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REVIEW ARTICLE

The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus

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Summary

Type 2 diabetes is a heterogeneous disorder characterized by defects in insulin secretion and action. Insulin resistance is a key feature of type 2 diabetes. However, insulin resistance alone does not appear to be sufficient to cause diabetes. Longitudinal studies have shown that the development of overt hyperglycemia is associated with a decline in β-cell secretion. In patients with impaired glucose tolerance or in the early stages of type 2 diabetes, first-phase insulin release is almost invariably lost despite the enhancement of second-phase secretion. Both animal and human studies support the critical physiologic role of the first-phase of insulin secretion in the maintenance of postmeal glucose homeostasis. This effect is primarily mediated at the level of the liver, allowing prompt inhibition of endogenous glucose production (EGP) and thereby restraining the mealtime rise in plasma glucose. In type 2 diabetes, the loss of the early surge of insulin release is a precocious and quite common defect that plays a pathogenic role in postmeal hyperglycemia and one that may require specific therapeutic intervention. This becomes even more apparent if the negative impact of prandial glucose spikes is taken into consideration. Epidemiological evidence exists to indicate that 2-h postload plasma glucose levels are strongly associated with all-cause and cardiovascular mortality relative risk. Indeed the acute elevation of plasma glucose concentration triggers an array of tissue responses that may contribute to the development of diabetic complications. Considering that type 2 diabetes begins with meal-related hyperglycemia in many patients, it becomes apparent that normalization of postmeal plasma glucose levels should be the target for rational therapy and the goal in the early stages of the disease. If a primary goal of diabetes therapy is control of postmeal glucose excursion, then the regulation of glucose absorption from the gut and entry into the circulation is an important mechanism to consider. The restoration of the rapid increase in plasma insulin concentration may be quite an efficient therapeutic approach. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords first-phase insulin secretion; prandial glucose; hepatic glucose production; cardiovascular risk; insulin secretagogues

Introduction

Type 2 diabetes is a heterogeneous disorder characterized by defects in β-cell function and insulin action. Insulin resistance is a key feature of type 2 diabetes as it can be demonstrated in the vast majority of affected individuals [1]. Impaired insulin action on the liver results in impaired modulation of glucose production and output, which accounts for fasting hyperglycemia, and which contributes to postprandial hyperglycemia. After an overnight fast,

plasma glucose levels are a function of the rate of endogenous glucose production (EGP) that primarily reflects gluconeogenic activity [1]. Recently it has been suggested that renal gluconeogenesis may also contribute to an overnight increase in plasma glucose levels [2]. Insulin resistance at the level of muscle tissue is mainly responsible for reduced glucose utilization in response to physiologic elevation of plasma insulin concentration [1]. These abnormalities are likely the consequence of molecular defects at the level of postreceptor signaling, glucose transport, and/or regulatory enzymes of intracellular glucose metabolism [1,3].

Impaired insulin action can be demonstrated in obese subjects with normal glucose tolerance [4], as well as in relatives of patients with type 2 diabetes [5–7] although this might not necessarily represent a genetic defect [8]. However, insulin resistance alone does not seem to be sufficient to cause diabetes. Longitudinal studies have shown that the development of overt hyperglycemia is also associated with a decline in β-cell secretion [1,5]. Patients who have type 2 diabetes with a fasting plasma glucose (FGP) <7.8 mmol/l may have a similar or even greater insulin response to glucose than matched healthy individuals; however, the overall plasma insulin levels are always inadequate with respect to prevalent plasma glucose concentration [1]. When hyperglycemia develops, it exerts a toxic effect on both the pancreas and insulin-sensitive tissues, a phenomenon known as 'glucose toxicity' [9], leading to a self-perpetuating cycle of worsening defects and further exacerbation of the hyperglycemic condition.

In patients with impaired glucose tolerance (IGT) or in the early stages of type 2 diabetes, first-phase insulin release is almost invariably lost despite the enhancement of second-phase secretion [10,11]. DeFronzo and colleagues summarized the results of the insulin response to glucose tolerance tests from 32 studies in patients with type 2 diabetes mellitus (Figure 1) [1]. In terms of total insulin response, insulin secretion was reduced in 16 individuals, was normal in 11, and increased in only five of those studied. A different picture emerged when early- (0–10 min) versus late-phase insulin secretion was examined. Late-phase insulin secretion was decreased in 13 individuals, whereas normal or even increased responses were reported in the remaining 19 subjects. This lack of difference, however, may be supported by much larger post-oral glucose tolerance test (OGTT) glucose excursion. In fact, if equivalent plasma glucose concentrations are ensured as can be done using the hyperglycemic clamp technique, a defect in both first- and second-phase insulin secretion can be found, as has been shown by some authors [8,12].

A more recent longitudinal study carried out in Pima Indians [13] has clearly demonstrated that a defect in acute insulin release (AIR) occurs early in the natural history of type 2 diabetes, and it may contribute to the conversion from normal to impaired glucose tolerance and, finally, to overt diabetes. This brief synopsis illustrates the altered insulin secretion dynamics in type 2 diabetes, underscoring the deficient acute early phase of insulin release.

