Editorial
GLP-1 agonists as an alternative to basal insulin in type 2 diabetes

Review
Blood pressure alterations in patients with type 1 diabetes

Seminars on diabetes
Hypoglycemia
Hypoglycemias in type 1 and 2 diabetes
Hypoglycemia unawareness syndrome. Risk factors and treatment
Postprandial reactive hypoglycemia: myth or reality?
Insulinoma. Diagnostic criteria and treatment

Original articles
Analysis of the results of continuous subcutaneous insulin therapy as an alternative to intensive treatment in type 1 diabetic patients
Knowledge of insulin treated diabetic patients about food carbohydrate content. Results of a survey
The impact of obesity and glycemic control on birth weight in gestational diabetes
Perioperative mortality in diabetic patients after non traumatic lower extremity amputations in Madrid from 1997 to 2005

Up-to-Date
Platelet flow cytometry in diabetes mellitus and in other metabolic-vascular pathologies

Case report of diabetes discussed by experts
Insulin treatment in an obese patient and a secondary diabetes due to pancreatectomy

New challenges in clinical practice
Potential risks of hypoglycaemia in patients with type 2 diabetes

Pictures in clinical diabetes
Diabetic patient with breastbone painful mass

Selected original articles analysed by experts

News
The maintenance of glycemic control in the T2D usually requires a series of progressive steps. The use of basal insulinization seems to be one of the main strategies, being a useful therapy, well evaluated and of a generalized use at present. However, such treatment is not exempt from certain limitations, and among which the following are of particular interest: the need of dose adjustment, with the consequent use of capillary glycemia self-control, its association with a relevant weight gain, which might have a negative effect on the disease course through the worsening of the metabolic control and cardiovascular risk profile; the possibility of hypoglycemia, which might have a negative impact on the morbidity, the mortality and patient’s life quality, and finally, the lack of action on the postprandial hyperglycemia.

The GLP-1 analogues (glucagon-like peptide-1) constitute a new therapeutic group, which is available at present for the treatment of the T2D. They act through the stimulation of the insulin secretion and the inhibition of glucagon, according to circulating glucose. Moreover, they count with a series of favorable characteristics, among which the following ones can be stated: lack of hypoglycemia, delay in the gastric emptiness and its beneficial effects on appetite regulation and body weight, its special action on the postprandial glycemia and positive actions on morphology and beta cell function. Exenatide is available at present in our country, the first representative of this therapeutic group. The main limitations of this drug are the secondary gastrointestinal effects that appear in approximately 40% of the subjects, though they are usually transitional and ease off during the first weeks of the treatment; therefore they are not a withdrawal cause beyond 5-6% of the cases. Exenatide induces the onset of antibodies in 50% of the patients who receive the drug, without affecting its efficacy or presenting relevant side effects. Another GLP-1 analogue, liraglutide, is in a very advanced investigation phase.

Several works have compared the use of these therapies in patients with T2D over 9 years of evolution under treatment with metformin and/ or sulphonylureas. An identical efficiency has been proved in all of them regarding to the HbA1c, though it takes place through a better control of the basal glycemia with insulin glargine and a higher effect on the postprandial glycemia with exenatide. A favorable ponderal evolution is also constant with exenatide and negative with insulin glargine, observing
differences at the end of the studies that range between −2.2 kg after 16 weeks and −4.6 kg after 52 weeks. The gastrointestinal effects were frequent with exenatide, 42.6-57.1% versus 3.1-8.6% with insulin glargine. A greater proportion of patients interrupted the treatment due to the side effects of the exenatide, mainly nauseas and vomiting. The frequency of hypoglycemias was similar to the addition of insulin glargine when exenatide was combined with sulphonylureas, but it was significantly lower when associated to the use of metformin (2.6% versus 17.4% with insulin glargine).

A randomized study has been published recently that compared the beta cell function with exenatide and insulin glargine. A similar reduction of HbA1c could be proved again (0.8 versus 0.7%) and both groups reached an HbA1c of 6.8% after 52 weeks. The final weight difference was of 4.6 kg. Both treatments improved the sensitivity to insulin identically, which was only kept after 4 weeks of treatment suspension with exenatide. The group that received the drug showed a relevant improvement in all the measurements of beta cell function. However, after 4 weeks of drug suspension, the beta cell function returned to the pre-treatment levels. The onset of nauseas was stated in 50% of the patients who received exenatide and the frequency of hypoglycemia was higher with glargine (8.3 versus 24.2%).

The LEAD 5 study compared the use of liraglutide and insulin glargine in 581 patients with T2D, with a mean duration of 9.4 years, who received treatment with metformin and one sulphonylurea during 6 months. The available data shows an adequate glycemic control with the treatment guideline compared to insulin (−1.33 versus −1.09; p= 0.0015), with similar reductions of the basal glycemia. weight developed favorably with liraglutide (−1.81 kg) and negatively with glargine (+1.62 kg). Nauseas appeared in 14% of the patients who received liraglutide, and hypoglycemia frequency was not different between both treatments. Antibodies were detected versus liraglutide in 9.8% of the cases, without associating them to any relevant clinical effect.

The studies about life quality show similar results between exenatide and insulin glargine, in spite of the need of a higher number of injections in the first drug. The available data about cost-efficacy are scarce and contradictory: the superiority of insulin glargine is noted as regards to the exenatide in some cases, and the contrary resulted in other works.

All these data allow reasserting that the GLP-1 analogues have a similar effect on the glycemic control (HbA1c) regarding to the basal insulinization, and a higher control of post-prandial glycemia can be observed. The additional advantages of the treatment with GLP-1 analogues are that the patients show a favorable ponderal evolution and a lower rate of hypoglycemia, they do not require a dose adjustment or capillary glycemia self-control, and there is a possibility of improvement in beta cell function. Its main limitation is the presence of gastrointestinal side effects (table 1).

The LEAD 5 study made us put on the scale the use of this therapeutic group as an effective and adequate alternative compared to the basal insulinization in patients with T2D.

### Table 1. Differences between the treatment with GLP-1 agonists and the basal insulinization

<table>
<thead>
<tr>
<th></th>
<th>Basal insulin</th>
<th>GLP-1 analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need of dose adjustment and glycemia self-control</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight</td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gastrointestinal side effects</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Postprandial hyperglycemia control</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Improvement of beta cell function</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Declaration of potential conflict of interests
The author stated that he has not received any sort of financing as regards to the drawing up of this paper. The author received some type of economic compensation (conferences, congresses, etc.) from Abbott, Almirall, GSK, Lilly, MSD, Novartis, Nutricia, Pfizer, Roche, sanofi-aventis, Schering-Plough and Solvay.

References
**Review**

**Blood pressure alterations in patients with type 1 diabetes**

*Alteraciones de la presión arterial en pacientes con diabetes tipo 1*

F.J. Vilchez López,1 C. Coserria Sánchez,2 F. Carral Sanlaureano,3 M. Aguilar Diosdado4


**Abstract**

Hypertension and subclinical alterations of blood pressure (non-dipper pattern) increase the risk of chronic diabetes complications. In spite of this, there are few studies that analyze this problem in type 1 diabetic patients. Because of this, we have made an exhaustive search about this item in bibliographic databases (PubMed, Ovid). Prevalence of hypertension and non-dipper pattern is different depending on the methodology and population characteristics (hypertension: 8-58%; non-dipper pattern: 18-78%). Non-dipper pattern increases significantly the risk of microalbuminuria and retinopathy. Although there is evidence about the beneficial effect of a strict control of hypertension, at the moment we do not know exactly the beneficial effect of treating subclinical alterations of blood pressure in patient with values at normal range during standard measurement.

