

Implications of Postprandial Glucose and Weight Control in People With Type 2 Diabetes

Understanding and implementing the International Diabetes Federation guidelines

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The International Diabetes Federation (IDF) recently published guidelines for the management of postmeal hyperglycemia. These guidelines were established in view of the risk of postmeal hyperglycemia for vascular events. Because of the rising incidence and prevalence of diabetes and its complications, the IDF took action to state useful strategies for the treatment of diabetes, focusing on the detection and therapy of postprandial hyperglycemia. Besides nonpharmacological measures (blood glucose self-control and diet), drugs such as short-acting insulinotropic agents (sulfonylureas and glinides), glucosidase inhibitors, insulin, and incretin-based therapies can specifically be used to act on postmeal glucose elevations. The specific action profiles of these agents are shown and discussed with respect to the IDF guidelines.

POSTMEAL HYPERGLYCEMIA AS A RISK FACTOR IN TYPE 2 DIABETES

Type 2 diabetes is a chronic and progressive disease that affects ~250 million people worldwide today, with an increasing incidence in the years to come (1). With this epidemic dimension, type 2 diabetes is of global concern. Poor control of the disease is a leading cause of death in most developed countries and is associated with microvascular complications (renal failure and blindness due to retinopathy) and macrovascular complications (cardiovascular disease and stroke) as well as neurological

complications such as diabetic neuropathy. Macrovascular complications are the major cause of death in type 2 diabetic patients (2–7).

Numerous epidemiological studies have shown that postprandial hyperglycemia substantially adds to the micro- and macrovascular risk not only in type 1 and type 2 diabetes, but already in impaired glucose tolerance (2–4,8). The associations between postmeal hyperglycemia and markers of cardiovascular disease such as oxidative stress, inflammation, endothelial dysfunction, and carotid IMT have been well characterized. In addition, postprandial hyperglycemia has also been connected with the incidence of carcinomas and cognitive dysfunction in elderly type 2 diabetic patients (9–11).

Large intervention trials showed that antihyperglycemic therapy with treatment goals aiming at normoglycemia can significantly reduce the risk or the progression for the above-mentioned vascular risk (11–16). However, normalizing A1C alone is not sufficient in risk reduction. A distinct glycemic threshold for the reduction of complications has not been found; therefore, the goal of antidiabetic treatment should be to achieve near-normoglycemia as safely as possible regarding A1C, fasting plasma glucose, and postprandial glucose concentrations. Because normal A1C levels cannot be reached by treating fasting plasma glucose alone, postprandial glucose also has to be considered in therapeutic strategies. Therefore, treatment of fasting and post-

meal hyperglycemia should be initiated simultaneously at any A1C level. Especially at lower A1C concentrations, the proportional contribution of postprandial glucose to A1C is greater than at higher A1C values (17). In addition, a prospective intervention study in a cohort with impaired glucose tolerance demonstrated that by reducing postmeal glucose with a pharmacological intervention by using an α -glucosidase inhibitor, macrovascular events could be reduced significantly (9).

OBJECTIVE OF THE IDF GUIDELINES FOR THE MANAGEMENT OF POSTMEAL GLUCOSE

The objective of the IDF guidelines for the management of postmeal glucose was to present data on the exact relationship of postmeal hyperglycemia and the development of diabetic complications. From this evidence, recommendations have been developed and stated in the guidelines to aid clinicians to effectively treat postprandial hyperglycemia in type 1 and type 2 diabetes.

Contents of the guidelines

The guidelines were developed evaluating and weighing the available literature and expert knowledge with established methods of evidence-based medicine with respect to specific questions concerning the treatment of postmeal glucose. The specific questions raised and their recommendations were as follows.

Is postmeal hyperglycemia harmful? Postmeal hyperglycemia is harmful and should be addressed.

Is treatment of postmeal hyperglycemia beneficial? Implement treatment strategies to lower postmeal plasma glucose in people with postmeal hyperglycemia.

Which therapies are effective in controlling postmeal plasma glucose? A variety of both nonpharmacologic and pharmacologic therapies should be considered to target postmeal plasma glucose.

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Table 1—Glycemic goals for clinical management of diabetes according to the IDF guideline “management of postmeal hyperglycemia”

Glycemic parameter	Target value
A1C	<6.5%
Premeal glucose (fasting)	5.5 mmol/l (<100 mg/dl)
2-h postmeal	7.8 mmol/l (<140 mg/dl)

What are the targets for postmeal glycemic control and how should they be assessed?

1) Two-hour postmeal plasma glucose should not exceed 7.8 mmol/l (140 mg/dl) as long as hypoglycemia is avoided. 2) Self-monitoring of blood glucose should be considered because it is currently the most practical method for monitoring postmeal glycemia. 3) Efficacy of treatment regimens should be monitored as frequently as needed to guide therapy toward achieving postmeal plasma glucose target.