Physiologic relevance of the first phase of insulin secretion

Many factors may contribute to excessive mealtime glucose excursion (Table 1). Reduced glucose utilization by peripheral tissues (muscle and adipose tissues) during the absorptive state may result in increased swings in glucose concentration. Insulin resistance at the level of the liver may lead to insufficient suppression of glucose production and output as well as an increase in mealtime glucose excursion. However, the liver is under the control of other potential influencing factors, such as inadequate suppression of mealtime plasma glucagon concentration [14], persistence of elevated mealtime plasma free fatty

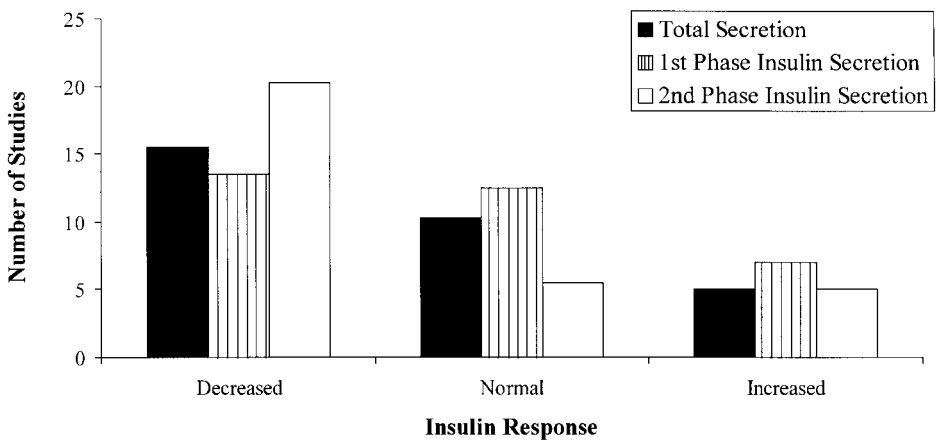

Figure 1. Results of 32 studies on the insulin response to an oral glucose challenge in patients with type 2 diabetes. The studies were classified as reduced, normal or increased according to the degree of the reported insulin response. Total insulin secretion, closed bars; first-phase insulin secretion, open bars; second-phase insulin secretion, cross-hatched bars. Adapted with permission from DeFronzo RA, Bonadonna RC, Ferrannini E, Pathogenesis of NIDDM: a balanced overview, *Diabetes Care* 1992; 15: 318–368. Copyright © 1992 American Diabetes Association

Table 1. Factors contributing to excessive mealtime glucose excursion in type 2 diabetes mellitus

- Peripheral (muscle and adipose tissue) insulin resistance
- Sustained mealtime endogenous glucose production
- Inadequate suppression of mealtime plasma glucagon concentrations
- Persistence of elevated mealtime plasma free fatty acid levels
- Accelerated gastric emptying

acid levels, and accelerated gastric emptying. Although each of these factors may independently affect endogenous glucose production, a common mechanism may be identified because it is possible that these factors could be sustained or caused by the loss of first-phase insulin secretion.

A strong negative relationship has been demonstrated between cephalic insulin release and initial glucose increment after commencement of a glucose infusion [15]. This finding suggested that an early surge of insulin secretion, such as the cephalic phase, could exert a restraining effect on rising blood glucose. Furthermore, the greater the insulin surge, the more prolonged the effect on glucose homeostasis. In a study of patients with IGT [16], Gerich and colleagues found an inverse correlation between plasma insulin levels 30 min after an oral glucose load and the plasma glucose concentration attained in the second hour. This suggests that the effects of an acute (first-phase) insulin secretion significantly impact subsequent glucose tolerance by ensuring more physiologic plasma glucose levels (Figure 2) [16].

The amount of insulin released during first-phase secretion suggests a more likely effect on the liver than on peripheral tissues. This is supported by animal studies conducted by Steiner and Cherrington [17]. They measured the increment in plasma glucose and EGP in response to glucagon infusion in dogs undergoing a pancreatic islet clamp, in which insulin secretion was completely abolished or either the first-, second-, or both phases of insulin secretion were reconstructed. With this experimental approach, the researchers showed that both first- and second-phase insulin secretion were critical in counterbalancing the hyperglycemic effect of glucagon. In addition, their results revealed that restoration of the early increase in the plasma insulin level, even in the absence of the late phase, was capable of reducing the glucagon-mediated rise in plasma glucose concentration. In a subsequent study, the same authors demonstrated that the primary effect on EGP was a reduction of gluconeogenesis [18], a finding that acquires even greater importance in light of the characteristic increase in gluconeogenesis seen in patients with type 2 diabetes [19].

Data from a number of rigorously designed human studies further support the critical role of first-phase insulin secretion in the modulation of EGP. In a hyperglycemic clamp study that measured EGP and glucose uptake in normal subjects [20], the acute elevation of plasma glucose concentration and subsequent biphasic insulin release were associated with progressive suppression of EGP and increase in glucose disposal through peripheral tissues. The abolition of first-phase insulin secretion by means of somatostatin and appropriate insulin replacement was not associated with changes in glucose utilization. However, the impact on EGP was dramatic: glucose appearance in the circulation proceeded at higher rates in spite of prevalent hyperglycemia and hyperinsulinemia, and suppression of EGP was only 50% as compared with the control study (Figure 3) [20]. This was a direct consequence of the deficit of first-phase insulin secretion, since its restoration via an insulin infusion was followed by completely normal