**Keywords:** ambulatory blood pressure monitoring, diabetes mellitus, non-dipper.

**Introduction**

The blood hypertension (BHT) increases potentially the risk of onset and progression of chronic complications in diabetic patients.1,2 It is considered that the increase of 20 mmHg as from 115 mmHg in the systolic blood pressure or 10 from 75 mmHg in the diastolic, duplicates the risk of cardiovascular events,3 and that between 35 and 75% of the diabetes complications are due to the coexistence of BHT.1 Moreover, the strict control of the blood pressure (BP) decreases significantly the morbidity and the mortality, both in patients with diabetes and in the general population.3,4
The prevalence of the BHT in patients with T1D differs significantly in the different publications according to the characteristics of the studied populations and the measurement method that is being used. Moreover, the normality criteria used vary depending on the date of each study, though the most common ones are 140/90 and 130/85 mmHg. At present, most of the scientific societies accept that the control objective of the BP in diabetic patients shall be lower than 130/80 mmHg.\(^5,6\)

The use of the ambulatory blood pressure monitoring (ABPM) is a more and more common technique that allows to detect subclinical alterations of the pressure values, as the non-dipper phenomenon or the masked BHT, that pass unnoticed in the isolated measurement of the BP. The results of the observational studies published during the last years suggest that the presence of these alterations is not innocuous, but it has an important repercussion. Thus, the loss of circadian rhythm of the BP increases the risk of developing complications, mainly microangiopathic, in diabetic patients.\(^7,8\)

The presence of these alterations in the usual follow-up is not usually evaluated among the patients with T1D. We count with scarce information about the prevalence and the potential relevance of these alterations of the BP in this population. Its early diagnosis would help to identify those patients with T1D at higher risk and would allow implementing the necessary measures to achieve the pressure control targets. In spite of that, prospective studies have not been designed so far that evaluate the potential benefit, which might suppose the pharmacology treatment in these patients.

The objective of this revision is to analyze the BHT prevalence and the subclinical pressure alterations in patients with T1D, as well as their clinical implications as regards to the development of diabetes chronic complications.

**Material and methods**

- Inclusion criteria. Randomized, prospective clinical studies, not prospective or not randomized clinical studies, systematic revisions, consensus documents of scientific societies and expert opinions. The search was limited to studies published in English and Spanish.

- Exclusion criteria. Not clinical studies, individual opinions.

**Methods**

Bibliographical search and revision of the works that comply with the inclusion criteria published up to December 2008 in PubMed and Ovid.

- Search terms: T1D; hypertension, blood pressure, circadian rhythm of blood pressure, non-dipper, ABPM, nephropathy, retinopathy, neuropathy, cardiovascular disease.

The clinical studies with greater interest have been chosen regarding both to the analysis of the BHT prevalence, and the pressure alterations detected by means of ABPM in patients with T1D; moreover those studies that related these alterations with triggering potential factors and with diabetes chronic complications have also been chosen.

The search was completed with the manual revision of the relevant quotations that appeared in the bibliography of the chosen articles.

**Results**

**Blood pressure measurement methods**

At present, we count with different techniques to measure the BP in ambulatory patients: the isolated BP measurement, the self-measurement blood pressure at home (SMBP) and the ABPM\(^9\) (table 1).

The most frequent technique is the isolated BP measurement, though this determination is usually left out in many patients with T1D during the medical visit,\(^10\) probably because these patients are considered normotensive, considering that they are usually young and without symptoms of cardiovascular disease. On the other hand, this technique does not reflect the variability of the BP: intrinsic factors to the patient himself, mistakes in the measurement technique and the turn of the observer induce the BHT diagnosis in 20-25% of the normotensive patients (isolated BHT at the office or white coat BHT).\(^11\)

The SMBP and the ABPM present several advantages compared to the isolated BP measurement: more reproducibility, limitation of the observer bias and lower alert reaction of the patient. Moreover, the results are better correlated to the affection of target organs and the
cardiovascular mortality, and provide valuable information about the effect of the hypertensive drugs. Moreover, the ABPM is the only technique that informs the BP while the patient carries out his daily activity and during the sleeping period, showing also the integrity or not of the circadian rhythm of the BP.9,12-16

The SMBP and the ABPM show also some limitations. The normality criteria, lower than those stated for the isolated measurement, are clearly determined for the general population, but we do not count with specific limits for the diabetic patients.3,16 In order to define the presence of BHT it has to be considered the BP mean during the activity period, as the 24-hour mean values might be affected by the higher or lower duration of the night rest and the sleep.15 Table 2 depicts the BP normality limits for the general population in each of the mentioned techniques.16 Other inconveniences of the ABPM are the possibility of interfering in the work or the sleep, the intolerance cases, its high cost and its limited reproducibility, though this is higher than the one obtained with the BP isolated measurements.17-19

**BHT prevalence in patients with T1D**

There are only a few studies, which have dealt with the prevalence and the level of BHT in patients with T1D. Below, the main results are detailed.

In the Pittsburgh Epidemiology of Diabetes Complications Study, published in 2001, 386 patients with T1D have been included (of 28 years of age and 20 years of mean evolution), observing an initial BHT prevalence of 12.9% (criterion: BP >140/90 mmHg or under the hypo-pressure treatment) that increased to 29% after 10 years of follow-up. Only 50% of the patients show BHT under control.20

Later, the Coronary Artery Calcification in type 1 diabetes Study (CACT1) analyzed a series of 652 patients with T1D aged 37 and with 23 years of diabetes mean evolution.21 43% of the patients was hypertensive (criterion: BP >130/85 mmHg) and though 83% received pharmacology treatment, only 55% complied with the control criteria according to the JNC-6 (recommended BP <130/85 mmHg).22

In Europe, the EURODIAB IDDM Complications Study23,24 analyzed the evolution of the BHT prevalence in a cohort of patients with T1D in the periods between 1989-1990 and 1997-1999. In the initial evaluation, 3,250 patients with T1D were studied, with a mean age of 33 years and 15 years of evolution, being 22% catalogued as hypertensive (criterion: BP >140/90 mmHg or under hypotensive treatment). Stratifying it according to the level of albuminuria, the BHT prevalence increased 15.2% in patients with normal albuminuria and 28.9 and 64.7% in patients with micro and macro-albuminuria, respectively.23 In the 1,886 patients evaluated 10 years after (1997-1999), the BHT prevalence increased up to 34%, though the increase was similar in all the age groups and the percentage of patients with diabetic nephropathy was not modified significantly. Likewise, the percentage of patients treated pharmacologically increased from 40 to 60%, and the rate of patients with BP levels lower than 130/85 mmHg passed from 12 to 28%.24

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**Table 1. Differences among the different blood pressure measurement methods**

<table>
<thead>
<tr>
<th>Blood pressure variable</th>
<th>BPSM</th>
<th>Conventional BP measurement</th>
<th>ABPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reliable information</td>
<td>Yes</td>
<td>Questionable</td>
<td>Yes</td>
</tr>
<tr>
<td>Circadian pattern</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dipper/non-dipper phenomenon</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Day increase</td>
<td>Yes</td>
<td>No</td>
<td>Questionable</td>
</tr>
<tr>
<td>Variability</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Duration of hypotensive drugs</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; BPSM: blood pressure self-measurement at home.

