Postprandial reactive hypoglycemia: myth or reality?

Defini
tion
The postprandial reactive hypoglycemia (PRH) is a physiopathological condition in which compatible symptoms to hypoglycemia in postprandial situation appear, usually during the 4 hours after food intake, coinciding with glycemia lower than 60 mg/dL. This entity has been widely questioned, mainly due to the different criteria used to define hypoglycemia, the lack of specificity concerning its clinical manifestations and to the inappropriate use of the glucose tolerance test. A large part of the confusion is due to the diagnostic procedure used. Most fundamental are the interpretation of the clinical manifestations reported by the patient together with the blood sugar concentration at the time when the symptoms occur. The clinical manifestations reported by the patients can be made evident through different diagnostic tests. The main tests are the glucose tolerance test, the hyperglucidic breakfast test, ambulatory capillary blood glucose monitoring and continuous interstitial glucose monitoring. At first these patients are treated with a low-carbohydrate diet, with meals spread throughout the day. However, some of those patients will require a pharmacological treatment. The most commonly used drugs are the α-glucosidase inhibitors, although many others have been used.

Keywords: reactive hypoglycemia, glucose tolerance test, hyperglucidic breakfast test, ambulatory capillary blood glucose monitoring, continuous interstitial glucose monitoring.

Abstract
Postprandial reactive hypoglycemia is characterized by symptoms that are compatible with hypoglycemia in a postprandial situation, usually within 4 hours of eating, coinciding with blood sugar levels below 60 mg/dL. This entity has been widely questioned, mainly due to the different criteria used to define hypoglycemia, to the lack of specificity concerning its clinical manifestations and to the inappropriate use of the glucose tolerance test. A large part of the confusion is due to the diagnostic procedure used. Most fundamental are the interpretation of the clinical manifestations reported by the patient together with the blood sugar concentration at the time when the symptoms occur. The clinical manifestations reported by the patients can be made evident through different diagnostic tests. The main tests are the glucose tolerance test, the hyperglucidic breakfast test, ambulatory capillary blood glucose monitoring and continuous interstitial glucose monitoring. At first these patients are treated with a low-carbohydrate diet, with meals spread throughout the day. However, some of those patients will require a pharmacological treatment. The most commonly used drugs are the α-glucosidase inhibitors, although many others have been used.

Keywords: reactive hypoglycemia, glucose tolerance test, hyperglucidic breakfast test, ambulatory capillary blood glucose monitoring, continuous interstitial glucose monitoring.

Resumen
La hipoglucemia reactiva postprandial se caracteriza por síntomas compatibles con hipoglucemia en situación posprandial, habitualmente durante las 4 horas postingesta, coincidiendo con glucemias menores de 60 mg/dL. Esta entidad ha sido muy cuestionada, fundamentalmente debido a los diferentes criterios utilizados para la definición de hipoglucemia, a la inespecificidad de la clínica y al uso inapropiado de la sobrecarga oral de glucosa. Gran parte de la confusión se debe al procedimiento diagnóstico utilizado. Lo fundamental es la interpretación de la clínica que refiere el paciente junto con la concentración glucémica en el momento de los síntomas. La clínica referida por los pacientes se puede poner de manifiesto con diferentes test diagnósticos. Los principales son la sobrecarga oral de glucosa, el test de desayuno hiperglucídico, la monitorización ambulatoria de glucemia capilar y la monitorización continua de glucosa intersticial. Inicialmente estos pacientes son tratados con una alimentación baja en hidratos de carbono, con ingesta repartida a lo largo del día. Sin embargo, algunos de ellos necesitarán tratamiento farmacológico. Los fármacos más utilizados son los inhibidores de las α-glucosidas, aunque se han utilizado otros muchos.

Palabras clave: hipoglucemia reactiva, sobrecarga oral de glucosa, test de desayuno hiperglucídico, monitorización ambulatoria de glucemia capilar, monitorización continua de glucosa intersticial.
Hofeldt classified the PRH in five categories: 1) those that appear in patients with incipient diabetes mellitus or carbohydrate intolerance (hypoglycemia might appear if the insulin secretion peak is delayed, when glycemia levels are decreasing...), 2) the secondary ones to a gastrointestinal dysfunction (the most frequent one is the dumping syndrome after gastrointestinal surgery); 3) PRH due to hormonal deficit; 4) PRH due to hepatic gluconeogenesis deficit (infrequent genetic enzymatic defects in carbohydrate metabolism, as hereditary intolerance to fructose and galactosemia, that take place during childhood), and 5) the idiopathic PRH.