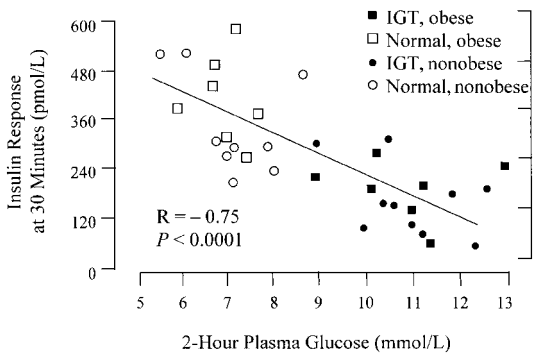

Figure 2. Correlation of 30-min plasma insulin response with 2-h plasma glucose concentrations following an oral glucose tolerance test in study subjects. Reproduced with permission from Mitrakou A, Kelley D, Mokan, *et al.*, Role of reduced suppression of glucose production and diminished early release in impaired glucose tolerance, *New Engl J Med* 1992; 326: 22–29. Copyright © 1992 Massachusetts Medical Society. All rights reserved

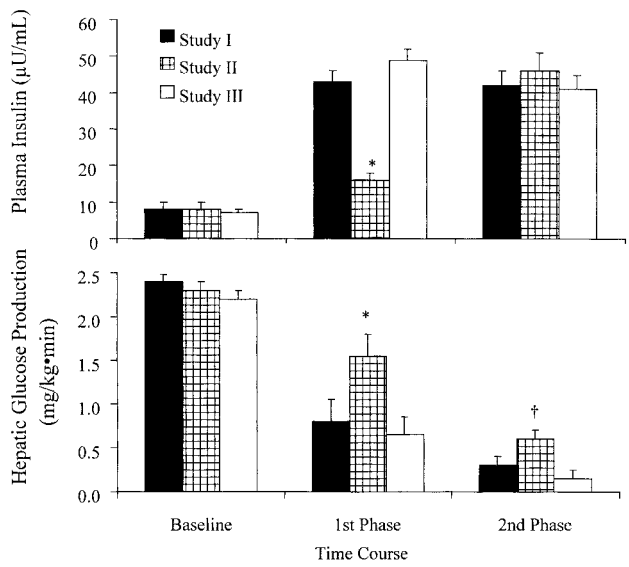

Figure 3. Mean (±SE) plasma insulin and HPG in healthy individuals during three hyperglycemic clamp studies. Study I, hyperglycemic clamp; Study II, hyperglycemic clamp plus somatostatin and insulin infusion mimicking only second-phase insulin secretion; study III, hyperglycemic clamp plus somatostatin and insulin infusion mimicking both first- and second-phase insulin secretion. *$p < 0.01$ vs studies I and III; †$p < 0.05$ vs studies I and III. Adapted with permission from Luzi L, DeFronzo RA, Effect of loss of first-phase insulin secretion on hepatic glucose production and tissue glucose disposal in humans, *Am J Physiol* 1989; 257: E241–E246. Copyright © 1989 The American Physiological Society

inhibition of EGP. The same finding has been replicated by Basu *et al*. [21] in response to an oral glucose load associated with a plasma insulin profile similar to that of type 2 diabetic subjects: i.e. delayed increase and persistent later hyperinsulinemia. In agreement with these results, Mitrakou *et al*. reported that in IGT patients, plasma insulin concentration 30 min after the ingestion of a glucose load correlated with the rate of glucose appearance (EGP as well as exogenous glucose) [16]. These authors also found an inverse correlation between the rate of glucose appearance and the insulin/glucagon ratio. This is particularly relevant to the degree of hyperglycemia in patients with type 2 diabetes following a mixed meal. In the postmeal phases, plasma glucagon concentrations remain higher than in normal individuals despite normal or increased plasma insulin, and the inability to suppress EGP and stimulate glucose disposal seems to account for hyperglycemia [22]. Not only are plasma glucagon concentrations higher in type 2 diabetic patients, but preliminary reports also indicate that the EGP response to increasing rates of glucagon infusions is consistently higher in these individuals than in matched normal controls [23], suggesting an increased sensitivity to the biologic action of the hormone.

In summary, both animal and human studies support the critical physiologic role of the first-phase of insulin secretion in the maintenance of postmeal glucose homeostasis. This effect is primarily mediated at the level of the liver, allowing prompt inhibition of EGP and thereby restraining the mealtime rise in plasma glucose. In type 2 diabetes, the loss of the early surge of insulin release is an early and quite common defect that plays a pathogenic role in postmeal hyperglycemia and one that may require specific therapeutic intervention. This becomes even more apparent if the role of postmeal hyperglycemic state in determining overall metabolic control is taken into consideration.

Role of postmeal hyperglycemia in the pathogenesis of diabetic complications

The Diabetes Control and Complications Trials (DCCT) demonstrated that the risks of retinopathy and other microangiopathic complications of type 1 diabetes are reduced with a regimen of intensive insulin therapy that maintains near-normal blood glucose concentrations, compared with conventional treatment regimen [24]. Although the results of the DCCT mainly focused on microangiopathy, there were also indications that macrovascular complications could be reduced or delayed by tight glucose control. In the Kumamoto study [25], intensive insulin treatment in patients with type 2 diabetes was also associated with a significant reduction/delay of microangiopathic complications. However, the study was limited to lean patients, which accounts for only a minority of those with the disease. Type 2 diabetic patients are more often obese, and their condition is associated with other metabolic and hemodynamic disturbances such as dyslipidemia and hypertension. Finally, the study did not provide strong information on rates of cardiovascular events.