**Table 2. Levels of recommended normality for the three techniques of BP measurement for the European Hypertension Society 2007**

<table>
<thead>
<tr>
<th></th>
<th>SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated measurement</td>
<td>140</td>
</tr>
<tr>
<td>BPSM</td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>130-135</td>
</tr>
<tr>
<td>Night</td>
<td>120</td>
</tr>
<tr>
<td>ABPM</td>
<td>130-135</td>
</tr>
</tbody>
</table>

ABPM: ambulatory blood pressure monitoring; BPSM: blood pressure self-measurement; DBP: diastolic blood pressure; SBP: systolic blood pressure.
In our country, at the end of the 90s, an observational and multicenter study has been performed in which 18 hospitals of several autonomous communities took place (DIAMANTE study), that objective was to evaluate the prevalence of the diabetic nephropathy among the patients with T1D. Together, 1,821 patients have been analyzed with a mean age of 30.5 and 14 years of evolution, from which 22% showed diabetic nephropathy (14.1% microalbuminuria, 5% macroalbuminuria and 3.5% renal failure). The 11% of the patients were hypertensive (criterion: BP >140/90 mmHg). When stratifying them by the nephropathy level, the BHT criterion was complied by 4% of the patients with normal albuminuria, 14.8% of the patients with micro-albuminuria and 70% of the patients with evident nephropathy (albuminuria or renal failure). The 14% was under hypotensive treatment, mainly with ACEI.

A similar study performed in the Canary Islands, which included 142 patients with a mean age of 28 years and 11 years of evolution, detected a global BHT prevalence of 59% (criterion: BP >130/85 mmHg). When stratifying them by albuminuria level the BHT criterion was complied by 4% of the patients with normal albuminuria, the 71.4% of the patients with micro-albuminuria and 83.3% of the patients with evident nephropathy.

Finally, the recently published study EDIC (Epidemiology of Diabetes Interventions and Complications Study) provides interesting data about the follow-up of 1,375 patients who have been previously included in the DCCT (Diabetes Control and Complications Trial). After a mean of 15.8 years of follow-up, 45.8% have been diagnosed as hypertensive (criterion: BP >140/90 in at least 2 occasions or hypotensive taking). The 21.1% of the patients developed micro-albuminuria and 6.5% macro-albuminuria. In spite that, since the end of the DCCT, all the patients included in the EDIC followed an intensive insulin therapy, the BHT incidence was of 24% lower between the group of patients assigned to the intensive group during the DCCT compared to the group that received conventional treatment.

Table 3 sums comparatively up the results of the main works published up to present about the BHT in patients with T1D.

### Table 3. BHT prevalence studies in patients with T1D

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age (years)</th>
<th>Years of evolution</th>
<th>BHT (%)</th>
<th>Albuminuria (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study DIAMANTE(1997)25</td>
<td>1,822</td>
<td>30.5 ± 9.7</td>
<td>14.1 ± 9.2</td>
<td>11.3</td>
<td>22.6</td>
</tr>
<tr>
<td>De Pablos et al.(1997)26</td>
<td>142</td>
<td>27.9 ± 11.5</td>
<td>10.9 ± 7.6</td>
<td>58.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Collado-Mesa et al.(1999)23</td>
<td>3,250</td>
<td>33 ± 1</td>
<td>15 ± 10</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Zgibor et al.(2001)20</td>
<td>386</td>
<td>28</td>
<td>20</td>
<td>12.9</td>
<td>–</td>
</tr>
<tr>
<td>Soedamah-Muthu et al.(2002)24</td>
<td>1,866</td>
<td>40 ± 10</td>
<td>22 ± 9</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Maahs et al.(2005)21</td>
<td>652</td>
<td>37 ± 9</td>
<td>23.2 ± 8.9</td>
<td>43</td>
<td>21.8</td>
</tr>
<tr>
<td>Baena et al.(2008)27</td>
<td>489</td>
<td>33.6</td>
<td>16.6</td>
<td>8.27</td>
<td>8.6</td>
</tr>
<tr>
<td>De Boer et al.(2008)27</td>
<td>1,375</td>
<td>42.8</td>
<td>19.8</td>
<td>44</td>
<td>27.6</td>
</tr>
</tbody>
</table>

*BHT: higher values than 140/90 mmHg; BHT: values higher than 130/85 mmHg; BHT: values higher than 130/80 mmHg.

*These percentages refer to the total of individuals with albuminuria in different stages.

### Alterations in the circadian rhythm of blood pressure in patients with T1D

The BP is not consistent throughout the day, but it presents a circadian rhythm: it reaches a minimum during the first hours of sleep and increases during the first hours in the morning, coinciding with the transition between the sleep and the wakefulness. The mean BP difference, during the day and night, is from 10 to 20%, both in healthy subjects and in hypertensive subjects, physiological situation known as dipper pattern. Night decreases lower than 10% define a non-dipper pattern (figure 1).

### Etiopathogenic factors

It has been described that the non-dipper pattern appears with a higher frequency in blacks, in patients treated with steroids, in renal failure and even, in healthy individuals if the daytime activity has been intense or if they suffer sleep alterations.

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Alteration in the circadian rhythm of blood pressure in patients with T1D

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### Etiopathogenic factors

It has been described that the non-dipper pattern appears with a higher frequency in blacks, in patients treated with steroids, in renal failure and even, in healthy individuals if the daytime activity has been intense or if they suffer sleep alterations.
However, the etiopathogenic factors implied in the onset of the non-dipper phenomenon in patients with T1D are not really known. The autonomous neuropathy is stated as one of the most relevant. In a recent series of 117 patients with T1D, the non-dipper was more prevalent in those who had autonomous neuropathy. In a similar way, another study of 47 diabetic patients, normotensive, and with normal albuminuria, showed a lower night reduction of SBP and DBP among those with autonomous neuropathy (night decrease of SBP and DBP in patients with neuropathy versus patients without neuropathy, respectively: 3.4 ± 9.3 versus 9.7 ± 5.6 mmHg and 8.3 ± 9.2 versus 16.0 ± 6.0 mmHg).

At present, it has not been proved conclusively that diabetes metabolic control, age, disease evolution time, type of insulin therapy and smoking habit are directly related to the onset of pressure alterations detected in the ABPM.

Prevalence

Though the prevalence of the non-dipper pattern is more frequent among patients with diabetes and nephropathy, the studies that have evaluated this question in patients with normal pressure and normal albuminuria with T1D are scarce. The main ones are presented below.

