Introduction

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) proved conclusively that the development of chronic complications of the diabetes can be prevented/delayed by means of a strict glycemia control. In the DCCT, the patients assigned to the intensive treatment received multiple doses of insulin with regular insulin and NPH insulin, or continuous subcutaneous insulin infusion (CSII) with regular insulin. However, in spite of

Hypoglycemia unawareness syndrome.

Risk factors and treatment

Síndrome de falta de reconocimiento de la hipoglucemia.

Factores de riesgo y tratamiento

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Abstract

Hypoglycemia unawareness is a major limiting factor in the management of type 1 and advanced type 2 diabetes. This common problem, which occurs in about 25% of patients treated with insulin, is characterized by loss of autonomic warning symptoms before development of neuroglycopenia. Hypoglycemia unawareness is also associated with ∼7-fold increase in the risk to suffer severe hypoglycemia. Several risk factors for hypoglycemia unawareness have been identified, including long duration of diabetes, tight glycemic control (low HbA1c values), and repeated episodes of hypoglycemia. Reduction of counterregulatory hormone responses to hypoglycemia are primarily responsible for hypoglycemia unawareness. Strict avoiding of hypoglycemia restores almost completely awareness of hypoglycemia. Therefore, several therapeutic strategies have been designed to prevent hypoglycemia. Among them, evening NPH insulin splitting, continuous subcutaneous insulin infusion, preferential use of insulin analogues and, more recently, continuous glucose monitoring have been proved to be effective in most cases.

Keywords: hypoglycemia, hypoglycemia unawareness, type 1 diabetes, intensive treatment, continuous glucose monitoring.

Resumen

La falta de reconocimiento de la hipoglucemia es un importante factor limitante del tratamiento en la diabetes mellitus tipo 1 y tipo 2 avanzada. Este problema, que ocurre hasta en un 25% de los pacientes tratados con insulina, se caracteriza por una pérdida de los síntomas autónomos de alarma antes de la aparición de la neuroglucopenia. La hipoglucemia inadvertida se asocia a un incremento aproximadamente 7 veces el riesgo de sufrir hipoglucemias graves. Se han identificado diversos factores de riesgo para la hipoglucemia inadvertida, incluida la diabetes de larga duración, el control metabólico estricto (valores bajos de HbA1c) y los episodios repetidos de hipoglucemia. La disminución de la respuesta contrarreguladora frente a la hipoglucemia es la causa principal de la hipoglucemia inadvertida. Evitar estrictamente las hipoglucemias restablece casi completamente su percepción. En consecuencia, se han desarrollado diferentes estrategias terapéuticas para prevenir las hipoglucemias. Entre ellas, el desdoblamiento de la insulina NPH nocturna, la infusión subcutánea continua de insulina, el uso preferente de los análogos de insulina y, más recientemente, la monitorización continua de glucosa, han demostrado ser efectivas en la mayoría de casos.

Palabras clave: hipoglucemia, hipoglucemia inadvertida, diabetes tipo 1, tratamiento intensivo, monitorización continua de glucosa.

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List of acronyms quoted in the text:
CSII: continuous subcutaneous insulin infusion; DCCT: Diabetes Control and Complications Trial; HUS: hypoglycemia unawareness syndrome; NPH: neutral protamine Hagedorn; T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; UKPDS: United Kingdom Prospective Diabetes Study.
the high motivation degree of the patients included in this study and the adequate educational support, the intensive insulin treatment was associated to a higher frequency of hypoglycemias (almost 3-folds more) than the conventional treatment.3

With the intention of achieving the normalization of glycemia reducing the risk of hypoglycemia to the minimum, new insulins have appeared during the last years with a more physiologic and reproducible profile.4 The new rapid-acting insulin analogues (lispro, aspart, glulisine), try to simulate the insulin secretion that takes place after the intake with a more early starting and a less duration of action.4 On the other hand, the long-acting insulin (glargine, detemir) have a more predictable and sustainable absorption, a longer duration of action and a lower variability, imitating the basal insulin secretion that takes place during the night and the pre-prandial period.4 However, in spite of the advantages described about the insulin analogues, hypoglycemias are still the most important adverse effect of the insulin treatment.