The UK Prospective Diabetes Study (UKPDS) was initiated in 1977 to evaluate whether long-term therapy to improve glycemic control would prevent or delay cardiovascular complications, which are the major cause of premature morbidity and mortality in patients with type 2 diabetes. A total of 4209 newly diagnosed patients with type 2 diabetes were randomly allocated to receive either conventional treatment (mainly comprising dietary control) or intensive treatment with either insulin, sulfonylureas or, in obese individuals, metformin [26,27]. Over an average 10-year follow-up period, maintenance of a lower HbA_{1c} value by means of intensive glycemic control (7.0% vs 7.9%, intensive vs conventional treatment, respectively) was associated with a 12% reduction in all diabetes-related end points, with the greatest effect on microvascular complications.

Both the DCCT and the UKPDS findings were based on the use of HbA_{1c} as the marker for glycemic control. Nevertheless, mean HbA_{1c} may not be the most complete measure of the degree of glycemia, and other features of glucose control that are not reflected in HbA_{1c} may add to or modify the risk of complications. For instance, HbA_{1c} does not necessarily account for glucose fluctuations, and mealtime glycemic excursions may increase the risk of complications [28]. Avignon and colleagues evaluated the relationship between HbA_{1c} and plasma glucose in patients with type 2 diabetes, measured at four time points during the day [29]. A correlation between plasma glucose and HbA_{1c} could be seen at each time point (Figure 4) [29]. However, after multiple regression analysis, HbA_{1c} was found to be significantly predicted by plasma glucose levels measured only at postlunch (2 h) and extended postlunch (5 h) time points. A recent analysis performed in the Horn Study [30] has indicated that the strongest age- and sex-adjusted relative risk (RR) for both all-cause and cardiovascular mortality were associated with 2-h postload plasma glucose levels. After additional adjustment for hypertension, body mass index, triglycerides, low density lipoprotein (LDL) cholesterol, and cigarette smoking, the correlation remained statistically significant. Interestingly, when newly diagnosed diabetic patients were excluded from the analysis, the age- and sex-adjusted RR for mortality had an even higher correlation with 2-h plasma glucose (statistically significant) and with HbA_{1c}. These observations suggest that plasma glucose fluctuations and glucose peaks, such as those occurring in the absorptive state, may not only be an important determinant of overall glucose control (i.e. HbA_{1c} levels) and overall risk of diabetic complications, but may also exert an independent effect on the long-term outcome of diabetes [31].

The acute elevation of plasma glucose concentration triggers an array of tissue responses that may contribute to the development of diabetic complications (Table 2).

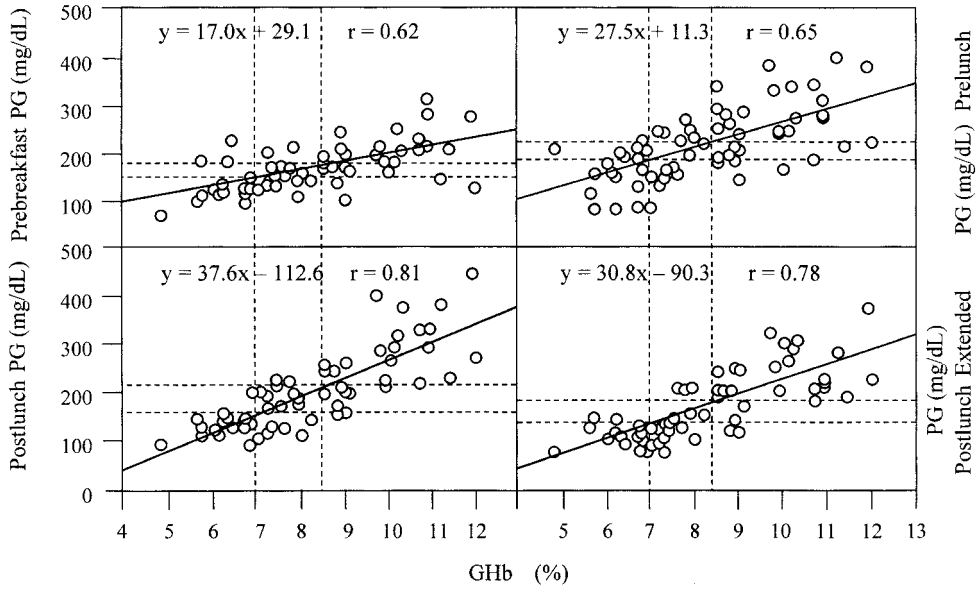

Figure 4. Correlation between HbA_{1c} and plasma glucose concentration before breakfast and lunch, postlunch, and extended postlunch in patients with type 2 diabetes. On a multiple regression analysis, only postlunch plasma glucose concentrations showed significant correlation to HbA_{1c}. Reproduced with permission from Avignon A, Radauceanu A, Monnier L, Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes, *Diabetes Care* 1997; 20: 1822–1826. Copyright © American Diabetes Association