In 1994, Gilbert et al. compared the results of the ABPM of 13 normotensive and normal albuminuria patients with T1D with a control group of 14 subjects without diabetes. The non-dipper phenomenon was defined as the presence of a BP night reduction lower than 10% or an absolute reduction of the SBP and DBP levels lower than 10/5 mmHg. Approximately 50% of the diabetic patients showed a non-dipper pattern of SBP and DBP (7 from the 13 patients showed a night reduction from SBP lower than 10%, 6 in the case of DBP and 5 showed a night reduction of the SBP/DBP lower than 10/5 mmHg).

Prevalence

Though the prevalence of the non-dipper pattern is more frequent among patients with diabetes and nephropathy, the studies that have evaluated this question in patients with normal pressure and normal albuminuria with T1D are scarce. The main ones are presented below.
control among the patients with dipper pattern and those with non-dipper pattern.\textsuperscript{37}

In the same year, Sivieri et al. carried out an ABMP to 17 patients with T1D, normal pressure and normal albuminuria and without autonomous neuropathy, and to a non-diabetic control group. Though the SBP and the DBP mean values during 24 hours were higher in the diabetic patients group, no relevant differences were found regarding to the variability of the 24 hours BP.\textsuperscript{38}

In 1996, Khan et al. detected a non-dipper pattern in 30.5\% or 41.6\% of the patients with T1D, normal pressure and normal albuminuria, versus 0.0\% or 13.0\% in the healthy control group, according to the criterion used (night decrease of BP lower than 10\% or an absolute reduction in the SBP/DBP levels lower than 10/5 mmHg, respectively). The changes in the BP variability were independent from the age, gender, HbA\textsubscript{1c} levels or isolated consultation BP.\textsuperscript{39}

Holl et al., in 1999, published a series of 354 adolescent patients with T1D and 1,121 healthy controls. The BP percentages in the different period were relevantly higher in the population with diabetes, in which the BP night reduction was, besides, lower (10 versus 13\% regarding to the SBP, and 18 versus 23\% regarding to the DBP), independent from the age. The authors did not detail the BHT prevalence nor subclinical alterations of the BP (non-dipper phenomenon) in this population.\textsuperscript{40}

In 2003, Cohen et al. informed the results of a series of 28 patients. In this case, the non-dipper phenomenon was considered as the BP night reduction lower than 10\% (systolic and diastolic). The non-dipper phenomenon was much more prevalent in the patients with diabetes (up to 78\% of the cases versus 43\% of the healthy patients). Only 18\% evidenced a joint systolic and diastolic non-dipper pattern.\textsuperscript{41}

In 2001, Lurbe et al. compared the circadian BP pattern of patients with T1D and different levels of nephropathy and a group of healthy controls, being the prevalence of the non-dipper pattern relevantly higher among the patients with nephropathy. In the subgroup of patients with normal albuminuria, including 57 subjects, 18\% showed a non-dipper pattern (defined as daytime DBP/night SBP lower than 1.07 or rate daytime DBP/night DBP lower than 1.12) and though this percentage was higher than in healthy controls (10\% non-dipper), the difference did not reach statistical significance.\textsuperscript{36}

Later, Darcan et al. diagnosed the BHT at 23.5\% of a pediatric series, when presenting the reading mean over the percentile 95 of BP for gender and age during a period of 24 hours (the 16.2\% were hypertensive during the daytime period and 32.4\% was at night). The 41.2\% showed a night reduction in the SBP or DBP lower than 10\% (non-dipper). In 16\% of the patients, micro-albuminuria was detected and in this group, non-dippers reached a prevalence of 63.6\%. There were no differences in the metabolic control level nor in the duration of the disease among the dipper and non-dipper patients.\textsuperscript{42}

Dost et al. informed in 2008 the results of the largest published series on this regard. They included 2,105 adolescents with T1D and 949 healthy controls. The mean pressures (SBP, mean BP [MBP] and DBP) both in the daytime period and at night were relevantly higher in the diabetic groups. Moreover, the night decrease of SBP and DBP was relevantly lower in this group compared with the controls (night reduction of SBP and DBP in patients versus controls, respectively: 10.00 \pm 5.7 versus 13.0 \pm 6.0\% and 16.8 \pm 8.1 versus 23.0 \pm 9.0\%, \textit{p} <0.0001). Among the diabetic patients, 49.1\% showed a non-dipper systolic pattern and 17.5\% a diastolic non-dipper pattern (criterion: night SBP reduction and DBP <10\%, respectively). Persistent microalbuminuria was detected in 6.1\% of the diabetic patients, which is a factor associated to a diastolic non-dipper pattern in the multivariate analysis.\textsuperscript{35}

Table 4 sums up the results of the commented works in relation to the prevalence of the dipper/non-dipper pattern in patients with T1D.

### Prognosis implications

The alterations in the BP circadian rhythm in patients with T1D constitute an independent risk factor regardless of the onset of micro and macro-angiopathic complications:

- **Diabetic nephropathy.** Up to some years ago, it has been accepted that the BHT in patients with T1D appeared as consequence of a renal affection, when there already existed an elimination of albumin in urine in pathological range. However, recent publications confirm that the onset of micro-albuminuria might be sec-

Lurbe et al. carried out periodically a ABPM to a cohort of 75 patients with T1D, with normal pressure and normal albuminuria, during 5 years of follow-up. In this study, it was shown that previously to the onset of micro-albuminuria (that happened in 19% of the sample) an increase took place in the night SBP, while in the patients with normal albuminuria the levels of the night SBP at the end of the study remained stable, without changes as regards to the ones at the beginning of the follow-up. Thus, the increase of 5 mmHg in the night SBP increased significantly the micro-albuminuria risk (relative risk [RR]: 1.44) and in the same way, a final non-dipper pattern showed a positive predictive value of 31% for the development of micro-albuminuria, regardless of the glycemic control. Lengyel et al., later, detected in the follow-up of 53 patients with T1D, normotensive and normal albuminuria that the development of microalbuminuria (45%) was associated directly to the reduction of the daytime DBP/night DBP quotient, with higher levels of HbA1c and the presence of retinopathy.

### Diabetic retinopathy

The BHT increases the risk of onset and progression of diabetic retinopathy in patient with T1D. The Renin-Angiotensin System Study included 194 patients with T1D, normal pressure and normal albuminuria, to whom a funduscopy and an ABPM were done. The 55% showed mild proliferative retinopathy and 13% serious-moderate non-proliferative diabetic retinopathy or proliferative. The seriousness of the retinopathy was positively correlated to the HbA1c levels and with the duration of the diabetes. Regardless of these variables, the night SBP levels were significantly higher in the group with higher retinopathy seriousness, 110 ± 9 mmHg in patients with retinopathy, 112 ± 9 mmHg in those with mild non proliferative retinopathy and 115 ± 9 mmHg in patients with serious non proliferative retinopathy or proliferative retinopathy (p= 0.002). The prevalence of the non-dipper pattern increased also in a parallel way to the seriousness of the retinopathy (19, 28 and 36% respectively), though in this case the differences did not reach the statistical value (p= 0.08). In this study, the patients with night SBP among the 3 higher quartiles (≥103 mmHg) showed a higher risk of retinopathy compared to those with night SBP in the first quartile (OR: 3.71; confidence interval (CI) of 95%: 1.5-9.16; p= 0.004). These results match with the previous studies, that detect association between retinopathy and night DBP or retinopathy and SBP and night DBP.