When the hypoglycemias are frequent, besides being potentially dangerous and feared by the patients, they can lead with time to the loss of alarm symptoms, generally of adrenergic origin, as trembling, perspiration, palpitations, etc. This phenomenon is known as hypoglycemia unawareness syndrome (HUS). It has been described both in patients with T1D and T2D under insulin treatment and it is one of the most important limiting factors of the treatment.5

The frequency of the HUS in patients with T1D and T2D are described below in detail as well as the risk factors that favor its onset, its potential consequences and the most appropriate treatment for its prevention and/or restoration of the hypoglycemia symptoms.

**Definition. Epidemiology**

The HUS is characterized by the lack of recognition when the levels of plasmatic glycemia decrease the values that trigger physiologically the onset of the alarm adrenergic symptoms versus the hypoglycemia (approximately 55 mg/dL [3 mmol/L]).6 Therefore, the patients with HUS do not perceive that the hypoglycemia is decreasing and that this decrease might end causing neuroglycopenia. Alternatively, if patients notice any symptomaticatology, this appears with lower glycemia levels.

The onset of HUS in patients under insulin treatment obliges to take into account several considerations. First, in the absence of symptoms, the patients do not correct the ongoing hypoglycemia and are not able to prevent the onset of neuroglycopenia and the hypoglycemia coma in extreme cases. Therefore, the HUS is a circumstance that predisposes the patient to suffer serious hypoglycemias, even with loss of consciousness up to 6-7 folds.7,8 Secondly, the HUS is a frequent problem that seems to affect one of 4 patients with T1D.9 In third place, it is necessary to take into account new insulin treatment strategies that favor the achievement of the glycemic objectives, reducing the hypoglycemia risk to the minimum and the HUS accordingly.

But, which is the incidence of serious hypoglycemias in patients with T1D and T2D? In the DCCT, the incidence of serious hypoglycemias that require the assistance of a third person was of 61.2 per 100 patients-year, increasing its incidence with the reduction of the HbA1c achieved in the patients under intensive treatment in Diabetes Control and Complications Trial1.

![Figure 1. Increase of serious hypoglycemia risks with the strict metabolic control in patients with T1D. Progressive increase in the serious hypoglycemia incidence (for 100 patients-years) with the reduction of the HbA1c achieved in the patients under intensive treatment in Diabetes Control and Complications Trial](image)
serious hypoglycemia are an important complication of the insulin treatment, both in the advanced T1D and T2D, especially in patients with a higher duration of insulin treatment.

As regards to the prevalence of HUS, a recent study evaluated this aspect in a sample of 518 patients with T1D, selected randomly during a period of 2 years. These authors proved a prevalence of HUS of 19.5% using a validated questionnaire to evaluate the presence of cognitive dysfunction associated to the hypoglycemia and a retrospective analysis of serious hypoglycemia events. These data suggest that even at present a high prevalence of HUS persist in patients with T1D, in spite of the pharmacokinetic advantages of the new insulins, the implementation of intensive treatments as preferable therapeutic option and the diffusion of the therapeutic education.

There exists few data about the presence of HUS in patients with T2D. It is admitted that the neuro-endocrinous response versus the hypoglycemia can be found so altered in patients with advanced T2D as in patients with T1D. In a classic study, Mitrakou et al., by means of the use of specific questionnaires, indicated that approximately 20% of the patients with T2D under insulin treatment showed the HUS. In spite that these data are similar to the ones obtained in T1D, it seems that the contra-regulatory response in the T2D shows some differential aspects, though they are not detailed in this article.

