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# THE IMPORTANCE OF POSTPRANDIAL HYPERGLYCEMIA POSITION STATEMENT OF THE DANUBE MCO EXPERTS

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## Abstract

*Both the prevalence and incidence of type 2 diabetes are increasing worldwide and over 60% of people with T2DM develop cardiovascular disease. There are many data supporting the view that glycaemic control plays a role in reducing cardiovascular complications. The relationship between hyperglycaemia and cardiovascular disease is complex with evidence suggesting that an acute increase of glycaemia, particularly after a meal, may have a direct detrimental effect on cardiovascular disease. Although control of fasting hyperglycaemia is necessary, it is usually insufficient to obtain optimal glycaemic control. A growing body of evidence suggests that reducing post meal plasma glucose excursions is as important, or perhaps more important for achieving HbA1c goals. New classes of therapies for managing post meal plasma glucose in people with diabetes (glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors) have shown significant benefits in reducing post meal plasma glucose excursions and*

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*lowering HbA1c. The individual properties of the various GLP-1 receptor agonists might enable incretin-based treatment of type 2 diabetes mellitus to be tailored to the needs of each patient.*

**key words**: *postprandial hyperglycemia, cardiovascular disease, GLP-1 receptor agonists*

Both the prevalence and incidence of type 2 diabetes (T2DM) are increasing worldwide, particularly in developing countries, in association with increased obesity rates and westernisation of lifestyle. The attendant economic burden for healthcare systems is skyrocketing, owing to the costs associated with treatment and diabetes complications [1]. Over 60% of people with T2DM develop cardiovascular disease (CVD), a more severe and costly complication than retinopathy [2].

There are many data supporting the view that glycaemic control plays a role in reducing cardiovascular complications, but it needs to be implemented early in the disease evolution and the benefits may take many years to manifest [3].

In people with diabetes, the total glucose exposure can be divided into two subcomponents – basal (BHG) and postprandial (PPHG) hyperglycemia [3].

In people with non-insulin-treated T2DM, the contribution of PPHG relatively to BHG is predominant when the HbA1c levels are below 7.5%. The proportional contribution of PPHG decreases progressively with increasing HbA1c levels [3].

In patients with T2DM who required intensification of antihyperglycemic therapy, the contribution of BHG to total hyperglycaemic exposure was uniformly high (76–80%) across the observed range of HbA1c levels at baseline [4]. After intensification of treatment leading to lower mean levels of HbA1c, there was a smaller (but important) contribution of BHG and a greater one from PPHG. Alteration of the contributions from BHG and PPHG was especially prominent when basal insulin was used. For all patients treated with basal insulin, an average of 34% contribution from residual BHG was present, in contrast with 68% after treatment intensification with other agents. After addition of basal insulin, a modest tendency towards higher residual BHG with increasing HbA1c category at endpoint was found, whereas this pattern did not emerge after treatment with other agents [4].

The relationship between hyperglycaemia and cardiovascular disease is complex with evidence suggesting that an acute increase of glycaemia, particularly after a meal, may have a direct detrimental effect on cardiovascular disease. Moreover, until recently, the predominant focus of therapy has been on lowering HbA1c levels, with a strong emphasis on fasting plasma glucose. Although control of fasting hyperglycaemia is necessary, it is usually insufficient to obtain optimal glycaemic control. A growing body of evidence suggests that reducing post meal plasma glucose excursions is as important, or perhaps more important for achieving HbA1c goals [3].

The Diabetes Epidemiology COllaborative analysis of Diagnostic criteria in Europe (DECODE) study reported data on cardiovascular disease mortality in Europeans in relation to fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) levels within a normoglycemic range. In individuals with both FPG and 2-h plasma glucose within the normoglycemic range, elevated 2-h plasma glucose conveyed increased mortality risk from CVD but not from non-CVD [5].

Several studies have shown that increasing HbA1c is associated with increasing CVD risk [2,6-8]. Studies that compared all three

glycaemic parameters – FPG, 2hPG and HbA1c for mortality and CVD risk revealed that the association is strongest for 2hPG and that the risk observed with FPG and HbA1c is no longer significant after controlling for the effect of 2hPG [2,9,10].

Some observations in T2DM patients showed that post meal plasma glucose is a stronger predictor of cardiovascular events than fasting plasma glucose, particularly in women [11]. These data have been confirmed in a longer follow-up [12].