### Macroangiopathic complications

We have not found prospective studies that evaluate the association between the circadian rhythm of altered BP and cardiovascular disease in patients with T1D, though we count with some data that suggest certain association between both. In this sense, Sturrock et al. published a retrospective study that included 75 patients with diabetes (41% with T1D), from which 50% were non-dippers. After a mean follow-up of 42 months, the cardiovascular mortality was higher in patients with altered circadian pattern (28 versus 8%). On the other hand, in a recently published study, which included 48 patients with T1D, normal pressure and normal albuminuria, aged 17 years and 8 years of diabetes evolution, it was demonstrated that the left ventricular mass was significantly higher among the non-dippers, as well as the ventricular diameters at the end of the systole and diastole.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age (years)</th>
<th>Years of evolution</th>
<th>HbA1c (%)</th>
<th>Non “dipper” (%)</th>
<th>BHT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert et al.</td>
<td>13</td>
<td>38 ± 14</td>
<td>9.1 ± 5.5</td>
<td>7.8 ± 1.6</td>
<td>25.5 ± 1.5</td>
<td>25.5</td>
</tr>
<tr>
<td>Khan et al.</td>
<td>36</td>
<td>14.4 ± 2.1</td>
<td>4.0</td>
<td>8.6 ± 1.7</td>
<td>30.5-41.6</td>
<td>30.5</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>28</td>
<td>27 ± 7.1</td>
<td>9 ± 6.6</td>
<td>8.9 ± 2.6</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Lurbe et al.</td>
<td>57</td>
<td>20.9 ± 10.5</td>
<td>6.4 ± 5.6</td>
<td>8.7 ± 1.9</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Darcan et al.</td>
<td>68</td>
<td>14 ± 4.2</td>
<td>5.7 ± 3.5</td>
<td>9.16 ± 1.25</td>
<td>20 ± 3.5</td>
<td>20</td>
</tr>
<tr>
<td>Dost et al.</td>
<td>2,105</td>
<td>14 ± 4.2</td>
<td>5.15 ± 4.02</td>
<td>8.0 ± 1.8</td>
<td>20 ± 3.5</td>
<td>20</td>
</tr>
</tbody>
</table>

*HbA1c timel measurement; HbA1c measured from the diagnosis (method used for the non-detailed estimation in the original study); approximately 50%, according the used criterion.
Treatment
If the presence of a non-dipper pattern of BP increases the development and progression of the diabetes chronic complications, should we implement a treatment in the subjects with T1D clinically normotensive and normal albuminuria in which a circadian rhythm is detected of altered BP? We do not count with studies at long term and we have only found a study that evaluates the effect of the antihypertensive treatment in patients with T1D “clinically normotensive”, normal albuminuria, but with a non-dipper pattern of BP. Twenty-eight patients with T1D were included with the mentioned characteristics, being 18 of them treated with 2 mg/day of trandolapril, and the effect with a ABPM was evaluated in all the cases. Considering the controls, in the patients treated pharmacologically it could be observed a relevant decrease of BP in both periods as from the treatment starting, as well as a more marked night decrease both in the SBP (from 3 to 17.6%; p <0.05) and the DBP (from 5.1 to 19.4%; p <0.05) after two weeks of treatment.\(^{53}\)

Discussion
The BHT is a risk factor independent from the development and progression of the diabetes chronic complications.\(^{1,2}\) In spite of its relevance, there are only a few studies that have evaluated its prevalence in patients with T1D, as well as its control level.

With the data we count with at present, it is difficult to draw conclusions about the prevalence of the BHT in this population, considering that the results differ significantly in the different series. The main reasons are the use of different criteria about normality and the scarce homogeneity of the studied populations (table 3). Moreover, the prevalence in the different studies might be overestimated by two main reasons. First, because most of the studies use as BHT criterion the administration of hypotensive drugs, being likely that some patients with normal pressure shall undergo treatment with ACEI or ARA II for presenting microalbuminuria. Secondly, because the prevalence of the “physician phenomenon” (high isolated BP levels) is very high in the patients with T1D, reaching up to 75% in some series.\(^{54}\) Therefore, it would be interesting to count with studies of prevalence based on more reliable techniques, as the ABPM, though broad studies performed with this technique have not been found in the bibliographic revision.

On the other hand, the BHT control level has not been uniform either, though it is poor in most of the series. In the revised studies, less than 50% of the patients showed an adequate BHT control, except in the CACT1 study, where 55% of the patients showed BP values within the therapeutic target, probably because 83% was under hypotensive treatment, which is a quite high percentage compared to the rest of the studies.\(^{21}\)

The ABPM is the unique technique that allows knowing the BP during the daily activity and during the sleep. In this sense, it provides information about the circadian rhythm of the BP, which in normal conditions decreased a 10% during the night period; a phenomenon known as BP dipper pattern.\(^{9}\) The non-dipper pattern is stressed by BP decreases lower than 10%, which is an entity that has been related to higher co morbidity in the patients with T1D. There are no conclusive data about the prevalence of this phenomenon in this population. The results of the different series are difficult to compare: the sizes of the different samples are frequently small and the characteristics of the populations are quite heterogeneous (table 4). Moreover, a main problem is the lack of uniformity in the definition of the non-dipper phenomenon. Except for The Hypertension Spanish Guideline, which bases the definition on the reduction of the mean BP,\(^{15}\) the rest of the guidelines do not specify if the BP variability should be considered in the MBP, in the SBP or in the DBP.\(^{3,16}\) The studies published on this regard in patients with T1D use different criteria: decrease of the night SBP lower than 10%,\(^{7}\) decreases of the SBP and the night DBP lower than 10%,\(^{31,47}\) decrease of the night SBP lower than 10% and the night DBP lower than 5%\(^{36}\) or absolute night decrease of 10 mmHg for the SBP or 5 mmHg for the DBP.\(^{37}\) Regardless from the used criterion, the non-dipper pattern is significantly higher in patients with T1D compared to the general population of the same age and gender, not only among the patients with diabetic nephropathy,\(^{36,55-59}\) but also among patients with normal albuminuria.\(^{36,38-42}\) Khan et al. observed that 42% of the diabetic patients versus 13% of the healthy controls have a non-dipper pattern;\(^{39}\) for Cohen et al. these values were of 78% versus 43%.\(^{41}\) In the greatest series that has been published on this regard, which included 2,105 patients, it has been concluded that the night BP decrease was lower in the diabetic patients compared to the healthy controls, with relevant statistically differences.\(^{35}\)
Publications arisen during the last years manifest the relevance of these subclinical alterations of the BP, that affect a not despicable percentage of patients with T1D and that usually pass unnoticed during the follow-up. The risk increase seems to be more consistent when considering the micro vascular complications. The group of Lurbe et al. demonstrated that the night increase of the SBP levels increase the risk of developing microalbuminuria significantly, regardless from the metabolic control of the diabetes. Moreover, both the frequency of the diabetic retinopathy and its seriousness are higher among patients with an altered circadian pattern. Finally, it seems that the presence of a non-dipper phenomenon also increases the cardiovascular risk, but the only study that we have found in this sense is retrospective and includes both patients with T1D and T2D. Therefore it would be necessary to conduct prospective studies and performed exclusively with patients with T1D in order to clarify this matter. In any case, recently published data suggest an early left ventricular failure among the patients with T1D with non-dipper pattern.