**Contra regulator altered response in the hypoglycemia unawareness syndrome**

The hypoglycemia takes place when there is an excess of insulin and a deficient contra-regulatory response (figure 2). The brain is the most exposed organ to the hypoglycemia, since the oxidation of the glucose is the main energy source. Moreover, this organ is not able to synthesize or store relevant quantities of glucose in glycogene form. Therefore, the correct functionality of the brain requires a constant and sufficient supply through the blood flow. Under normal circumstances, the brain glucose sensors are the ones that activate the defense mechanisms facing the hypoglycemia, and trigger the release of contra-regulatory hormones and the onset of symptoms afterwards. If the neuro-endocrinous response is deficient, the hypoglycemia might be even longer and serious.

The physiologic neuro-endocrinous response versus the hypoglycemia is relevant according to the level of plasmatic glycemia decrease. Initially, the insulin endogenous secretion suppression takes place (with glycemia of 78-80 mg/dL), which produces the portal hyperinsulinemia. Then, when the glycemia achieves values of approximately 65 mg/dL, the release of contra-regulatory hormones is activated (glucagon, adrenalin, cortisol, growth hormone). Afterwards, the onset of characteristic symptomatology takes place (autonomic and neuroglycopenic) when glycemia is placed in levels close to 55 mg/dL. Finally, a deterioration of the cognitive function takes place with glycemia levels of 50-54 mg/dL.
Seminars on diabetes
Hypoglycemia unawareness syndrome. F.J. Ampudia-Blasco

For further information on this regard, another seminar can be consulted which is included in this edition.

However, these thresholds of response are dynamic and might vary according to the precedent glycemia levels. In healthy individuals, the controlled induction of hypoglycemia during the day or the night is able to alter the hormonal response on the next day as well as the moment of the symptoms onset. Similar effects have also been observed in patients with T1D. This neuro-endocrinous dysfunction, especially the increase of adrenalin levels after a recurrent hypoglycemia, though present, might be of less magnitude in women. In these patients, the thresholds that activate the hormonal response and the onset of the symptoms might decrease after chronic or recurrent hypoglycemias. Therefore, the responses versus the hypoglycemia take place with lower levels, increasing the risk of cognitive dysfunction and serious hypoglycemia.

Moreover, with time, a progressive loss of glucagon response versus hypoglycemia in patients with T1D takes place. Under these conditions, the secretion of adrenalin turns into the essential component of the contra-regulatory response. However, many patients show also deficient adrenergic responses, especially after recurrent hypoglycemias and/or in the context of long duration diabetes. These patients with glucagon and adrenalin deficient response have a risk up to 25 folds of suffering serious hypoglycemias with the intensive treatment, especially during the sleep. Fortunately, these alterations are potentially reversible. Avoiding the hypoglycemias during at least 2 days it is possible to normalize the neuro-endocrinous response and increase the perception of symptoms versus the hypoglycemia.

The hypoglycemias are less frequent in patients with T2D. When these hypoglycemias take place or are recurrent, the alterations associated to the contra regulator response are less serious than in T1D, and the thresholds for the hormonal response are higher (between 7 and 23 mg/dL). In general, these defects appear in patients with advanced T2D, especially in those who have not undergone an insulin treatment during years.

Risk factors
Several risk factors of HUS have been identified during the last years, as age, the longest duration of the disease, a stricter glycemic control (lower values of HbA1c) and the existence of previous recurrent hypoglycemias (table 1). In the study of Geddes et al., the patients with HUS were older (45.9 versus 39.3 years; p <0.001), with an evolution time of the higher diabetes (23 versus 14 years, p <0.001) and showed up to 6 folds more hypoglycemia events in the preceding year (2.36 versus 0.38 events per person-year; p <0.001).

In the usual clinical practice, the patients under insulin intensive treatment showed frequent hypoglycemias. But, unlike serious hypoglycemias, there is not much information about the real frequency of mild and asymptomatic hypoglycemias. The frequency of mild hypoglycemias in the DCCT was of 0.1-0.3 events/patients-day. These mild events, treated generally by the patients themselves, are often underestimated and not too documented. However, the recurrent mild hypoglycemias, especially the night hypoglycemias, might alter deeply the recognition of these situations and the contra-regulatory response. In this context, the patients loose the alarm symptoms initially (autonomous) and the HUS appears afterwards. With time, besides the loss of glucagon secretion, an alteration of adrenalin secretion takes place versus hypoglycemia, increasing the risk of serious and recurrent hypoglycemias.

