Cardiovascular risk in type 2 diabetics and pharmacological regulation of mealtime glucose excursions

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SUMMARY
In type 2 diabetic patients mealtime glucose fluctuations are important determinants of overall glucose control and overall risk of diabetes cardiovascular complications. In fact, acute elevation of plasma glucose concentrations trigger an array of tissue response that may contribute to development of such vascular complications since it may result in a thrombophilic condition, causes endothelial dysfunction (possibly through a reduction of nitric oxide availability) and is responsible for non-enzymatic glycation and production of free-radicals with ensuing oxidative stress. To keep post-prandial glucose with narrow range, metiglinide analogues drugs have been developed. In particular, repaglinide and nateglinide seem the most useful ones. In fact, both drugs improve 1st phase insulin release but they do not affect the total daily amount of insulin released by the pancreas. Due to the mechanism of action and to pharmacokinetic properties, repaglinide and nateglinide allow diabetic patients to get a more tight metabolic glucose control with a contemporary reduction in the cases of severe hypoglycaemia. In conclusions, repaglinide and nateglinide are new and powerful pharmacological tools not only for achieving a better metabolic glucose control but also for preventing the development of diabetes-related cardiovascular complications.

Key-words: Type 2 Diabetes · Fasting Hyperglycaemia · Post-Prandial Glucose · Cardiovascular Risk Factor.

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Diabète mellitus et ses complications représentent un problème de santé majeur dans les sociétés modernes.

La prévalence de la maladie a augmenté au cours des 20 dernières années alors que la prévalence actuelle est d'environ 7,8% de la population adulte dans les pays industrialisés et environ un tiers des patients sont maldiagnostiqués. Il est estimé que 15% de la consommation de soins de santé globale est consacrée au traitement du diabète et de ses complications à long terme. La plupart de ces données souligne l’importance de l’âge, du sexe ajusté RR mortalité avait une très haute corrélation avec 2-h post-prandial glucose leviers. Toutes ces observations suggèrent que la glycémie postprandiale et la glycémie maximale, ainsi que ceux qui se produisent dans l’absorbant, ne doit pas être un simple indicateur de la glycémie et le contrôle global des complications diabétiques, mais peuvent aussi exécuter un effet indépendant sur la longue durée de la durée de vie de diabétiques. En effet, une élévation de glycémie postprandiale stimulate un depot de tissu réponse qui peut contribuer au développement de telles complications vasculaires (Tab I). Acute hyperglycemia causes an increase in retinal blood flow and is associated with a concomitant increase in the glomerular filtration rate in patients with diabetes. Moreover, intermittent rather than constant hyperglycemia induces an increase in collagen production by cultured mesangial cells and has marked effects on the coagulation processes by shortening the half-life of fibrinogen and increasing the circulating levels of fibrinopeptide, thrombin, prothrombin fragments and factor VII [3]. Hence, the acute changes in plasma glucose concentrations may result in a thrombophilic condition as platelet adhesion is also enhanced by hyperglycemia [3]. Finally, acute hyperglycemia causes endothelial dysfunction (possibly through a reduction of nitric oxide availability) and is responsible for non-enzymatic glycation and production of free radicals with ensuing oxidative stress [4].

La plupart de ces effets font que le glucose post-prandial a le potentiel d'être un facteur de risque cardiovasculaire potentiel pour le diabète de type 2.

| Table I |
| Effects of acute hyperglycemia potentially contributing to the development of diabetic complications. |
| — Increased glomerular filtration rate and renal plasma flow; |
| — Increased retinal blood flow; |
| — Reduction of motor and sensory nerve conduction velocity; |
| — Impairment of endothelial NO-mediated function; |
| — Procoagulative state; |
| — Increase in adhesion proteins; |
| — Oxidative stress; |
| — Protein labile glycation |

Is post-prandial glucose a cardiovascular risk factor?

Elevated fasting plasma glucose, frequently occurring in type 2 diabetic patients, have been considered a marker for the overall disturbance of glucose control responsible for later complications. However, FPG levels may be considered an incomplete index of glucose control in light of the fact that mealtime glucose oscillations are also responsible for the degree of the overall disturbance of glucose control. In addition, it has been proved evidence that several epidemiological trials have pointed out the fact that FPG and glycosylated haemoglobin were good but not absolute risk factor for the development of diabetic complications. Thus, other parameters than FPG and HbA1c, would be taken into account. Post-prandial glucose levels have been reported to be a major determinant of daily glycaemic control and are therefore a major candidate in promoting and determining the development of complications in diabetes [5]. More recently, Monnier et al. outlined the different contribution of post-prandial and fasting hyperglycemia on the diabetic control showing that the relative contribution of postprandial glucose excursions is predominant in poorly controlled patients, whereas the contribution of fasting hyperglycemia increases gradually with diabetes worsening [6].

