Comment on: Nathan DM, Buse JB, Davidson MB et al. (2006) Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes.

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Letter –comment

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Introducing insulin therapy in patients with type 2 diabetes: mealtime dosing with a rapid-acting insulin analogue as an initial insulin regimen

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Glucose-responsive insulin secretion is frequently impaired prior to the onset of type 2 diabetes [1]. In addition, considering the reduced pancreatic beta cell mass in patients with type 2 diabetes [2], defects in insulin secretion appear heterogeneous in this patient group. In some patients, only postprandial insulin secretion appears impaired, whilst in others, basal insulin secretion is also affected. However, postprandial insulin secretion is impaired in almost all patients with type 2 diabetes.

In the recently published consensus statement from the American Diabetes Association [3] and the European Association for the Study of Diabetes [4] concerning the initiation and adjustment of therapy for managing hyperglycaemia in type 2 diabetes, initial insulin therapy is aimed at increasing basal insulin supply with intermediate- or long-acting insulins. Such a regimen cannot completely mimic a physiological pattern of insulin secretion. Consequently, postprandial glycaemic control tends to be inadequate, and a risk exists of fasting hypoglycaemia. Furthermore, the postprandial hyperglycaemia observed in patients with early-stage or mild type 2 diabetes increased the risk of microangiopathy or arteriosclerosis in two large-scale clinical studies of type 2 diabetes, the United Kingdom Prospective Diabetes Study [5] and the DECODE study [6]. It has also been suggested that therapy focussed on lowering postprandial glucose, rather than fasting glucose, may be superior for lowering HbA$_{1c}$ [7] and glucose variability (spike) [8]. Insulin preparations have been developed to provide insulin replacement that more closely reflects physiological insulin secretion; the introduction of rapid-acting insulin analogues and long-acting soluble insulin analogues has been a further step in this direction. Rapid-acting insulin analogues have been particularly effective at targeting postprandial hyperglycaemia [8]. They can, therefore, effectively reduce postprandial plasma glucose, even if administered immediately before a meal, and also minimise the risk of hypoglycaemia prior to the next meal [8].

The exact contribution of postprandial and fasting glucose increments to overall hyperglycaemia remains controversial. Monnier and colleagues reported that postprandial glucose excursion contributes up to ~70% of the glucose load in patients with diabetes whose HbA$_{1c}$ levels are <7.3%, whereas the contribution of fasting hyperglycaemia increases gradually as diabetes worsens [9]. However, even in patients whose glycaemic control is poor, studies have demonstrated that treatment targeting postprandial hyperglycaemia, which improves glucose-responsive insulin secretion in patients with glucose desensitisation, improves both postprandial and also morning fasting plasma glucose (FPG) in such patients [10–12].

We hypothesised that mealtime dosing with rapid-acting insulin analogues strictly controls postprandial and daytime plasma glucose levels, and thereby improves glucose desensitisation and glucose-responsive insulin secretion. To test these hypotheses, we recently evaluated the effect of a mealtime, rapid-acting insulin analogue on the minimum early morning FPG levels (nadir FPG) in 40 Japanese patients with type 2 diabetes whose existing antidiabetic medication was discontinued [12]. Approximately half (52.5%) of the patients achieved a nadir FPG of <6.7 mmol/l with mealtime dosing of a rapid-acting insulin analogue alone. No basal insulin replacement was needed in these patients. Patients, on the other hand, whose FPG levels remained high, even after postprandial hyperglycaemia improved, were presumed to have defects in basal insulin secretion [12]. To further confirm our finding, we prospectively followed 160 patients with type 2 diabetes treated with mealtime dosing of a rapid-acting insulin analogue. After 1 year of treatment at our out-patient clinic, about 60% of these patients were able to continue this therapy successfully; FPG was 6.4±1.6 mmol/l and HbA$_{1c}$ was 6.5±1.1%, compared with FPG of 6.0±1.2 mmol/l and HbA$_{1c}$ of 6.9±1.1% in the patients who required additional basal insulin replacement (Takamura et al., unpublished observation). This suggests that basal insulin secretion was

maintained in these patients, and only prandial insulin secretion was impaired. For such patients, glycaemic control achieved with sulfonylureas, which continuously promote insulin secretion, or with a long-acting insulin, may increase the risk of fasting hypoglycaemia. It may also contribute to obesity as a result of differentiation or hyperplasia of adipocytes during episodes of hyperinsulinaemia. Such patients may benefit instead from treatment with rapid-acting insulin analogue preparations, which more closely mimic physiological insulin secretion. These formulations may reduce the risk of hypoglycaemia by achieving a better balance between glucose and insulin levels, and also minimise increases in obesity, which might otherwise result from persistent hyperinsulinaemia during periods of fasting or after meals.

Based on these findings, we propose mealtime dosing with a rapid-acting insulin analogue as an initial insulin regimen for patients with type 2 diabetes. This regimen may be superior in lowering postprandial glucose excursion and the glucose spike, which are cardiovascular risk factors. The regimen may also help reduce the risk of hypoglycaemia and obesity associated with insulin therapy. Because not only postprandial, but also FPG can be modestly reduced by this regimen, the requirement for basal insulin replacement should be considered only in patients who do not achieve good FPG levels thereafter.

We suggest that further discussion is needed for better care of patients with type 2 diabetes.

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