Acute hyperglycemia causes an increase in retinal blood flow [32,33] and is associated with a concomitant increase in the glomerular filtration rate in patients with diabetes [34]. Moreover, intermittent rather than constant hyperglycemia induces an increase in collagen production by cultured mesangial cells [35]. Rapid changes in plasma glucose concentration reduce motor and sensory nerve conduction velocity [36,37]. Mealtime glucose excursions exert marked effects on the coagulation process by shortening the half-life of fibrinogen [38] and increasing the circulating levels of fibrinopeptide A [39], thrombin [40], prothrombin fragments [41] and factor VII [42]. Hence, the acute changes in plasma glucose concentrations may result in a thrombophilic condition as platelet adhesion is also enhanced by hyperglycemia [43]. The atherogenic process may be facilitated by the increase in adhesion proteins triggered by hyperglycemic peaks [44]. Finally, acute hyperglycemia causes endothelial dysfunction [45,46], possibly through a reduction of nitric oxide availability [47]. The negative effects of acute hyperglycemia are likely the result of labile non-enzymatic glycation [48] and production of free radicals [49] with ensuing oxidative stress [50], while still unclear are the mechanisms responsible for elongation of the QT tract in response to acute elevation of plasma glucose concentration [51,52].

Table 2. 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

In summary, although it is still not possible to dissect the relative impact of glucose fluctuations and chronic hyperglycemia in the development of diabetic complications, postmeal hyperglycemia is capable of triggering a series of events involved in both micro- and macrovascular complications.

Data from large studies support the independent role of postmeal hyperglycemia in the increased mortality risk. The Honolulu Heart Study found a strong correlation between postchallenge (1-h) glucose levels and the incidence of cardiovascular mortality [53]. In the Chicago Heart Study, which evaluated the RR of coronary death in a cohort of about 12 000 men over 22 years, the cardiovascular risk was found to be much higher in individuals with asymptomatic postmeal hyperglycemia [54]. Even stronger evidence has recently emerged from studies designed to assess the impact of fasting versus postload plasma glucose levels. The DECODE Study [55], which included more than 25 000 subjects with a mean follow-up of 7.3 years, indicated that an increased mortality risk was associated with 2-h postload plasma glucose levels to a much greater extent than with FPG (Figure 5) [55]. The latter, after adjustment for the 2-h glucose value, lost any association with all-cause mortality. The Cardiovascular Health Study [56] also provided evidence for the greater value of postload glucose (54%) in predicting cardiovascular disease mortality compared with FPG levels (28%). The Diabetes Intervention Study [57], carried out in newly diagnosed patients with type 2 diabetes, reported that postmeal – but not FPG – is an independent factor for cardiovascular mortality. Considering that type 2 diabetes begins with meal-related

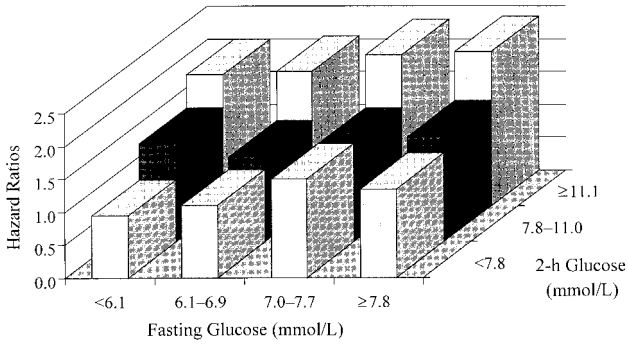

Figure 5. Hazard ratios (HR) for death adjusted for age, sex and study center, according to the fasting glucose and 2-h glucose classifications in individuals not known to have diabetes. HR increases with the progressive increase of 2-h plasma glucose but not with increasing FPG. Adapted with permission from The DECODE Study Group, Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria, *Lancet* 1999; 354: 617–621. Copyright © The Lancet Ltd

hyperglycemia in many patients, it becomes apparent that normalization of postmeal plasma glucose levels should be the target for rational therapy and the goal in the early stages of the disease.

Therapeutic control of postmeal hyperglycemia

If a primary goal of diabetes therapy is control of postmeal glucose excursion, the regulation of glucose absorption from the gut and entry into the circulation is an important mechanism to consider. The goal of dietary modifications is reduction of postmeal glucose peaks. Alpha-glucosidase inhibitors, such as acarbose, delay intestinal glucose absorption and reduce mealtime glucose excursion without affecting pancreatic β-cell secretion [58]. Although these agents may be useful in the early stages of the disease when hyperglycemia is mainly limited to the absorptive state, their use in the more severe diabetic condition may not be sufficient. The UKPDS has recently indicated that the average reduction in HbA_{1c} seen in patients who tolerated the drug was 0.3% [59].

Taken together, the above considerations indicate the need for agents capable of intervening at the level of the basic pathogenic deficiencies responsible for altered glucose tolerance. Amylin and its analogue, pramlintide, slow down gastric emptying, and the latter has been suggested to suppress plasma glucagon concentration after ingestion of a mixed meal [60]. In a larger study of patients with type 2 diabetes, administration of pramlintide before each meal was associated with a 0.5% reduction in HbA_{1c} [61]. Nevertheless, its therapeutic advantage remains to be fully elucidated. Suppression of EGP has been attempted primarily with the use of inhibitors of fatty acid oxidation [62,63], however no safe agent has become available.