We will focus on the idiopathic PRH (IPRH) in this revision. After considering several values as hypoglycemia diagnostic, there seems to be a consensus to use the threshold of 60 mg/dL in venous blood, since that the contra-regulatory mechanisms start under this value to recover from hypoglycemia. In the Third International Symposium on Hypoglycemia, held in Rome in 1986, a consensus was reached in which it was indicated that, though this entity was over diagnosed, there was no doubt that some patients showed suggestive hypoglycemia symptoms each day, and if these symptoms came together with glucose levels between 50 and 45 mg/dL or lower (determined by capillary or arterial glycemia, respectively), the diagnosis of IPRH was correct.

**Physiopathology**

The physiopathology of IPRH has been quite clarified during the last years. As it can be observed in the figure 1, two settings can be defined. One of them is characterized by the existence of hyperinsulinism, with a delay in the insulin peak compared to the glycemia peak. The cause of the hyperinsulinism has been classically assumed by the existence of insulin resistance, but it has been set out that a fast postprandial increase in the glycemia might induce to an excessive response in insulin secretion mediated by the previous secretion of incretines, as glucagon-like-peptide-1 (GLP-1), originating the reduction of glycemia levels finally. Consequently, the contra-regulatory hormones are activated (catecholamine, cortisol, growth hormone and glucagon) to restore the glycemic balance. Some of these hormones, especially the adrenalin, might cause the IPRH suspicion symptoms.

The other setting takes place without hyperinsulinism and might be applied by a urinary glucose loss, that in some series represent 15% of the cases. It has also been pointed out the possibility of a higher insulin-sensitivity in studies with euglycemic hyperinsulimic clamp or with the minimal model, with an increase in the glucose cap- tation by means of non-oxidative mechanism. Other authors considered an alteration in the secretion and sensitivity of the glucagon. An example of serious PRH with hyperinsulinism and absence of glucagon response after the hypoglycemia is the deficit of the hepatic-glucose-6-phosphatase described by Pears et al. The possibility of immunologic and genetic alterations have also been analyzed, but no anti-insulin antibodies nor mutations in the genes Kir6.2 or Sur1 have been found to present.

**Diagnosis**

The frequency and even the existence of this entity is a matter of discussion, and a wide part of the confusion is
due to the used diagnostic procedure. The main aspect is the interpretation of the clinic that refers the patient together with the glycemic concentration at the moment of the symptoms.\textsuperscript{2}

Thus, it has to exist first a clinical suspicion of the existence of IPRH. The usual symptoms mentioned in the bibliography are quite unspecific (table 1),\textsuperscript{12} and though it has been tried to determine its onset with a score of 0 to 5, it is not used in the usual clinical practice. On the other hand, these patients might show postprandial hypoglycemia with hyperinsulism and it is necessary to rule out the organic causes of the hyperinsulinism previously, especially all the insulinoma, which will be the subject of another article.

The clinic that the patients refer can be considered with different diagnosis tests. The most usual ones mentioned in the bibliography are summarized in table 2.

### Oral glucose overload

This is the most used diagnosis test, in spite of being advised against due to different reasons.\textsuperscript{9} Results should be understood with precaution, as at least 10% of the asymptomatic patients show a glucose nadir of <50 mg/dL after 4-6 hours from the OGO,\textsuperscript{13} and up to 5% might show glucose concentrations of <43 mg/dL. Several studies have proved that there is no correlation between the glucose concentration and the onset of symptoms during the test,\textsuperscript{14} and the abnormalities are not so reproducible.\textsuperscript{15} Many patients with postprandial adrenergic symptoms show similar symptoms after the administration of placebo.\textsuperscript{13} Moreover, the findings encountered in the response to an OGO are not reproducible after a test of mixed meal. In view of the aforementioned, other diagnosis strategies have been proposed.

### Mixed meal test (breakfast)

Theoretically, it is a more physiological test than OGO. The initial studies have been performed with too balanced breakfasts from the nutritional point of view, therefore no hypoglycemia events were found, which leads to the conclusion that the IPRH did not exist. Then, Brun et al. described a hyperglycicidic breakfast that depicted the diet habits of the patients with IPRH suspicion more accurately. This test supposes an intake of 80 g of bread, 10 g of butter, 20 g of ham, 80 mL of concentrated skim milk, 10 g of sugar and soluble coffee (2.5 g), what suggests 500 kcal with 9.1% of proteins, 27.5% of lipids and 63.4% of carbohydrates. It has to be mentioned that it provides an equivalent quantity of carbohydrates to the OGO of 75 g, it originates similar increases of glycemia in patients with carbohydrate intolerance and proved its usefulness in the diagnosis of hypoglycemia.\textsuperscript{16} These authors found it strange to observe glycemies lower than 60 mg/dL in individuals without hypoglycemia symptoms (1-2.2%), while in patients with IPRH suspicion values of <60 mg/dL were found in 47.30% of the cases. However, they hardly detected glycemia cases lower than 50 mg/dL. After these findings, the authors propose the hyperglycicidic breakfast test as an alternative to the OGO for the IPRH diagnosis.\textsuperscript{16}

