactory global results in terms of HbA_{1c} but allow major postprandial peaks to persist. For example, if oral antidiabetic drugs fail, combined therapy with oral antidiabetics and an insulin glargine injection carefully titrated on the FG value restores these

FG values to close to normal and HbA_{1c} to close to 7%. However, mean PPG values never reach their target levels and, on average, remain above 1.40 g/L.[76,77] In patients whose diabetes did not respond to oral antidiabetics and who received mixed therapy with isophane human (NPH) insulin at bedtime, there was a linear relationship between FG and HbA_{1c} values. It is possible to normalise morning glycaemia values (1 g/L) but concomitant HbA_{1c} will remain at 7.3%.[78] This clearly shows that strict treatment of FG does not ensure normalisation of HbA_{1c}, probably because of the persistence of postprandial glycaemic peaks. It is likely that this phenomenon is even more marked when patients are more insulinopenic. In order to prevent complications rather than ensure 'comfort' (i.e. aiming to prevent symptoms such as thirst, fatigue and weight loss, rather than achieving tight glycaemic control) it is probably necessary to aim for a close to normal 24-hour glycaemic profile rather than optimum control of HbA_{1c}. This choice of a therapeutic strategy to prevent cardiovascular complications (or to ensure 'comfort') depends on concomitant morbidity factors and the patient's life expectancy. It should be borne in mind that mean life expectancies for the general French population aged 60 or 75 years in 2005 are 26 years for women and 21 years for men, and 13.5 years for women and 10.5 years for men, respectively.

No consensus has been reached regarding target PPG. The data from the Kumamoto study suggested a threshold for the onset of complications of PPG >1.80 g/L,[3] which is also the threshold recommended by the American Diabetes Association;[79] however, the American Association of Clinical Endocrinologists proposes lowering this threshold to 1.40 g/L.[80] A sufficiently wide range of medication is now available to be able to achieve this goal, although lipid and calorie restrictions and physical exercise will probably suffice in patients with IGT. The therapy of choice for IGT is α-glucosidase inhibitors and, in particular, the use of acarbose was associated with a reduction in the incidence of cardiovascular events by 50% and the risk of progression to diabetes by 25% during the 3.3 years of the STOP-NIDDM study. This also applies to the onset of diabetes, when diet or oral monotherapy are no longer sufficient, particularly in the event of moderate residual hyperglycaemia. At later stages, when baseline insulin therapy has been instituted and control of PPG remains unsatisfactory, medication may include α-glucosidase inhibitors, glinides, rapid-acting insulin analogues or soon-to-be-approved inhaled insulin; however, the effectiveness of these therapeutic strategies must be confirmed by prospective studies. Whatever the case, the clinician must target not only the optimum control of baseline blood glucose and moderate chronic hyperglycaemia, as indicated by HbA_{1c} values, but also ensure satisfactory control of postprandial hyperglycaemic peaks[81] in order to give the patient the maximum chance of avoiding cardiovascular complications.

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