Over the past two decades, sulfonylureas have been used to enhance insulin secretion in patients with type 2 diabetes. However, out of several sulfonylurea compounds only gliclazide was claimed to affect both first- and second-phase insulin secretion. Hosker *et al*. [64] reported that first-phase insulin secretion in response to different degrees of hyperglycemia was enhanced though not normalized by administration of gliclazide. In our experience [65], the acute administration of gliclazide in newly diagnosed patients prior to receiving a constant infusion of glucose was associated with an improvement in glucose tolerance, expressed as the incremental plasma glucose area above baseline compared with placebo (352 ± 42 vs 461 ± 52 mmol/240 min). However, no significant differences were observed in the insulin secretion rate, which only became apparent after 2 months of treatment. These data suggest that the amelioration of first- and second-phase insulin secretion that occurs with sulfonylureas may be partly mediated by relief of glucose toxicity [9].

The presumed clinical advantages of sulfonylureas are not fully supported by other experimental results. EGP and peripheral glucose disposal in response to different plasma insulin concentrations were assessed before and after treatment with either tolazamide or insulin in patients with type 2 diabetes [66]. Although a certain degree of improvement in EGP and glucose utilization was observed with both treatments, the use of tolazamide did not provide significant advantages over insulin treatment. This sulfonylurea is unlikely to exert a preferential stimulation of first-phase insulin secretion.

More recently, meglitinide, a non-sulfonylurea benzoic acid derivative, has been shown to elicit an acute insulin release [67]. This compound and its analogues increase insulin secretion in a glucose-dependent manner by reducing membrane conductance in pancreatic β-cell [67,68]. These features suggest that meglitinide analogues may be the agents of choice for acute stimulation of insulin secretion in response to a meal. Repaglinide is the currently available analogue of meglitinide. In an early comparative study with glibenclamide, repaglinide exhibited a greater effect on postmeal plasma glucose concentration [69], although a more recent study reported no significant differences after a 1-year treatment [70]. Nateglinide, a D-phenylalanine derivative, is characterized by a rapid and short-lasting stimulatory effect on insulin secretion [71]. Nateglinide has been shown to have a more rapid and shorter insulin-secreting effect on both *Cynomolgus* monkeys [72] and humans [73] than repaglinide. In type 2 diabetic patients, nateglinide caused a dose-dependent increase in plasma insulin levels within 30 min of drug intake and reduced mealtime glucose excursions [74,75]. Nevertheless, the restoration of the early rise in plasma insulin concentration is likely to provide a more physiologic liver exposure to insulin, a faster suppression of EGP, and glucose excursions of lower magnitude. The extent of EGP is a determinant of mealtime glucose levels, since a direct correlation has been found between the two parameters (Figure 6) [65,76].

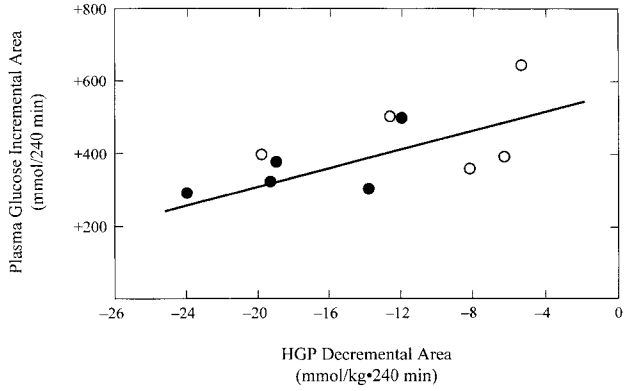

Figure 6. Correlation ($r = 0.63$, $p < 0.05$) between the incremental area of plasma glucose levels above baseline and the decremental area below baseline EGP following a 11.1 μmol/kg min glucose infusion in patients with type 2 diabetes treated with gliclazide (closed symbols) or placebo (open symbols) administration. Reproduced with permission from Riccio A, Lisato G, Vigili de Kreutzenberg S, *et al.*, Gliclazide potentiates suppression of hepatic glucose production in non-insulin dependent diabetic patients, *Metabolism* 1996; 45: 1196–1202. Copyright © 1996 W. B. Saunders

Oral glucose elicits a larger insulin response than intravenous glucose. Plasma glucose concentrations after intravenous glucose tend to remain higher than levels following the ingestion of the same amount of glucose, and plasma insulin concentrations are greater after oral than intravenous glucose administration [77]. This observation has been explained by the action of the so-called entero-insular axis [78]. Several hormonal factors (incretins) have been shown to play a potentiating effect on β-cells after ingestion of a carbohydrate meal [79]. Glucagon-like peptide-1 (GLP-1), the most potent incretin, is an insulinotropic intestinal hormone released in response to enteral nutrient challenge [80]. Nathan *et al.* [81] clearly demonstrated the potentiating effect of GLP-1 on insulin secretion in type 2 patients. A 30-min infusion of GLP-1 was associated with a prompt and sustained acute increase in mealtime insulin secretion. The increased insulin concentration dropped to basal levels after interruption of GLP-1 infusion and remained lower than in control individuals. As expected, the initial rise was followed by a second phase of plasma insulin increase that was primarily supported by prevalent hyperglycemia. The initial increase in plasma insulin concentrations abolished the early rise in plasma glucose levels that followed the ingestion of a mixed meal. After the interruption of GLP-1 infusion, plasma glucose concentrations remained lower compared with control individuals, suggesting that early modulation of the postmeal glucose concentration may result in an overall improvement in glucose tolerance in the face of lower circulating insulin levels. GLP-1 has been shown to enhance insulin action as well as suppress plasma glucagon concentration. Nauk *et al.* [82] showed that plasma elevations of exogenous, infused GLP-1 are associated with a constant decline in plasma glucose levels, a possible consequence of the effects on insulin secretion and the concomitant suppression of plasma glucagon levels. Evidence supporting the clinical use of GLP-1, however, is lacking because of its rapid proteolytic degradation [83]. Peptidase-resistant analogues are being currently tested [84] along with exendin, a peptide with 53% homology to GLP-1 and a prolonged glucose-lowering action [85].

