

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.

Paolisso G, Rizzo MR, Barbieri M, Manzella D, Ragno E, Maugeri D. Cardiovascular risk in type 2 diabetics and pharmacological regulation of mealtime glucose excursions *Diabetes Metab* 2003,29,335-40

RÉSUMÉ

Risque cardiovasculaire chez le diabétique de type 2 et régulation pharmacologique des excursions glycémiques prandiales

Chez les diabétiques de type 2, les fluctuations glycémiques prandiales sont des déterminants importants du contrôle glycémique global et du risque globale de complications cardiovasculaires. En fait, une élévation aiguë de la glycémie déclenche toute une gamme de réponses tissulaires qui peuvent contribuer au développement de telles complications vasculaires, puisqu'elle peut causer un état thrombophile, une dysfonction endothéliale (possiblement par réduction de la disponibilité du monoxyde d'azote), une glycation non enzymatique et une production de radicaux libres générateurs d'un stress oxydant. Pour conserver la glycémie post prandiale dans une fenêtre étroite, des substances analogues du metiglinide ont été développées. En particulier, le repaglinide et le nateglinide semblent les plus puissants. En fait, les deux médicaments améliorent la première phase de l'insulinosécrétion, mais ils n'affectent pas la quantité quotidienne totale d'insuline libérée par le pancréas. En raison de leur mécanisme d'action et de leurs propriétés pharmacocinétiques, le repaglinide et le nateglinide permettent aux diabétiques d'obtenir un contrôle métabolique de la glycémie plus strict avec une réduction du risque d'hypoglycémie sévère. En conclusion, le repaglinide et le nateglinide sont de nouveaux et puissants outils pharmacologiques, permettant non seulement d'obtenir un meilleur contrôle glycémique, mais aussi de prévenir le développement des complications cardiovasculaires du diabète.

Mots-clés : Diabète de type 2 · Hyperglycémie à jeun · Glycémie post prandiale · Facteur de risque cardiovasculaire.

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Received: May 19th, 2003

Diabetes mellitus and its complications represent a major health problem in modern societies. The prevalence of the disease has increased over the last 20 years while the present prevalence is approximately 7.8% of the adult population in Western Countries and almost one-third of patients are undiagnosed. It is estimated that about 15% of the total health care expenditure is spent on the treatment of diabetes and its long-term complication. The whole of such data prompt us to underline that there is urgency to the need to improve the management of diabetes mellitus. In general, a rationale approach to diabetes mellitus therapy is a firstly modification of lifestyle encompassing: reducing bodyweight, enhancing physical exercise and diet. When the non-pharmacological therapy fails, a drug therapy is required. In general drug therapy has two main targets: increasing insulin availability and decreasing insulin requirements. As far as increasing insulin availability is concerned, it can be obtained throughout the day (or independently of meal consumption) or in a specific day-time (for avoiding fasting hyperglycemia and mealtime glucose excursion). Since long time, fasting hyperglycemia (FPG) and glycosylated hemoglobin (HbA_{1c}) were considered the best indices of degree of metabolic control. Indeed, mean HbA_{1c} may not be the most complete measure of metabolic control since it does not account for glucose fluctuations. In fact, Avignon *et al.* [1] evaluated the relationship between HbA_{1c} and plasma glucose in patients with Type 2 diabetes, measured at four time points during the day. A correlation between plasma glucose and HbA_{1c} was found to be significantly predicted by plasma glucose levels measured at post-lunch (2-hr) and extended (5hr) post-lunch time points. In the Horn Study [2] the age- sex adjusted RR mortality had a very high correlation with 2-hr plasma glucose levels. All those observations suggest that plasma glucose fluctuation and glucose peak, such as those occurring in the absorptive state, may not be only an important determinant of overall glucose control and overall risk of diabetes complications, but may also exert an independent effect on the long-term outcome of diabetes. In fact, acute elevation of plasma glucose concentrations triggers an array of tissue response that may contribute to development of such vascular complications (*Tab I*). Acute hyperglycaemia 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 results in a thrombophilic condition as platelet adhesion is also enhanced by hyperglycemia [3]. Finally, acute hyperglycemia causes endothelial dysfunction (possibly through a reduction

Table I

Effects of acute hyperglycemia potentially contributing to the development of diabetic complications.

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- 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
-

of nitric oxide availability) and is responsible for non-enzymatic glycation and production of free- radicals with ensuing oxidative stress [4].

The whole of such effects make mealtime glucose excursion a potential risk factor for cardiovascular disease in diabetic patients and especially in type 2 diabetics.