Such main role of post-prandial glucose is emphasized by several epidemiologic studies, evaluating both 2 hour post challenge glucose excursion in patients with impaired glucose tolerance and post meal glucose excursion in type 2 diabetes patients.

In individuals with normal FPG, a plasma glucose concentration of >11.1 mmol/l measured two hours after a 75 glucose load was associated with an increased risk of mortal-
diabetic patients supports the results from oral glucose toler-
tance was a better predictor of mortality than FPG in the general population was also confirmed in diabetic pa-
tients without prior history [10]. In the Decode study, 2-hr glucose con-
centrations were evaluated and both trials confirmed 2-hr plasma glucose levels to be the best predictor of CHD. The strongest evidence for post-glucose levels as risk factor for CHD came from the Decode study [10] in which more than 25,000 indi-
viduals across Europe were investigated. Decode study showed that fasting plasma glucose levels without a 2-hr post-prandial glucose assessment to screen for diabetics as recommended by the American Diabetes Association would not be sufficient to identify all individuals at risk of diabetic complications [10]. In the Decode study, 2-hr glucose concentration was a better predictor of mortality than FPG in people without prior history [10].

The same risk associated with glucose spikes observed in the general population was also confirmed in diabetic pa-
tients. Assessment of post-meal blood glucose levels in type 2 diabetic patients supports the results from oral glucose toler-
ance testing. Hanefeld et al. [11] assessed the risk factors for CHD and mortality in an 11 year follow-up of newly diag-
nosed type 2 diabetics. Baseline post-prandial hyperglycaemia, but not FPG, was a strong predictor of, and an independent risk factor for mortality. More impressive are the data in older patients. In the Verona Diabetes Study [12] 566 elderly type 2 diabetics were followed up for 5 years to assess mortal-
ity and causes of death. All FPG determinations of 3 years preceding the follow up available in the clinical records were collected and analyzed. Patients were grouped in tertiles of mean FPG, coefficient of variations of FPG as well as the slope of FPG. These parameters of glucose control, as well as sex, age, duration of diabetes, insulin treatment, cigarette smoking, hypertension and total cholesterol, were included in a multivariate analyses of mortality. During the follow up, 63 men and 128 women died and cardiovascular related mortality was independently associated with coefficient of variation — FPG but not with the mean of FPG. In partic-
ular, the relative risk of cardiovascular mortality in subjects at III tertile of coefficient of variations FPG was 2.40. Such data allowed the authors to conclude that FPG instability is a predictor of cardiovascular related mortality in elderly patients with NIDDM. More recently, the Cardiovascular Health Study [13] has strengthened such result since 4014 — dwelling adults 65 years or older were investi-
gated. All patients without treated diabetes or previous myoc-
cardial infarction or stroke were eligible for analyses. Inci-
dent myocardial infarction or stroke or coronary death, was the outcome of interest. The result of such study demon-
strated that both FPG and 2-hour plasma glucose were car-
diovascular risk factors, but performing a joint analysis of both metabolic parameters only 2-hr plasma glucose levels remained predictive of cardiovascular events. Very recently, the Paris Prospective Study [14] in 7 018 men aged 44-55 years with undiagnosed diabetes at baseline and after 17-
year follow up period, provided further evidence that 2-
hour plasma glucose is unequivocally a prognostic factor for all- causes of mortality in men with normal fasting plasma glucose but not in patients with impaired fasting glucose. The whole of such data allow us to conclude that a more effective therapeutic strategy for reaching a good metabolic control should take into mainly account 2-hr-plasma glucose rather than only FPG.