The presence of autonomous neuropathy seems to be another additional HUS risk factor, and therefore, the serious hypoglycemias. The patients with autonomous dysfunction have up to 1.7 folds more risk of suffering serious hypoglycemias than those without neuropathy. However, the relation between autonomous neuropathy and the HUS is not completely clarified. Many patients with determined HUS show curiously normal cardiovascular tests.

Consequently, the intention is to achieve glycemic objectives without increasing the hypoglycemia risk by means of the most advanced insulin treatments. Therefore, to design strategies for the prevention of hypoglycemia is a fundamental aspect in the therapy with insulin in diabetic patients.

Potential consequences of recurrent hypoglycemias
Some of the possible consequences derived from recurrent hypoglycemias are summarized below.
Lower therapeutic compliance

The patients with HUS show a lower compliance of the recommended changes to reduce the frequency of hypoglycemias, even using structured prevention programs. The habituation to the stress associated to hypoglycemias reduce the risk perception, reducing the results of the therapies addressed to the recovery of symptoms and to the prevention of serious hypoglycemias.

Restrictions to driving vehicles

The presence of HUS might increase potentially the risk of accident in case of driving vehicles. For this reason, there are driving restrictions in many countries of Europe for diabetic patients, with implications going from the performance of more frequent medical revision to the denial of a driving license to risk groups, as the patients with HUS. The guideline 91/439 of the European Union states that the diabetic patients under treatment with insulin might not drive trucks, heavy vehicles or buses.

Cognitive dysfunction?

Several periodical evaluations have been carried out in the DCCT of multiple psychosocial and behavior parameters in both treatment groups. In spite of the largest frequency of serious hypoglycemias in the intensive treatment group, no signs of cognitive dysfunction were found, even in patients with recurrent hypoglycemias. However, other studies suggest possible defects in certain motor skills or spatial vision that seem to be linked to the frontal lobule, especially in patients with recurrent hypoglycemias.

Treatment: prevention/reversion of hypoglycemia unawareness syndrome

Fanelli et al. have been the first ones who proved that the careful prevention of hypoglycemias in patients who had them previously (at least one hypoglycemia event per day) entails the disappearance of HUS, with a recovery of the symptoms and the hormonal response versus hypoglycemia. These findings have been confirmed in other reports afterwards. Moreover, to avoid the hypoglycemia allows restoring the altered adrenalin secretion in diabetic patients of long evolution at least in part.

Several strategies have been used with the aim of preventing hypoglycemias and consequently avoid/revert the HUS. Some of them are detailed below:

• Avoid night hypoglycemias by means of a splitting of a mixture of regular/NPH insulin before dinner, in a regular insulin dose before dinner and another NPH insulin dose before lying down. This strategy was used (and is still in use) mainly in patients wit T1D, before the introduction of the long-acting insulin analogues.

• Substitution of the NPH night insulin for CSII during the night.

• Preferable use of fast insulin analogues (lispro, aspart, glulisine), immediately before the meals. These analogues reduce the late hypoglycemia risk, besides achieving a better postprandial glycemic control.

• Use of long-acting insulin analogues (glargine, detemir) that allow the most appropriate substitution of the basal and interprandial needs of insulin versus the NPH insulin. Several works have proved that these drugs reduce the risk of serious hypoglycemias, especially night hypoglycemias, both in T1D and T2D with an efficiency comparable to the NPH insulin.

• The CSII treatment represents the insulin therapy modality with lower hypoglycemia risk. This treatment is specially indicated in patients motivated who do not achieve the therapeutic objectives. The use of the Paradigm Real-Time system (Medtronic, Minneapolis, United States) that associates the administration of insulin to the continuous glucose monitoring (in the interstitial liquid of the subcutaneous cell tissue), might be useful in patients with serious and recurrent hypoglycemias.