The guideline contains a conclusion that the glycemic goals stated in Table 1 should be reached, unless there are other concerns (mainly safety regarding hypoglycemia) or other limitations of therapy.

IMPLEMENTING THE GUIDELINE

Lifestyle intervention

Type 2 diabetes is a chronic condition where metabolic control and therapy are to a large extent patient driven. For this reason, the majority of treatment guidelines have implemented patient education and lifestyle intervention as an important first step to improve the metabolic parameters and risk factors. Patients should be taught to change to a healthier lifestyle with increased physical activity and to change to a diet with an appropriate caloric intake with a reduction in fat and refined carbohydrates. Patients should be instructed, supported, and motivated to make the necessary changes to successfully implement an appropriate lifestyle intervention.

The glycemic index (GI) describes the postmeal incremental area under the plasma glucose curve of carbohydrates in individual foods. Most modern starchy foods have a relatively high GI. Foods with a lower GI (vegetables, most fruit, whole grains) contain starches and sugars that are more slowly digested and ab-

sorbed. In a meta-analysis, diets with a lower GI were associated with modest improvements in A1C. Furthermore, glycemic load has been identified as an independent risk factor for myocardial infarction. In summary, the GI has a positive effect on postmeal glucose and cardiovascular risk factors (18).

Furthermore, the patient should know his or her therapeutic goals for glycemic parameters and how to monitor them according to the disease state and to the treatment strategy. Self-monitoring of blood glucose allows patients with type 2 diabetes to obtain actual concentrations of their blood glucose with sufficient accuracy. By measuring fasting and postmeal glucose, patients have good feedback on their glucose excursions and can make therapeutic decisions based on those measurement results. The frequency of testing depends on the kind of therapy; in treatment with an intrinsic hypoglycemia risk such as insulin therapy or treatment with sulfonylureas and glinides, more frequent measurements should be recommended, and measurements should also be performed when hypoglycemic symptoms occur (19).

Treatment with agents that lower postprandial hyperglycemia

Considering pharmacological treatment, besides an initial therapy with metformin that is suggested as first-line therapy in type 2 diabetes for all patients that have no contraindications to this drug, there is a variety of agents that by their mode of action act on postmeal hyperglycemia. The choice of drugs should always take the efficacy for the patient, safety, and cost-benefit aspects into account.

SULFONYLUREAS AND GLINIDES

— These agents stimulate insulin secretion in a glucose-independent manner by closing the potassium/ATP channel on the β -cells. This action leads to a depolarization of the β -cells with a consecutive rise in intracellular calcium that triggers insulin release. Glinides (repaglinide and nateglinide) have a much shorter action of only a few hours compared with sulfonylureas because of their pharmacokinetic properties. When given at mealtimes with the beginning of the meal, postprandial glucose is lowered effectively. The occurrence of hypoglycemia is associated with the glinides, but some studies report a lower incidence of hypoglycemia compared with sulfonylurea therapy (20). When choosing a sul-

fonylurea, the action time should be considered. In patients with renal impairment, sulfonylureas may show a longer duration of action, whereas the pharmacokinetics of glinides is not affected.

Sulfonylureas and glinides are effective in stages of type 2 diabetes when β -cell mass is still sufficient to secrete appropriate amounts of insulin. From clinical studies, it is known that the failure rate to sulfonylurea therapy amounts to at least 5–10% per year (4).

α -Glucosidase inhibitors

α -Glucosidase inhibitors competitively inhibit the intestinal enzyme catalyzing the degradation of disaccharides into monosaccharides that are finally absorbed from the small intestine. In this respect, α -glucosidase inhibitors specifically act on the slowing of carbohydrate absorption after a meal and specifically lower postprandial glucose. Because of their unique mechanism of action, they can be given at any stage of type 2 diabetes, either as monotherapy (where they have even shown a reduction in the progression from the pre-diabetic state of impaired glucose tolerance to type 2 diabetes) or in combination with other agents (9,21,22).

Insulin therapy

Short-acting insulins specifically address postprandial hyperglycemia when given in a meal-adapted manner. Regular human insulin has a maximal action \sim 2 h after injection and a duration of action of \sim 4 h, depending on the dose injected. The fast-acting insulin analogs were developed to mimic the physiological insulin response after a meal with a better action profile than regular human insulin and can also be used for prandial insulin therapy (23).

Biphasic premixed insulins contain a certain proportion of fast-acting insulin (either regular human insulin or a fast-acting analog) together with an intermediate-acting insulin and can also lower the postprandial glucose excursions of the meals, especially those that are ingested after the insulin injection (24–27).