Considering the frequency of the non-dipper phenomenon in the patients with T1D, with normal pressure and normal albuminuria, and the increase of the complications risk that represent, is it convenient to treat these patients pharmacologically? The group of Czupryniak et al. demonstrated an early correction of the BP circadian rhythm when treating a group of patients with these characteristics with ACEI. However, we do not count with long term studies that prove the potential benefit of the hypotensive treatment in these patients, as regards to the risk of chronic complications, therefore it is necessary to perform intervention studies to show the efficiency of this measure.

Finally, the use of ABPM might identify susceptible patients on whom to intensify the follow-up or start an early treatment if they progress to BHT, but to present it is not known which patients should be benefited nor the periodicity that the ABPM should be carried out. The revised clinical studies include heterogeneous samples as regards to age, diabetes evolution time, metabolic control etc., without the non-dipper pattern has been related clearly with none of these variables. Probably, these matters shall be clarified in the future, as far as the ABPM is incorporated in a more generalized manner to the clinical attention of T1D patients.

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**Practical considerations**

- Among the patients with T1D clinically normotensive and without nephropathy, the prevalence of a blood pressure (BP) non-dipper pattern is higher compared to the general population. This alteration passes unnoticed with the BP isolated measurement, therefore it is essential to define which patients with T1D catalogued as with normal pressure would be benefited with the performance of an ABPM, as well as the periodicity of it.

- The presence of BP subclinical alterations, as the non-dipper pattern, increases significantly the risk of onset and progression of chronic complications (mainly microangiopathic) in patients with T1D.

- It is necessary to design intervention studies at long term to clarify if the antihypertensive treatment of these subclinical alterations of BP is efficient in the prevention/progression of chronic complications in subjects with T1D clinically normotensive and with normal albuminuria.

**Conclusions**

At present, most of the evaluation and follow-up evaluation of patients with T1D incorporate the BP isolated measurement. However, this technique offers partial information; it presents a high variability, classifies wrongly the pressure status of some patients and does not reflect the presence of clinical alterations as important as the existence of a BP non-dipper pattern. This can be found altered in a high percentage of patients with T1D clinically “normotensive”, and constitutes a risk factor for the development and progression of chronic complications, mainly micro vascular. It is a need to perform follow-up studies at long term to prove if the early antihypertensive treatment in patients with BP subclinical alterations is translated into a decrease of the onset and progression of chronic complications in this population and, in that case, to design screening protocols of subsidiary patients of this measure.

**Declaration of potential conflict of interests**

F.J. Vilchez López, C. Coserría Sánchez, F. Carral Sanlaureano and M. Aguilar Diosdado state that there are no conflicts of interest as regards to the content of this article.


Hypoglycemia and fear to suffer them are limiting factors, both in patients with type 1 diabetes as well as type 2 diabetes, to achieve and maintain an adequate glycemic control to avoid appearance/progression of chronic complications. Frequency of hypoglycemic events mostly depends on the type of diabetes, employed treatment and individual risk factors. Events may be minor, asymptomatic, or severe even with loss of consciousness. Hypoglycemia may have important clinical outcomes due to an increase in morbidity and mortality and a reduction in quality of life. This situation is feared either by patients or their relatives. Economic implications of severe events, both as direct hospital costs as well as indirect costs due to inability to work are considerable. Therefore, hypoglycemia is the basic limiting factor to achieve glycemic control goals in patients with diabetes mellitus.

Keywords: minor hypoglycemia, severe hypoglycemia, type 1 diabetes mellitus, type 2 diabetes mellitus.

Introduction

Notwithstanding the advantages of trying to achieve the strict glycemic control objectives in the diabetes mellitus (DM), this fact might increase the mild, serious, unnoticed and night hypoglycemias.\textsuperscript{1-4} The frequency of hypoglycemia events depends on the type of DM, on the used hypoglycemic treatment and the individual risk factors. The brain depends on the continuous glucose contribution as a main energy source; when the plasma levels decrease up to a critical level, brain functions are affected which might cause confusion, convulsions or coma. The potential complications at long term of serious hypoglycemias, mainly those that develop with coma or epileptic crisis, have always been a reason of concern for the professionals and anguish for the patients. The transitory reduction of the cognitive functions might affect the most relevant daily activities, as driving.\textsuperscript{5} This seminar describes several considerations related with this complication in patients with T1D and T2D.

Abstract

Hypoglycemia and fear to suffer them are limiting factors, both in patients with type 1 diabetes as well as type 2 diabetes, to achieve and maintain an adequate glycemic control to avoid appearance/progression of chronic complications. Frequency of hypoglycemic events mostly depends on the type of diabetes, employed treatment and individual risk factors. Events may be minor, asymptomatic, or severe even with loss of consciousness. Hypoglycemia may have important clinical outcomes due to an increase in morbidity and mortality and a reduction in quality of life. This situation is feared either by patients or their relatives. Economic implications of severe events, both as direct hospital costs as well as indirect costs due to inability to work are considerable. Therefore, hypoglycemia is the basic limiting factor to achieve glycemic control goals in patients with diabetes mellitus.

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Introduction

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**Definition of hypoglycemia. Diagnosis**

The hypoglycemia work group of the American Diabetes Association (ADA)\(^6\) defines the hypoglycemia as a clinical event in which the typical symptoms of an hypoglycemia and a measurement of plasmatic glycemia <70 mg/dL (3.9 mmol/L), based on the reduction of the endogenous insulin and the increase of the pancreatic glucagon that is detected in healthy persons when they reach this glycemic level. Moreover, the ADA divides this entity in several categories that are depicted in table 1. The Canadian Diabetes Association (CDA)\(^7\) takes also the same value as considered by the ADA (<4 mmol/L [72 mg/dL]) and shares the definition that in 1938 Whipple offered, when he stated his “diagnostic triad”: compatible symptoms, concentration of low glycemia in plasma and fast restoration of the clinical normality after the increase of glycemia to normal levels by means of carbohydrate administration.\(^8\)

The European Agency for Evaluation of Medical Products (EMEA)\(^9\) recommends a value of <54 mg/dL (3 mmol/L) in order to define the hypoglycemia when determined the risk of different treatments, as it has been noticed a worsening of the cognitive function with glycemics under threshold. This value has the virtue of detecting reliably the clinically relevant hypoglycemia. A clear response of the contra regulatory hormones takes place under 63 mg/dL, while it has been observed that the exposure to glycemia values between 63 and 72 mg/dL it seems not to have a relevant clinical effect. Thus, this value of intermediate glycemia (63 mg/dL) suggests a reasonable value for some authors in order to speak about glycemia as lower limit of a therapeutic objective that logically will be fixed in higher values: 70-72 mg/dL.

Among the medical societies there seems to be a certain consensus about the definition of serious hypoglycemia as an event in which the mental condition of the patient is so altered that the patient is unable to treat himself alone. But, as we have observed, the same does not happen with the cataloguing of the mild hypoglycemia and it is this lack of consensus what has made the comparisons difficult among the studies and the quantification of the frequency of this entity in DM.

