New challenges in the clinical practice

Postprandial glycemia and glycemic variability: new targets to achieve optimal glycemic control in patients with type 2 diabetes

Glucemia posprandial y variabilidad glucémica: nuevos objetivos para conseguir el control glucémico óptimo en los pacientes con diabetes tipo 2

F. Gómez Peralta, C. Abreu Padín
Endocrinology and Nutrition Unit. Health Care Complex of Ávila. "Endocrinology and Nutrition Unit. Health Care Complex of Segovia

Postprandial hyperglycemia: definition and psychopathological implications

In persons with a normal glucose tolerance, the levels of plasmatic glucose do not usually exceed the 140 mg/dL after the meals and they recover the pre-prandial values in 2-3 hours. When this does not happen, we talk about the postprandial hyperglycemia (PPH). The International Diabetes Association (IDF) has recently published a guideline for the control of the postprandial glucose. The IDF and other organizations define the normal glucose tolerance as a plasmatic glucose lower than 140 mg/dL, 2 hours after an oral glucose overload (OGO) of 75 g. This temporal reference is usually used for the measurement of the PPH, though the peak might occur between 1 and 4 hours after the intake. The American Diabetes Association (ADA) has suggested that, “generally, a measurement of plasmatic glucose 2 hours after the beginning of a meal is practical, it usually gets close to the peak value in diabetic patients and provides a reasonable assessment of the PPH”. In persons with T2D, the PPH is an early phenomenon in its natural history, preceding the fasting hyperglycemia. The hyperglycemia and the postprandial hyperlipemia (“postprandial condition”) cause disturbances considered atherogenic: oxidation of the LDL cholesterol, disturbance of the endothelial function, activation of the coagulation (“prothrombotic condition”), increase of the production of pro-inflammatory cytokines (“pro-inflammatory condition”) and oxidative stress.

The contribution of the fasting and postprandial glycemia to the global glycemic control is different depending on the level of glycosylated hemoglobin (HbA1c) (figure 1). The contribution of the PPH increases when the level of the HbA1c is lower. Thus, in patients with HbA1c between 7.3 and 8.4%, the postprandial hypoglycemia contributes in more than 50% to the total daytime hyperglycemia. Several epidemiological studies demonstrated that the level of glucose 2 hours after an OGO is a strong predictor of cardiovascular risk, better than the fasting glucose.

Based on several intervention studies with drugs which hypoglycemic effect is especially postprandial, it is recommend- ed to control the postprandial hyperglycemia in order to reduce cardiovascular events. Recently, the HEART2D study has tried to compare specifically the difference in the reduction of cardiovascular events through an intervention addressed to improve the PPH (“prandial strategy”: 3 doses of insulin lispro) and an other addressed to reduce the fasting/pre-intake glycemia (“basal strat-
Glycemic variability: definition and physiopathologic implications

Different studies have demonstrated that the complications associated to the DM are due, partially or to a great extent, to the dysglycemia. This concept includes at present not only the sustained hyperglycemia, but also the acute fluctuations of the glycemia. The glycemic variability (GV) is a measurement that quantifies the frequency and intensity of these fluctuations (therefore, it includes the PPH), and might contribute to the description of the glycemic control additionally to the information provided by the classic methods for its assessment (fasting and/or postprandial glucose and HbA1c). Recent studies show that the glycemic variability increases the oxidative stress in patients with T2D, as well as certain inflammatory parameters in subjects with metabolic syndrome.

The methods to quantify the glycemic variability have been revised recently in an exhaustive way by Ruiz de Adana et al. in this same journal. The systems of continuous glucose monitoring allow a measurement both of the glycemic control and the GV. Besides its application in investigation, these systems might be very useful as an education tool and to adjust treatments with the specific objective of reducing the PPH and the GV.

PPH and GV as targets of the T2D treatment

The relation that exists between the fasting glucose or the HbA1c and the macroangiopathy is weaker than the one observed with the microangiopathy. These data support the hypothesis that the fasting glucose or the HbA1c are not able to explain the glycemic disturbances of the T2D exclusively and completely neither its association to the increase of cardiovascular risk and other chronic complications. The therapeutic strategies focused to improve the PPH and the GV tend to achieve a glycemic profile close to the physiological and not only a mean glycemia or a global glycemic load (HbA1c) within the proposed ranges.