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 degree of glucose control. In addition, it has been provided 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 HbA_{1c} 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 diabetics [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 fairly 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-

ity [3]. In older women, this post-mealtime hyperglycemia doubled the risk of heart diseases and fatal cardiovascular diseases [7]. In the Honolulu Heart Program the role of 1-hour post-load glucose levels and the risk of cardiovascular events in more than 6,000 subjects was studied along 12 years [8]. The results of such study demonstrated that the incidence of fatal coronary heart diseases increased linearly with increasing post-challenge blood glucose and this relationship was independent of other cardiovascular risk factors. Interestingly enough, extending the observation to 23 years, the link among cardiovascular mortality and post-load glucose was even stronger [8]. In the Islington Diabetes Study [9] and Hoorn study [3], the relationship among 2-hour plasma glucose, HbA_{1c} and vascular concentration was also 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 individuals across Europe were investigated. Decode study showed that fasting plasma glucose levels without a 2-hr post-challenge glucose assessment to screen for diabetes 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 patients. Assessment of post-meal blood glucose levels in type 2 diabetic patients supports the results from oral glucose tolerance testing. Hanefeld *et al.* [11] assessed the risk factors for CHD and mortality in an 11 year follow-up of newly diagnosed type 2 diabetics. Baseline post-meal 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 mortality 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 particular, the relative risk of cardiovascular mortality in subjects at III -tertile *vs* I 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 myocardial infarction or stroke were eligible for analyses. Incident myocardial infarction or stroke or coronary death, was the outcome of interest. The result of such study demonstrated that both FPG and 2-hour plasma glucose were cardiovascular 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 diabetes occurs when insulin secretion can no longer overcome an individual's levels of insulin resistance. Thus, insulin secretion 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 glucose tolerant must have an efficient 1st phase insulin secretion 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 relationship between integrity of 1st insulin secretion and development of type 2 diabetes come from 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 predominantly confined to the postprandial phase early in the disease, alpha glucosidase inhibitors, short acting sulphonylureas 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. Insulinotropic 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 from 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 HbA_{1c} (-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 HbA_{1c} 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 repaglinide [28-30]. Experiments in isolated rats islets

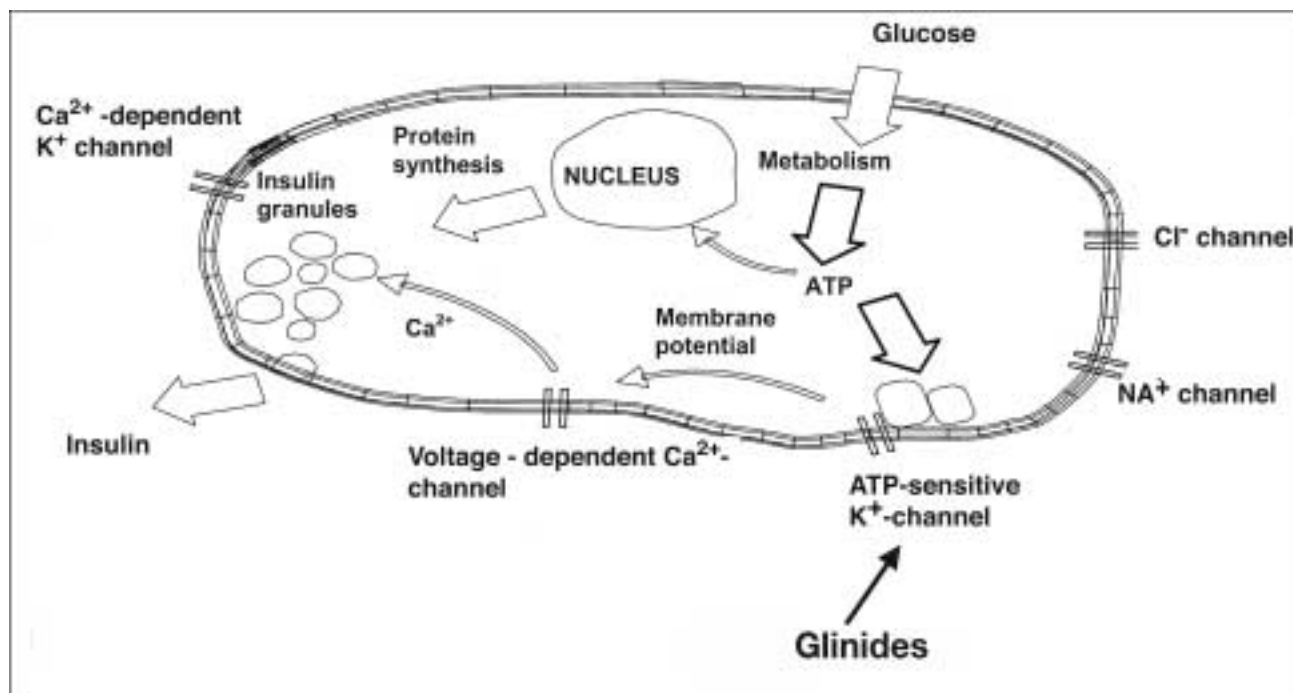


Figure 1
Mechanism of action of glinides on pancreatic β -cells.

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 between 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 HbA_{1c} 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.

Metiglinide 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 HbA_{1c} of 1.7% which was greater than the reduction seen with the respective monotherapies in the same trials.

Similarly, insulin secretion enhancers combined with α -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 secretory 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.

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