The 2012 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement mentions that it is well established that the risk of microvascular and macrovascular complications is related to glycemia, as measured by HbA1c. This remains a major focus of therapy and effective management strategies are of obvious importance. Glycemic targets and glucose-lowering therapies must be individualized [1].

Diet, exercise and education remain the basic element of any T2DM treatment programme. Lifestyle Interventions designed to impact an individual's physical activity level and food intake are critical parts of T2DM management. All patients should receive standardised general diabetes education (individual or group, preferably using an approved curriculum), with a specific focus on dietary interventions and the importance of increasing physical activity. While therapeutic lifestyle changes are most important at diagnosis, periodic counselling should also be integrated into the treatment programme [1].

The diabetes treatment used by patients can be a more significant factor affecting the contribution of basal versus postprandial glucose elevations to the total hyperglycemia burden. To illustrate this point, with oral therapies alone at baseline, participants with HbA1c<8.0% (mean 7.6%) had 76% contribution from BHG. After intensification of treatment with basal insulin, people with HbA1c 7.5–7.9% (mean 7.7%) had 34% contribution from BHG. After intensification with premixed insulin, prandial insulin, or additional oral therapy, individuals with HbA1c in the same range (mean 7.7%) had 68% contribution from BHG [4].

Although many agents improve overall glycaemic control, including post meal plasma glucose levels, several pharmacologic therapies specifically target post meal plasma glucose. Therapies targeting post meal blood glucose which have been available for some time include α-glucosidase inhibitors, glinides, short-acting sulfonylureas, and insulin (rapid-acting human insulin/rapid acting insulin analogues and biphasic [premixed] human insulin/ insulin analogues).

In addition, new classes of therapies for managing post meal plasma glucose in people with diabetes (glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors) have shown significant benefits in reducing post meal plasma glucose excursions and lowering HbA1c. These therapies address gut hormones effects (clinical and pharmacological) that affect insulin and glucagon secretion, satiety and gastric emptying [3].

From these classes of non-insulin pharmacological agents, the glucose-lowering effectiveness is said to be high for sulfonylureas and GLP-1 agonists (expected HbA1c reduction ~1.0–1.5%) and generally lower for meglitinides, DPP-4 inhibitors, AGIs (~0.5–1.0%) [1]. Properties of currently available glucose-lowering agents targeting mainly post meal blood glucose that may guide treatment choice in individual patients with type 2 diabetes mellitus are shown in Table 1.

**Table 1.** Properties of currently available glucose-lowering agents targeting mainly post meal blood glucose that may guide treatment choice in individual patients with type 2 diabetes mellitus (adapted from [1]).

| Class | Cellular mechanism | Primary physiological action(s) | Advantages | Disadvantages | Cost |
|---|---|---|---|---|---|
| Sulfonylureas (short acting especially) | Close $K_{ATP}$ channels on beta cell plasma membranes | ↑Insulin secretion | Extensive experience<br>↓Microvascular risk | Hypoglycaemia<br>Weight gain<br>? Blunts myocardial ischaemic preconditioning<br>Low durability | low |
| Meglitinides | Close $K_{ATP}$ channels on beta cell plasma membranes | ↑Insulin secretion | ↓Postprandial glucose excursion<br>Dosing flexibility | Hypoglycaemia<br>Weight gain<br>? Blunts myocardial ischaemic preconditioning<br>Frequent dosing schedule | high |
| α glucosidase inhibitors (AGIs) | Inhibit intestinal α glucosidase | Slows intestinal carbohydrate digestion/absorption | No hypoglycaemia<br>↓Postprandial glucose excursion | Generally modest HbA1c efficacy<br>Gastrointestinal side effects (flatulence, diarrhoea) | Moderate |
| DDP-4 inhibitors | Inhibit DDP-4 activity, increasing postprandial active incretin (GLP1, GIP) concentrations | ↑Insulin secretion (glucose-dependent)<br>↓ glucagon secretion (glucose-dependent) | No hypoglycaemia<br>Well tolerated | Generally modest HbA1c efficacy<br>Urticaria/angio-oedema<br>?Acute Pancreatitis | High |
| GLP-1 receptor agonists | Activate GLP-1 receptors | ↑Insulin secretion (glucose-dependent)<br>↓ glucagon secretion (glucose-dependent)<br>Slows gastric emptying<br>↑Satiety | No hypoglycaemia<br>Weight reduction<br>?Potential for improvement of beta cell mass/function<br>?Cardiovascular protective actions | Gastrointestinal side effects (nausea/vomiting)<br>?Acute pancreatitis<br>C cell hyperplasia/medullary thyroid tumours in animals<br>Injectable<br>Training requirements | High |
| Insulin | Activates insulin receptors | ↑glucose disposal<br>↓hepatic glucose production | Universally effective<br>Theoretically unlimited efficacy<br>↓Microvascular risk | Hypoglycaemia<br>Weight gain<br>Injectable<br>Training requirements<br>Stigma (for patient)<br>?Mitogenic effects | Variable |