**Clinic**

There are no specific hypoglycemia signs and symptoms; therefore it has to do with a clinical picture that it “is suspected” quite often, more than a confirmative picture. Moreover, it has to be mentioned that the symptomatology varies significantly among the patients, and even the onset form changes throughout the time in the same subject.\(^5\)

The symptoms and autonomous signs (or neurogenic) are the result of the autonomous nervous system by the hypoglycemia. Some of these symptoms, as trembling, palpitations or anxiety, are adrenergic, in other words, are mediated by catecholamines. Others, as perspiration, sensations of hunger or the paresthesia are cholinergic, mediated by acetylcholine. The neuroglycopenic symptoms are the result of per se glucose brain deprivation: heat sensa-

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**Table 1. Classification of hypoglycemias**

<table>
<thead>
<tr>
<th><strong>American Diabetes Association (ADA)</strong>(^6)</th>
<th><strong>Canadian Diabetes Association (CDA)</strong>(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious hypoglycemia</strong></td>
<td>Requires the assistance of another person to help reverting the clinical picture</td>
</tr>
<tr>
<td><strong>Documented symptomatic hypoglycemia</strong></td>
<td>Typical symptoms of hypoglycemia and plasmatic glycemia &lt;70 mg/dL (3.9 mmol/L)</td>
</tr>
<tr>
<td><strong>Asymptomatic hypoglycemia (biochemical and unnoticed)</strong></td>
<td>Plasmatic glycemia &lt;70 mg/dL (3.9 mmol/L) but without symptoms</td>
</tr>
<tr>
<td><strong>Probable symptomatic hypoglycemia</strong></td>
<td>Hypoglycemia symptoms, but without glycemia measurement. Presumably the person showed values of &lt;70 (3.9 mg/dL)</td>
</tr>
<tr>
<td><strong>Relative hypoglycemia</strong></td>
<td>Typical hypoglycemia symptoms, but with glycemic values of &gt;70 mg/dL (3.9 mmol/L)</td>
</tr>
<tr>
<td><strong>Serious hypoglycemia</strong></td>
<td>Requires the assistance of another person. A loss of conscience can take place. The plasmatic glycemia is &lt;50 mg/dL (2.8 mmol/L)</td>
</tr>
<tr>
<td><strong>Moderate hypoglycemia</strong></td>
<td>Presence of autonomous and neuroglycopenic symptoms. The individuals are able to undergo self-treatment</td>
</tr>
<tr>
<td><strong>Mild hypoglycemia</strong></td>
<td>Present autonomous symptoms. The individual is able to undergo self-treatment. The plasmatic glycemia is &lt;72 mg/dL (4 mmol/L)</td>
</tr>
</tbody>
</table>
Seminars on diabetes


<table>
<thead>
<tr>
<th>Plasmatic glucose (mg/dL)</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>4,2</td>
</tr>
<tr>
<td>70</td>
<td>3,9</td>
</tr>
<tr>
<td>65</td>
<td>3,6</td>
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<tr>
<td>60</td>
<td>3,3</td>
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<tr>
<td>55</td>
<td>3,1</td>
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<tr>
<td>50</td>
<td>2,8</td>
</tr>
<tr>
<td>45</td>
<td>2,5</td>
</tr>
<tr>
<td>40</td>
<td>2,2</td>
</tr>
<tr>
<td>35</td>
<td>1,9</td>
</tr>
<tr>
<td>30</td>
<td>1,6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormonal response (glucagon, epinephrine, GH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression of endogenous secretion of pancreatic insulin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Acetylcholine</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Autonomic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trembling</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Perspiration</td>
</tr>
<tr>
<td>Hunger</td>
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<tr>
<td>Paresthesia</td>
</tr>
</tbody>
</table>

### Physiopathology, etiopathogeny and conditioning factors

The activation glycemic thresholds of the contra-regulatory mechanisms, as well as the clinical manifestations, present a great individual variability. In general, the inhibition of the endogenous insulin and the increase of pancreatic glucagon is produced when the glucose concentrations in venous plasma decrease to normal values of 70-72 mg/dL, the autonomous symptoms to less than 56-63 mg/dL and the neuroglycopenic symptoms to less than 48-57 mg/dL (figure 1).

Several factors contribute to the onset of this clinical circumstance (table 2). Among them, it is worth mentioning the alteration in the contra-regulatory hormone response (see other seminar of this same edition), as well the strict metabolic control of the DM.

The regimes of the present intensive treatments used with insulin, oral antidiabetics, or both, sometimes cause a relative or absolute excess of insulin that together with the contra-regulation alteration give place to iatrogenic hypoglycemias. An inverse relation has been proved among the concentrations of mean glycemia and the frequency of biochemical hypoglycemias. It seems clear that the best metabolic control confers this risk. The levels of the glycosylated hemoglobin ($\text{HbA_1c}$) ≤6.5% explain statistically the 60% of risk to show them. The paradigm “when the glycemia is more reduced, more benefit takes place” might be questioned after the results of the study ACCORD (The Action to Control Cardio-
vascular Risk in diabetes Study Group) and the study VADT (Veterans Affaire Diabetes Trial), as reducing the glycemia under the recommendations for normal glycemias levels seems to increase the mortality of the patients with T2D of mean-advanced age with high vascular risk. The major frequency of serious hypoglycemias in the intensive group was one of the mortality prognosis factors, together with values of HbA1c, age and low cholesterol levels bond to high-density lipoproteins.

**Frequency of hypoglycemias in T1D**

The assessment of incidence and prevalence of this entity is quite heterogeneous taking in account the lack of uniformity among the studies as they do not assess exactly the same premises. Some times it is the cut off point, others it is the definition of hypoglyemia itself that varies according to different authors. But this fact does not take away the so high hypoglycemias indexes of our patients. The patients with T1D have a 3 times higher frequency of showing serious hypoglycemias than the patients with T2D, both under intensive treatment (with an index of events/year of 10% versus 2.3%, respectively). Only one from three serious events might cause the patients’ coma. The values of prevalence of serious hypoglycemias are placed in the region of 30-40%.

These values have not been modified in the last two decades in spite of the substantial changes in the insulin formulation, the treatment regimes and the control targets. Table 3 depicts the serious and mild hypoglycemia events obtained in different clinical studies.

As regards to the type of insulin recommended to avoid or reduce these events, the fast action analogues and the long-acting ones are associated to a lower level of hypoglycemias in both types of DM (evidence A level). A meta-analysis indicates that the incidence of symptomatric, night and serious hypoglycemias is approximately of 50% less during the treatment with insulin glargine than with insulin NPH. The insulin detemir has also proved to cause less serious and night hypoglycemias than the insulin NPH. When comparing these insulins between them, the global hypoglycemia risk was similar with both treatments: 5.8 versus 6.2 events/patients/year for detemir and glargine, respectively (relative risk= 0.94; confidence interval [CI] of 96%: 0.71-1.25), the index of night hypoglycemia was of 1.3 events per patient/year with both insulins, and the serious hypoglycemia risks was exceptional. The treatment with continuous subcutaneous insulin infusion pump seems to improve the metabolic control and reduces hypoglycemia at the same time.