**Pharmacological regulation of mealtime plasma glucose excursion**

The overt hyperglycaemia that characterizes type 2 dia-
betes occurs when insulin secretion can no longer overcome an individual’s levels of insulin resistance. Thus, insulin se-
cretion has a main role in the development of diabetes mellitus [15]. With regard to this latter evidence, it is important to point out that timing and magnitude of the first phase of B-cell response to glucose is critical for receptor-mediated insulin action and glucose tolerance as well as for controlling for the mealtime glucose excursions. In fact, Bergman et al. [16] have recently showed that an individual to remain glu-
cose tolerant must have an efficient 1st phase insulin secre-
tion in order to match any increase in insulin resistance. In contrast, loss or attenuation of early phase insulin secretion is associated with development of type 2 diabetes. The relation-
ship between integrity of 1st insulin secretion and devel-
opment of type 2 diabetes come form longitudinal studies in Pima Indians in whom all subjects with a loss of 1st phase of insulin secretion are destined to develop type 2 diabetes. Therefore, the improvement of 1st insulin secretion may be helpful either for preventing a further worsening of glucose control — through a strict control of post-prandial glucose excursion — and for avoiding the development of vascular complications. Thus, ideally a pharmaceutical agent would restore early-phase insulin secretion and, by promoting physiological insulin secretion into the portal vein, optimize suppression of hepatic glucose output and thus minimize post-prandial hyperglycaemia. If the problem is predomi-
nantly confined to the postprandial phase early in the dis-
case, alpha glucosidase inhibitors, short acting sulphony-
lureas and enhancers of early phase insulin secretion are good option for treatment when potential adverse effects are also taken into account [17].
It is possible that the older sulphonylureas, by increasing overall insulin secretion, accelerate B-cell demise. Indeed, the mechanism of action of sulphonylureas only became apparent in the late 1980s when the sulphonylurea receptor was found to be a subunit of the ATP-sensitive potassium channel [18]. Binding of sulphonylurea to the B-cell leads to depolarization, and influx of calcium ions and insulin secretion. Insulinitropic and antidiabetic properties of non-sulphonylurea moiety of glibenclamide, subsequently called metiglinide, was discovered more than 20 years ago. Repaglinide, a acid benzoic derivative, was the first metiglinide analogue to become available. It initiates insulin secretion by closing the K-ATP channel [19] (Fig 1). A high affinity repaglinide binding site with lower affinity for glibenclamide has been identified with B-TC3 insulinoma cells. By contrast, with glibenclamide, repaglinide does not stimulate insulin secretion from B-TC3 insulinoma cells in the absence of glucose, nor it enhances exocytosis in voltage clamped B-cells. Unlike conventional sulphonylureas, repaglinide is not internalized within B-cell, and it has no direct biosynthetic activity and is mainly metabolized at liver level by the CYP3A4 isoform of the P450 cytochrome enzyme [20]. This latter pharmacological characteristic made repaglinide available even in patients with mild to moderate renal failure. Clinical studies have shown that repaglinide, taken before a meal, induce a rapid post-prandial insulin response. The short half life of the drug ensure that insulin concentrations peak at 1-2 h and by 6 hours are back at fasting concentrations. Repaglinide is not detectable in the circulation 4 h after a dose, so there is little risk of hypoglycaemia if the patient misses a meal, which is, on the other hand, a severe problem with the old sulphonylureas. A support to such clinical evidence comes form studies showing the risk of severe hypoglycaemia to be less than half that seen with traditional sulphonylureas [21]. Compared to short-acting sulphonylureas glipizide, repaglinide has been demonstrated to be more effective on reducing HbA1c (−1.5%) and post-prandial glucose (−2.3 mmol/l) without affecting weight gain [22-24]. Quality of life seems also improved as compared to old sulphonylurea. In fact, Landgraf et al. [25] studied 6000 patients with type 2 diabetes and showed that eating patterns improved when they switched to repaglinide monotherapy before meals. When on their usual treatment, 38% of the patients admitted to eating even when not hungry, due to fear of hypoglycaemia. However, this proportion dropped to only 10% when repaglinide replaced usual therapy. Repaglinide may be also used in combination therapy with metformin thus resulting in a drop of HbA1c of 1.4% which was significantly more than the value found after repaglinide and metformin by itself [26].