An alternate approach for regulating postmeal hyperglycemia is the restoration of a more physiologic profile of mealtime insulin secretion. The importance of the timing of insulin administration in glucose control following a meal has been appreciated for many years in the treatment of type 1 (insulin-dependent) diabetes. It has been demonstrated that adjustments in the timing as well as in the amount of insulin administered premeal are necessary in the management of this disease. Prolonging the interval between administration of insulin and meal ingestion could reduce insulin requirements and thus decrease the hyperinsulinemia associated with insulin therapy [86]. The beneficial effects of restoring first-phase insulin secretion in type 2 diabetes have also been evaluated. In a study by Bruce *et al.* [87], patients with type 2 diabetes received an identical dose of insulin in three distinct regimens at mealtime. Insulin was given intravenously over 30 min at the beginning of a meal, in a profile that simulated a normal insulin response; in the profile but delayed by 30 min; or as a constant infusion over the entire duration of the study. A significant improvement in postmeal glucose tolerance was demonstrated only with early administration of insulin, in keeping with the proposed regulatory role of the acute insulin peak on EGP. The use of fast-acting insulin analogs may produce similar benefits [88]. In normal subjects, injection of an insulin analog was followed by a rapid and short-lived increase in plasma insulin levels, whereas a smoother and more prolonged increase was observed with the injection of regular insulin. The plasma insulin profiles were paralleled by the rate of glucose infusion required to maintain euglycemia. Therefore, the capability of the insulin analog to approximate the acute phase of insulin secretion could be expected to exert a more efficient action on the liver when administered to patients with type 2 diabetes who have an impaired first-phase insulin secretion. Similar results were obtained in our laboratory [89]. An insulin analog, administered subcutaneously 5 min before a 50 g oral glucose load, was associated with a more rapid rise in plasma insulin and a less prolonged insulin stimulation compared with administration of an equivalent amount of regular insulin, which produced a longer-lasting hyperinsulinemic tail (Figure 7) [89]. As a result of the rapid appearance of insulin in the circulation, glucose tolerance was significantly improved. Figure 8 [89] depicts the incremental areas under the curve of plasma glucose, insulin and C-peptide. With similar plasma insulin concentrations, the incremental plasma glucose area under the curve (AUC) was reduced by nearly 50%. Interestingly, the incremental plasma C-peptide AUC was reduced by 60%,

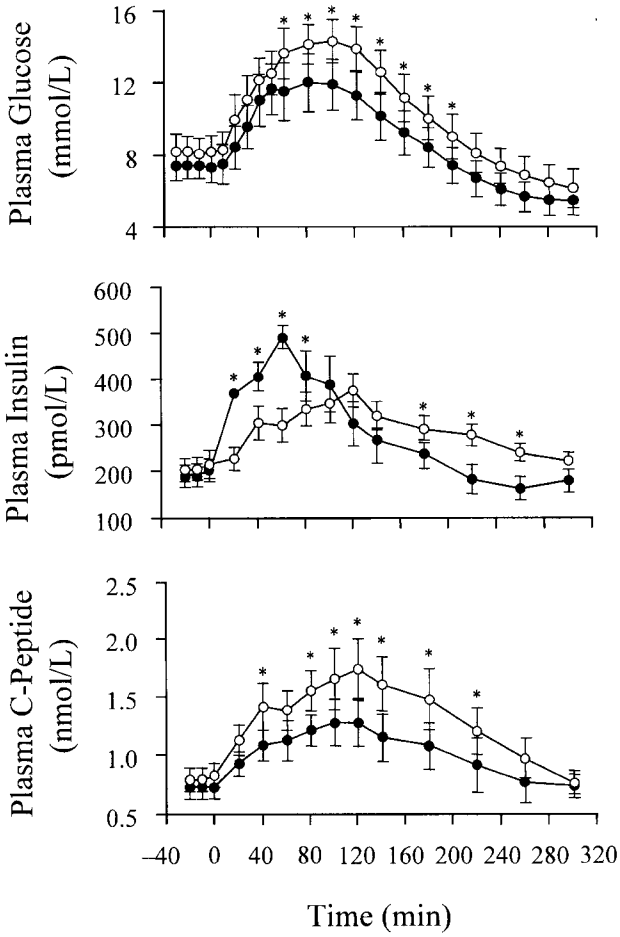

Figure 7. Time course of plasma glucose (upper panel), insulin (middle panel), and C-peptide (lower panel) concentrations after a 50 g oral glucose load preceded by subcutaneous injection of an equivalent dose (0.075 U/kg lean body mass) of regular (open symbols) and lispro (closed symbols) insulin. *$p < 0.05$. Reproduced with permission from Bruttomesso D, Pianta A, Mari A, *et al.*, Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetic patients, *Diabetes* 1999; 48: 99–105. Copyright © 1999 American Diabetes Association