The GLP‑1 receptor agonists can be categorized as either short-acting compounds, which provide short-lived receptor activation (such as exenatide and lixisenatide), and long-acting compounds (for example albiglutide, dulaglutide, exenatide long-acting release, and liraglutide), which activate the GLP‑1 receptor continuously at their recommended dose. The pharmacokinetic differences between these drugs lead to important differences in their pharmacodynamics profiles. The short-acting GLP‑1 receptor agonists primarily lower postprandial blood glucose levels through inhibition of gastric emptying (this effect is not mediated by alterations of insulin or glucagon secretion). The long-acting compounds have a stronger effect on fasting glucose levels, which is mediated predominantly through their insulinotropic and glucagonostatic actions [13], while the effect on gastric emptying is reduced due to a de-sensitisation effect (tachyphylaxia), through prolonged stimulation of gastric and

vagus nerves [14]. The adverse effect profiles of these compounds also differ. The differences are summarized in Table 2 [13].

**Table 2.** Comparison of short-acting versus long-acting GLP-1 receptor agonists (adapted from [13]).

| Parameters | Short-acting GLP-1 receptor agonists | Long-acting GLP-1 receptor agonists |
|---|---|---|
| Compounds | Exenatide Lixisenatide | Albiglutide Dulaglutide Exenatide-Long Acting Release (LAR) Liraglutide |
| Half-life | 2–5 h | 12 h–several days |
| *Effects* | | |
| Fasting blood glucose levels | Modest reduction | Strong reduction |
| Postprandial hyperglycaemia | Strong reduction | Modest reduction |
| Fasting insulin secretion | Modest stimulation | Strong stimulation |
| Postprandial insulin secretion | Reduction | Modest stimulation |
| Glucagon secretion | Reduction | Reduction |
| Gastric emptying rate | Deceleration | No effect |
| Blood pressure | Reduction | Reduction |
| Heart rate | No effect or small increase (0–2 bpm) | Moderate increase (2–5 bpm) |
| Body weight reduction | 1–5 kg | 2–5 kg |
| Induction of nausea | 20–50%, attenuates slowly (weeks to many months) | 20–40%, attenuates quickly (~4–8 weeks) |

The individual properties of the various GLP‑1 receptor agonists might enable incretin-based treatment of type 2 diabetes mellitus to be tailored to the needs of each patient [13]. On the basis of the differential pharmacology of GLP-1-mediated therapies, selection of the agent to use should depend, at least in part, on the glycaemic disturbance that is in most need of correction. Because postprandial hyperglycaemia is the major contributor to HbA1c in subjects close to the target goals, short-acting GLP-1R agonists should be considered early in the disease and as part of combination therapy for patients nearing glycaemic goals, especially if weight loss would be beneficial. Long-acting GLP-1R agonists should be considered when larger reductions in HbA1c are needed, when fasting glucose elevations are the main problem, and when weight loss would be beneficial [15].

**Expert position:**

- There are studies showing that in people with diabetes the post meal plasma glucose might be a stronger predictor of cardiovascular events than fasting plasma glucose in type 2 diabetes
- Although many agents improve overall glycaemic control, including post meal plasma glucose levels, several pharmacologic therapies specifically target post meal plasma glucose: α-glucosidase inhibitors, glinides, short-acting sulfonylureas, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors and short acting insulin.
- From these classes the glucose-lowering effectiveness of non-insulin pharmacological agents is said to be high for sulfonylureas and GLP-1 agonists (expected HbA1c reduction ~1.0–1.5%) and generally lower for meglitinides, DPP-4 inhibitors and AGIs (~0.5–1.0%)
- Because postprandial hyperglycaemia is the major contributor to HbA1c in subjects close to the target goals, short-acting GLP-1R agonists should be considered early in the disease and as part of combination therapy for patients nearing glycaemic goals, especially if weight loss would be beneficial. Long-acting GLP-1R agonists should be considered when larger reductions in HbA1c are needed, when fasting glucose elevations are the main problem, and when weight loss would be beneficial.

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