### Ambulatory capillary glycemia monitoring

Another method to determine the IPRH diagnosis is the demonstration that there is a relation between the onset of the symptoms and a concentration of abnormally low postprandial glucose when taking normal meals and carrying out the usual activities, that might be corrected quickly with the intake of carbohydrates. The ambulatory capillary glycemia monitoring (ACGM) is the choice method. Palardy et al.\textsuperscript{17} investigated 28 patients referred due to IPRH suspicion by means of this technique and they found glycemias <60 mg/dL at the moment of the symptoms in 46% and values of <50 mg/dL in 18%. These findings made this test to be considered as the reference pattern for the diagnosis of the IPRH. However, it might happen that when the patient experiences the...
symptoms, the contra-regulatory response has already been triggered versus the hypoglycemia and no low values of glycemia are detected (false negative).  

Continuous interstitial glucose monitoring
The continuous interstitial glucose monitoring (CIGM) allows a practically constant measurement of the glucose concentration in the interstitial liquid, that shows a great parallelism with its blood concentration. This characteristic overcomes the problem of the false negatives commented in the case of using ACGM. Simpson et al. conclude in their study that most of the symptoms attributed to hypoglycemia were not accompanied by low concentrations of glucose in the CIGM. Especially, the neurogenic symptoms and all the mixed events did not have any relation with the glycemic alterations. These authors suggest the role of the intake of food with high sugar content as trigger of such symptomatology.

Figure 2 depicts a diagnosis strategy for the patients with clinical IPRH suspicion.

Treatment
Initially, these patients should be treated with a diet low in carbohydrates and rich in proteins, with intakes distributed throughout the day. It is recommendable to avoid the intake of foods with carbohydrates of fast absorption and drinks rich in glucose or sucrose and alcohol. Another usually recommended measurement is the addition of soluble dietetic fiber, with the aim of delaying the absorption of carbohydrates. Most of the patients respond to the diet changes. In case of worsening of the symptoms with a diet low in carbohydrates, a deficiency in the fructose enzyme 1-6 diphosphatase has to be suspected and the intake should be increased.

However, some patients shall need besides pharmacological treatment (Table 3). The inhibitors of the alpha-glycosidases are the choice treatment of the postprandial hyperglycemia due to the capacity to delay the absorption of carbohydrates. The acarbose, an inhibitor of alpha-glycosidases, has proved that it prevents the hypersecretion of insulin and PRH. The biguanides have also been recommended: it has been suggested the taking of metformin in a dose of 500-850 mg in each meal. As regards to the glitazones, the usefulness of the pioglitazones have recently been communicated as treatment of the PRH in a patient with previous diagnosis of intolerance to carbohydrates.

Other treatments have also been used, as the following ones: anticolinergic, adrenergic antagonists, calcium antagonists, fenitoin, calcium gluconate, chromo, diazoxide, somatostatin analogues and adrenal extracts. Some authors have proposed the surgical treatment with the reversion of a proximal jejunal segment.

Case report
As example of the existing controversy about this entity, we provide a recently studied case in our Depart-
ment. A patient aged 30 with suggestive symptoms of postprandial hypoglycemia, consisting in perspiration, trembling and postprandial weakness (3 hours after intake) of 3 months of evolution, that appear once a week. As relevant clinical data, it has to be pointed out that anxiety has been diagnosed 6 months before, starting treatment with venlafaxine and presented a body mass index of 25.6 kg/m$^2$. Besides proving the normality of the renal, hepatic and suprarenal function, an OGO was done with 75 g of 5 hours of duration, whose results are depicted in table 4. The patient showed symptoms as the ones mentioned in the consultation coinciding with the glucose nadir, after 3 hours of starting the OGO. Afterwards, a CIGM of 120 hours was carried out during which no value under 70 mg/dL (figure 3) appeared despite of appearing compatible symptoms in two occasions. Moreover, the ACGM necessary for the correct calibration of the CIGM did not either objectified hypoglycemia at any moment during the study (values between 71 and 108 mg/dL). ACGM: ambulatory capillary glycemia monitoring; CIGM: continuous interstitial glucose monitoring.

Our conclusion, even taking into account the contrary opinions to the use of the OGO, is that this patient has an IPRH, considering the results of the ACGM. Therefore, the diet modifications recommended for this pathology started, achieving the onset of the symptoms in the patient up to now, without needing any additional pharmacological treatment.

**Conclusions**

The IPRH is a controversial entity and probably over diagnosed due to different reasons. However, during the last years a consensus has been reached about the definition of the hypoglycemia and there are diagnostic tests that might help for a more objective identification (hyperglycemic breakfast, ACGM and CIGM) and to know...
better its real prevalence. The treatment is still based on the diet measures, and when these measures are not sufficient, some drugs might help to its control.

Declaration of potential conflict of interests
F.J. Escalada, S. Laguna and S. Botella state that there are no conflicts of interest as regards to the content of this article.

References