Nateglinide is a further metiglinide analogue and is a d-phenylalanine derivative. In rat pancreatic B-cells, nateglinide inhibits K-ATP channel faster than repaglinide but slower than glibenclamide [27]. However, a faster reversal of channel inhibition occurs with nateglinide compared with repaglinide or glibenclamide. In vitro-data suggest that nateglinide differs mechanistically from both glibenclamide and repaglinde [28-30]. Experiments in isolated rat islets
show that nateglinide-induced inhibition of K-ATP current is enhanced 16-fold when the glucose concentration is raised from 3 mmol/l [31]. The potency of glibenclamide is much reduced under these conditions whereas the potency of repaglinide is enhanced 4-fold. Nateglinide is rapidly and extensively absorbed after oral administration. In vivo, nateglinide administered 5 min before and oral glucose load increased early-phase insulin release and eliminated post-challenge glucose excursion in both mild insulin and resistant high-fat fed rats and very insulin resistant Zucker fatty rats [27]. In 152 type 2 diabetic patients, the 12-h insulin area under the curve was two-fold higher in patients receiving glibenclamide compared with those receiving nateglinide. Furthermore, plasma insulin returned to pre-treatment concentrations before meals in patients treated with nateglinide and this insulin secretion profile was associated with 45% reduction in the incremental glucose area under the curve after a liquid meal challenge. Horton et al. [32] have also provided evidence on the effectiveness of nateglinide in combination with metformin. Combination therapy lowered HbA1c more effectively than did either monotherapy, and again the decrease was similar to the sum of the reductions achieved by the monotherapy regimens individually. In particular, the reduction were of 0.9%, 1.2% and 1.9% for nateglinide, metformin and combination therapy respectively.

Mitiglinide is the last compound of such a group of drugs but it is still pre-marketing phase trials. Metiglinide, as repaglinide and nateglinide, stimulates calcium influx binding to the sulphonylurea receptor and closing K-ATP channel and through this mechanism normalizes impaired glucose tolerance in a streptozotocin rat model of type 2 diabetes [33-34]. An important property of metiglinide is to have additional extrapancreatic effects on hepatocyte carbohydrate metabolism as shown in isolated hepatocytes [35].

Given their mechanism of action, it is feasible that nateglinide or repaglinide would be more effective when used in combination with, for example an insulin sensitizer [36]. The thiazolidinediones, rosiglitazone and pioglitazone do not stimulate insulin release or cause hypoglycaemia [37] making them potentially suitable candidates for combination therapy with insulin secretion enhancers. Although troglitazone is no longer available, a combination study of troglitazone with nateglinide [38] and a similar study with repaglinide [39] both showed a reduction of HbA1c of 1.7% which was grater than the reduction seen with the respective monotherapies in the same trials.

Similarly, insulin secretion enhancers combined with a-glucosidase inhibitors should be effective in controlling postprandial hyperglycemia. Trial investigating nateglinide plus acarbose are currently under-way while others with repaglinide combined with voglibose are planned [36].

Adding repaglinide to NPH insulin mono therapy has recently been shown to be a possible combination therapy for patients with type 2 diabetes, still providing a secretary reserve for insulin release [40].

Insulin therapy is ultimately necessary for the control of post prandial glucose levels in a majority of patients with type 2 diabetes mellitus. Modern diabetes therapy has positively introduced insulin administration to prevent or delay the development of long-term complications. Advances in molecular genetic engineering have made possible the development of insulin analogues with pharmacokinetics that more closely mimic the needs of patients with type 2 diabetes. Lys-Pro insulin and insulin aspart, rapid-acting insulin analogues, have demonstrated improved post-prandial glucose control in comparison with regular insulin, even although they are usually administered immediately prior to the meal [41-42]. Surprisingly, the new fast-acting analogues have not achieved the expected commercial success, which emphasizes the need for new strategies for basal insulin supplementation, exercise, diet and blood glucose monitoring [36].

Conclusions

The data available prompt us to conclude that mealtime plasma glucose fluctuations are important cardiovascular risk factors in type 2 diabetic patients. It is therefore very important to use pharmacological tools allowing to keep post-meal glucose oscillations within narrow range. Sulphonylureas are useful drugs for controlling plasma glucose levels in type 2 diabetics but, they fails in controlling for plasma glucose excursions. In contrast, mitiglinide analogue, such as repaglinide and nateglinide, can improve the 1st phase of insulin response to glucose and thus are much more useful for lowering post-meal plasma glucose excursions being therefore of great interest for preventing the development of cardiovascular complications in type 2 diabetics. It is possible that in a near future a further advancement in pharmacological research will provide new more powerful drugs for controlling mealtime glucose excursions.

References