• The use of continuous glucose monitoring systems in the detection of hypoglycemias, especially night hypoglycemias. This technique can also allow the identification of improvable aspects that have not been de-

Table 1. Risk factors of the hypoglycemia unawareness syndrome*

<table>
<thead>
<tr>
<th>Dependent of the patient</th>
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<tbody>
<tr>
<td>T1D or T2D under insulin treatment</td>
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<tr>
<td>Advanced age</td>
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<td>Longer duration of the diabetes</td>
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<td>Presence of autonomous neuropathy</td>
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<tr>
<td>Dependent of the treatment</td>
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<tr>
<td>Intensive treatment with insulin (versus conventional treatment)</td>
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<tr>
<td>Longer duration of the insulin treatment (T2D)</td>
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<tr>
<td>Therapeutic guidelines with regular insulin and/or NPH</td>
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<tr>
<td>Stricter metabolic control (lower levels of HbA1c)</td>
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<tr>
<td>Recurrent hypoglycemias, especially at night</td>
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<td>Serious hypoglycemia history</td>
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*For a better understanding of the table, the enclosed text can be looked up.
to achieve and keep an HbA1c level of <7%. Therefore, it is necessary to protect previously for a better implementation of the insulin therapy. Application of hypoglycemia risk prediction models helps to prevent / revert the HUS, contributing to the clinical practice as it affects 1 over 4 patients.

However, in order to prevent the onset / progression of the chronic complications of the diabetes it is necessary to achieve and keep an HbA1c level of <7%. Therefore, it will be necessary to increase the motivation of the patients with advanced T1D and T2D. This problem is frequent in the clinical practice as it affects 1 over 4 patients.

To avoid strictly hypoglycemia restores almost completely the perception of them. Consequently, any therapeutic strategy associated with lower hypoglycemia risk (insulin analogues, CSII, etc.) is indicated in patients affected by the hypoglycemia unawareness syndrome.

Conclusions

When the HUS appears, it represents an important limitation to the treatment with insulin in patients with advanced T1D and T2D. This problem is frequent in the clinical practice as it affects 1 over 4 patients.

However, in order to prevent the onset / progression of the chronic complications of the diabetes it is necessary to achieve and keep an HbA1c level of <7%. Therefore, it will be necessary to increase the motivation of the patients with advanced T1D and T2D. This problem is frequent in the clinical practice as it affects 1 over 4 patients.

To avoid strictly hypoglycemia restores almost completely the perception of them. Consequently, any therapeutic strategy associated with lower hypoglycemia risk (insulin analogues, CSII, etc.) is indicated in patients affected by the hypoglycemia unawareness syndrome.

Practical considerations

• The lack of recognition of the hypoglycemia is very important limiting factor of the insulin treatment, which might affect up to a forth part of the patients with advanced T1D and T2D.
• The unnoticed hypoglycemia is associated to an increase of approximately 7 folds the risk of suffering serious hypoglycemia. This risk might increase up to 25 folds in case of serious glucagon and adrenaline deficit.
• To avoid strictly hypoglycemia restores almost completely the perception of them. Consequently, any therapeutic strategy associated with lower hypoglycemia risk (insulin analogues, CSII, etc.) is indicated in patients affected by the hypoglycemia unawareness syndrome.

Declaration of potential conflict of interests

F.J. Ampudia-Blasco received fees for conferences and/or consultancy of Abbott, Bristol-Mayers-Squibb, GSK, LifeScan, Lilly, Madaus, MannKind Corp., Medtronic, Menarini, Merck Funay y Quimica S.A., MSD, Novartis, NovoNordisk, Pfizer, Roche, sanofi-aventis, Schering-Plough and Solvay. He has also taken part in clinical trials totally or partially financed by Astra-Zeneca, Bayer, GSK, Life-Scan, Lilly, MSD, NovoNordisk, Pfizer, sanofi-aventis and Servier.

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