The first suggested measure to improve the PPH is to monitor it. The self measured capillary glucose (SMCG) has demonstrated the improvement of the HbA1c (priority clinical objective with the current scientific evidence) in T2D structured programs in which the patients receive the necessary information about the way of performing a SMCG, and both these and the professionals in charge of the T2D treatment know about the changes to carry out depending on the results. The proposed capillary glycemia targets vary in the different clinical guidelines of the T2D treatment (table 1). Probably, it is very important in this aspect to agree on customized targets coherent with the HbA1c target. As regards to the nutritional treatment, it seems reasonable, and there exists scientific data, which guarantee it, the use of diet plans with a low glycemic index.

Regarding to the pharmacological treatment, though there are no definitive evidences about the superiority of some options versus others in the treatment of the T2D, the use of drugs that have a satisfactory cost-efficiency profile and that are adequate at the moment of the natural history of the patient are recommended. Some of them have shown a special reduction of the postprandial glycemia and additional benefits for the reduction of the already mentioned atherogenic changes in the PPH. Most of them have an action mechanism and a pharmacodynamics that make less probable the hypoglycemics in the last postprandial or interprandial period (2-5 hours after the intake), which might reduce the GV also.

The alpha-glucosidase inhibitors (acarbose and miglitol) are one of the first proposed options. The trial with acarbose STOP-NIDDM, besides reducing the PPH and other benefits, proved a reduction of 49% of cardiovascular event risk. This might be an interesting option in initial phases of T2D, especially in obese persons. The glinides (repaglinide and nateglinide) have a faster starting action and a half-life lower than the sulphonylureas, showing interesting reductions of the PPH. They might be associated to other drugs addressed more to the control of the preprandial glycemia, as the basal insulins and/or the insulin sensitizers. A study that compared repaglinide with glibenclamide could demonstrate a reduction of the intima-media thickness with the first one that is correlated to the reduction of the PPH and not with the basal glycemia. The new insulin fast analogues (lispro, aspart, glulisine) have faster action starting and a shorter half-life than the sulphonylureas, showing interesting reductions of the PPH. They might be associated to other drugs addressed more to the control of the preprandial glycemia, as the basal insulins and/or the insulin sensitizers. The dipeptidyl peptidase 4 (DPP-4) (sitagliptine, vildagliptine) have been recently commercialized. They increase the active form of the peptide similar to the glucagon 1 (GLP-1) and stimulate the insulin secretion on glucose dependent basis. They improve the PPH with low risk of

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**Table 1. Objectives recommended by different international organizations for HbA1c, fasting glycemia and postprandial glycemia in T2D**

<table>
<thead>
<tr>
<th>Organization</th>
<th>HbA1c (%)</th>
<th>Fasting glucose (mg/dL)</th>
<th>Postprandial glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Diabetes Federation (IDF)†</td>
<td>&lt;6.5</td>
<td>&lt;100</td>
<td>&lt;140</td>
</tr>
<tr>
<td>American Diabetes Association (ADA)‡</td>
<td>&lt;7</td>
<td>70-130</td>
<td>&lt;180</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists (AAE)§</td>
<td>≤6.5</td>
<td>&lt;110</td>
<td>&lt;140</td>
</tr>
</tbody>
</table>

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hypoglycemics and, therefore, the GV. The GLP-1 analogues (exenatide, liraglutide) also achieve the stimulation of the insulin secretion on a glucose dependent basis and might reduce the weight. Compared to other regimes, such as isolated basal insulin-therapy, they have demonstrated a better postprandial control and less hypoglycemics.

Conclusions

Many epidemiologic and experimental data point out the harmful effects of the PPH and the GV. Very smartly, they have been integrated to the current description of the dysglycemia physiopathology and the T2D. Specific measures for the monitoring and handling are recommended as collected recently by the guideline of the IDF for the treatment of the postprandial glucose, besides global glycemic control measurements, as the HbA1c or the fasting glycemia. Anyway, more trials are needed to prove the expected benefits of strategies addressed expressly to improve the PPH and the VG in persons with T2D, and its efficiency and safety at mean and long term, both of each individual drug and of combinations designed with a physiological model.

Declaration of potential conflict of interest

F. Gómez Peralta and C. Abreu Padín state that there are no conflicts of interest as regards to the content of this article.

References