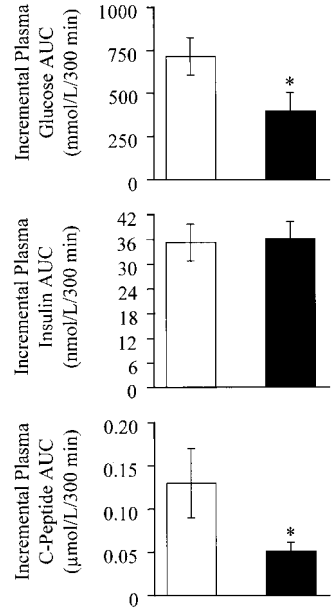

Figure 8. Area under the incremental curve (AUC) of plasma glucose (upper panel), insulin (middle panel) and C-peptide (lower panel) after a 50 g oral glucose load preceded by subcutaneous injection of an equivalent dose (0.075 U/kg lean body mass) of regular (open bars) and lispro (closed bars) insulin. *$p < 0.05$. Reproduced with permission from Bruttomesso D, Pianta A, Mari A, *et al.*, Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetic patients, *Diabetes* 1999; 48: 99–105. Copyright © 1999 American Diabetes Association

suggesting a sparing effect on endogenous insulin secretion, possibly due to a relieved pressure on the β-cells by lower plasma glucose levels. The study was conducted using a double tracer technique that enabled the assessment of glucose production and utilization. The early rise in plasma insulin concentration after the glucose load was associated with a faster and short-lived suppression of EGP that accounted for the improvement in glucose tolerance. Following injection of the lispro analogue, plasma glucose concentrations remained lower in spite of lower plasma insulin levels (Figure 7) [89]. In agreement with Mitrakou *et al.* [14], these results suggest that restoration of the early rise in plasma insulin concentration may improve mealtime glucose tolerance without incurring late hyperinsulinemia. Though ours was an acute study, a prevalent effect on postmeal glycemic control was demonstrated during a 6-month treatment with lispro insulin in patients with type 2 diabetes [90].

Clinical implication of the restoration of first-phase insulin secretion

The benefits of reducing mealtime glucose excursion have been discussed in the preceding paragraphs. Avoiding excessive elevation of plasma insulin levels also has clinical advantages as persistent elevations of plasma insulin concentrations can cause downregulation of the insulin receptor [91], therefore increasing insulin resistance [92], favor body weight gain [93] and cause late hypoglycemia.

In conclusion, the restoration of the dynamics of insulin secretion following a meal should be seen as a rational therapeutic approach in the treatment of type 2 diabetes because it induces an overall improvement in glucose tolerance with the advantage of possibly lowering chronic hyperinsulinemia. The previously described inverse relationship between early insulin secretion and 2-h plasma glucose levels following an oral glucose tolerance test [16], together with the experimental results obtained with lispro analogue [89], stress the concept that a prompt increase in plasma insulin in the early postmeal phase is a determinant of plasma glucose concentration in the late phases. Further, a positive correlation is observed when 2-h plasma glucose is plotted as a function of 2-h plasma insulin levels [16]. This suggests that the loss of the acute burst of insulin secretion leads to postmeal hyperglycemia, which in turn maintains a non-physiologic stimulatory stress on the β-cell with resultant

hyperinsulinemia. Therefore, restoration of the early dynamics of insulin secretion may allow for the simultaneous reduction of both glucose and insulin plasma levels. This has potentially significant clinical implications because type 2 diabetes mellitus cannot be considered as an unrelated pathologic entity, but rather as part of the syndrome of insulin resistance [94,95]. As has been shown, insulin resistance and its compensatory hyperinsulinemia may lead, in the long term, to the development of hypertension, dyslipidemia and atherosclerosis. Therefore, if restoring early postmeal rise in insulin secretion could improve glucose tolerance with significantly reduced hyperinsulinemia, restoration of first-phase insulin secretion would represent a rational treatment approach to improve metabolic control and reduce the risk of macrovascular complications. Moreover, since acute insulin release plays a major role in ensuring normal glucose tolerance, and its impairment occurs early in the natural history of type 2 diabetes [13], not only does restoration of first-phase insulin secretion appear to be a rational therapeutic approach but it may also prove of value in preventing diabetes.

However, the full benefits of the new therapeutic tools designed to control mealtime glucose excursions will not be realized unless specific parameters for the evaluation of their efficacy are defined. Though HbA_{1c} does and will play a central role in the definition of overall glycemic control, integrated measures of postmeal glucose levels will help define the specific role of the hyperglycemic peaks in the pathogenesis of diabetic complications. Perhaps there are lessons to be learned from a re-evaluation of old indices of glucose control, such as the mean amplitude of glycemic excursions, the mean M-value, and the mean of daily differences [96]. These indices do require the collaboration of patients who will be required to perform careful blood glucose monitoring at home. Nevertheless, the development of markers of the daily fluctuations of plasma glucose concentrations such as 1,5-anhydro-D-glucitol [97] are likely to facilitate the task of the diabetologist and to provide the patients with even better opportunities for reducing the burden of their disease.

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