INCRETIN-BASED THERAPIES

Dipeptidyl peptidase IV inhibitors

Dipeptidyl peptidase IV (DPP-4) inhibitors inhibit the enzyme dipeptidyl-peptidase IV, which cleaves and inactivates the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-

gon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP). These hormones are physiologically secreted by endocrine cells in the intestine postprandially and stimulate insulin secretion in a glucose-dependent manner after a meal. They contribute to ~70% of the postprandial insulin secretion. The biological half-life of both hormones amounts to only a few minutes after a meal due to DPP-4 action. Besides stimulating insulin secretion under hyperglycemic conditions, GLP-1 also suppresses glucagon secretion and thereby lowers glucose by inhibiting hepatic glucose output. It further slows gastric emptying and increases satiety. DPP-4 inhibitors raise endogenous GLP-1 (and GIP) concentrations, resulting in a significant improvement of glycemic parameters by enhancing the above-described actions of GLP-1 including normalized postprandial glucose. DPP-4 inhibitors are effective in early stages of type 2 diabetes, either as monotherapy or in combination with metformin or other oral monotherapies for type 2 diabetes. They are weight neutral and have no intrinsic risk for hypoglycemic episodes. The DPP-4 inhibitors have few known side effects; nasopharyngitis and skin reactions are side effects that occur with a low incidence (28,29). Currently, sitagliptin is approved in many countries and vildagliptin has just received approval from the European Medicines Agency (EMA). Further DPP-4 inhibitors are in development.

GLP-1 receptor agonists

GLP-1 receptor agonists are peptides that use GLP-1 action and can be used as an injectable therapy in type 2 diabetes. Presently, exenatide is the only GLP-1 receptor agonist approved. It is a synthetic version of the naturally occurring peptide exendin-4 that has a high amino acid sequence similarity to native GLP-1, but is DPP-4 resistant. In comparison to DPP-4 inhibitors, weight loss is observed in patients treated with exenatide and amounts to 3–5 kg in clinical studies. Exenatide has been shown to be equally effective in lowering A1C in patients failing oral therapy (with metformin and/or sulfonylurea) as insulin. In contrast to insulin therapy, the reduction of postprandial glucose was superior with exenatide compared with insulin glargine. For this reason, exenatide can be advantageous for patients where hypoglycemic episodes have to be avoided and an increase in body weight as observed with insulin therapy is not de-

sirable. The main adverse effect of exenatide is nausea, which affects ~40% of patients at the beginning of therapy but is mild to moderate and transient. Antibodies are observed in >30% of patients treated, but these are not cross-reacting with endogenous GLP-1 and are not neutralizing (28,30). Liraglutide, a human GLP-1 analog, is in phase III clinical trials. Besides, a long-acting release form of exenatide (exenatide LAR) is also in clinical testing as well as other GLP-1 receptor agonists on a peptide basis.

A POSSIBLE TREATMENT ALGORITHM FOR POSTMEAL HYPERGLYCEMIA: WHAT DO WE KNOW, WHAT DO WE NEED?

— All the drugs discussed above have shown their efficacy in lowering postmeal glucose. Dietary intervention is always (independently from the disease state and duration of diabetes) a fundamental cornerstone in the therapeutic strategy addressing postmeal hyperglycemia.

Acarbose specifically acts on postmeal hyperglycemia and has lowered cardiovascular events in a prospective randomized double-blind clinical trial in subjects with impaired glucose tolerance. In type 2 diabetic patients, a meta-analysis also showed a reduction of cardiovascular events in patients treated with acarbose. However, gastrointestinal side effects and costs are a barrier to a broad use of this compound (9,22).

Presently, many epidemiological studies show an association of postmeal (or postchallenge) hyperglycemia and cardiovascular risk. However, data on the beneficial effect of a pharmacological intervention on cardiovascular end points are scarce and still missing for the just recently released compounds (DPP-4 inhibitors, GLP-1 receptor agonists).

An intensified insulin therapy in type 2 diabetes significantly reduces microvascular complications. The reduction of macrovascular risk, however, has not clearly been established.

In recent long-term trials addressing glycemic goals for the treatment of type 2 diabetes, a lowering of A1C to levels not below 6.5% leads to a significant reduction in microvascular end points, but macrovascular end points were not reduced significantly. A vigorous reduction of the A1C below levels of 6.5% lowered nonfatal cardiovascular events but increased mortality for reasons that are not fully understood. In this intensively treated group

of patients, the majority of participants with a baseline A1C >8.0% received an antidiabetic combination therapy of more than two drugs and gained significantly more weight than the patient group having a higher A1C goal (31,32). In this respect, a safe antihyperglycemic treatment not leading to hypoglycemia and weight gain may be favorable, especially in patients with A1C values in the range below 7.5%, where postprandial hyperglycemia contributes to a higher degree to the A1C reduction.

In general, however, we will need intervention studies to investigate the effect of postmeal hyperglycemia and its treatment on outcomes. These studies will have to be large and will need to have a long duration to clarify the open questions that still remain.

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