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**Table 2. Factors that might increase the hypoglycemia risk during the treatment of T1D and T2D**

<table>
<thead>
<tr>
<th>Factor</th>
<th>T1D</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration of the drugs depuration</td>
<td>- Renal failure</td>
<td>- Malabsorption</td>
</tr>
<tr>
<td>Alteration of the glucose absorption</td>
<td>- Hepatic failure</td>
<td>- Anorexia</td>
</tr>
<tr>
<td>- Hypothyroidism</td>
<td>- Concurrent medication</td>
<td></td>
</tr>
<tr>
<td>- Smokers</td>
<td>- Artificial use of insulin/SU/glinides</td>
<td></td>
</tr>
<tr>
<td>- Alteration in the contra regulator hormonal response</td>
<td>- Reduction of renal excretion of SU (eg. AAS, allopurinol)</td>
<td></td>
</tr>
<tr>
<td>- Addison disease, GH deficit, adenohipophysis failure</td>
<td>- Displacement of the albumin SU (eg. ASS, warfarin, sulphonamides, trimetropine, fibrate).</td>
<td></td>
</tr>
<tr>
<td>- Autonomous neuropathy</td>
<td>- Reduction of the hepatic metabolism of the SU (eg. warfarin, (-) of the MAO, H2 blockers)</td>
<td></td>
</tr>
<tr>
<td>- Diabetes of more than 9-10 years of evolution</td>
<td>- Increase of the secretagogues activity (eg. non steroid anti-inflammmatories)</td>
<td></td>
</tr>
<tr>
<td>- Advanced age</td>
<td>- Reduction of requirements</td>
<td></td>
</tr>
<tr>
<td>- Strict control of DM</td>
<td>- Evident loss of weight</td>
<td></td>
</tr>
<tr>
<td>- High doses of insulin (&gt;0.1 IU/kg/day)</td>
<td>- Existence of anti-insulin antibodies or insulin anti-receptor</td>
<td></td>
</tr>
<tr>
<td>- Previous existence of serious hypoglycemia events</td>
<td>- Interruption of steroid treatment and maintenance of hypoglycemiant treatment</td>
<td></td>
</tr>
<tr>
<td>Increase of the glucose peripheral captation</td>
<td></td>
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<tr>
<td>Physical exercise</td>
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</tr>
<tr>
<td>Inhibition of the neoglycogenesis</td>
<td></td>
<td></td>
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<tr>
<td>- Hepatic failure</td>
<td></td>
<td></td>
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<tr>
<td>- Alcohol</td>
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</tbody>
</table>

AAS: acetylsalicilic acid; GH: growth hormone; DM: diabetes mellitus; SU: sulphonylureas; (-) of MAO: monoamino oxidase inhibitors.
Frequency of hypoglycemia's in T1D documented in several clinical trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>HbA&lt;sub&gt;1c&lt;/sub&gt; (%)</th>
<th>Follow-up time</th>
<th>Frequency of serious hypoglycemia (nr. of events per patient/year proportion of affected patients [%])</th>
<th>Frequency of moderate hypoglycemia’s (nr. of events per patient/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramming et al.</td>
<td>411</td>
<td>8.7</td>
<td>Prospective (1 v)</td>
<td>1.4/3</td>
<td>94</td>
</tr>
<tr>
<td>MacLeod et al.</td>
<td>600</td>
<td>10.7</td>
<td>Retrospective (1 year)</td>
<td>1.6/29</td>
<td>–</td>
</tr>
<tr>
<td>Muhlhauser et al.</td>
<td>684</td>
<td>8.0</td>
<td>Retrospective (1 year)</td>
<td>0.21/13</td>
<td>–</td>
</tr>
<tr>
<td>Ter Braak et al.</td>
<td>195</td>
<td>7.8</td>
<td>Retrospective (1 year)</td>
<td>1.5/41</td>
<td>–</td>
</tr>
<tr>
<td>Pedersen-Bjergaard et al.</td>
<td>1,076</td>
<td>8.6</td>
<td>Retrospective (1 year)</td>
<td>1.3/37</td>
<td>104</td>
</tr>
<tr>
<td>Leckie et al.</td>
<td>243</td>
<td>9.1</td>
<td>Prospective (1 year)</td>
<td>0.98/34</td>
<td>42</td>
</tr>
</tbody>
</table>

UK Hypoglycaemia Study Group<sup>20</sup>

- <5 years of evolution
  - 46 | 7.3 | Prospective (9-12 months) | 1.1/22 | 35
- >15 years of evolution
  - 54 | 7.8 | Prospective (6 weeks) | – | 160

Janssen et al.<sup>21</sup>

- 31 | 7.2 | Prospective (6 weeks) | – | 160

Donnelly et al.<sup>22</sup>

- 94 | 8.3 | Prospective (4 weeks) | – | 42

Frequency of hypoglycemias in T2D

It has been proved that the frequency of hypoglycemia is inversely proportional to the HbA<sub>1c</sub>, and increases with the duration of the insulin therapy, the duration of the T2D and the magnitude of the insulin secretion deficit and the defects on the glucagon responses. The frequency can vary according to the levels of HbA<sub>1c</sub>, at the beginning of the trial, the glycemic objectives of each study, the used methodology, the definition of hypoglycemia that each group has considered, etc. It is thought that the incidence of the hypoglycemia is underestimated due to the variability of the symptomatology that the clinical picture might cause and passes unnoticed in several occasions.<sup>13</sup>

The most frequent cause of hypoglycemia in this type of DM is iatrogenic and obeys to the use of insulin secretagogues (sulphonylureas [SU] and glinides), as well as the treatment with insulin. If patients with T2D have an insulin deficit, the predisposition to have hypoglycemia is similar to the hypoglycemia of the patients with T1D. This assertion is not shared by all the authors, in a recent work it could be proved that the serious hypoglycemia indexes in patients with T2D treated with insulin were lower than those shown by the diabetic patients with T1D of less than 5 years of evolution (0.2 and 1.1 events per subject/year, respectively; p <0.001).<sup>20</sup> Table 4 depicts the incidence indexes of hypoglycemia obtained in several clinical trials considering the administered treatment.<sup>12,22,24,25-38</sup>

The patients who undergo monotherapy treatments together with changes in the lifestyle, sensitizing drugs (thiazolidinedione, metformin [MF], inhibitors of the alpha-glycosides and drugs with incretin action (analogues of the glucagon like-peptide 1 [GLP-1] and inhibitors of the dipeptidyl-peptidase-4 [DPP-4], they usually do not show serious hypoglycemias and do not have a relevant risk of symptomatic glycemia.<sup>6</sup> The risk increases when these drugs are combined with insulin or secretagogues. It is known that if hypoglycemia appear when the patients undergo treatment with inhibitors of the alpha-glycosides, they shall have to take glucose tablets, grape juice or honey in order to restore the normal glycemia, as these compounds inhibit the normal absorption of the sucrose and the starch.

The treatment with SU confers indeed a significant hypoglycemia risk. The hypoglycemia indexes, defined by a value <40 mg/dL (2.2 mmol/L) during at least 20 minutes, with continuous glucose monitoring sensors (CGMS), were of 14% in the patients with T2D treated with SU.<sup>20</sup> A database of the United Kingdom that comprised 719 consultations of general medicine, stated that in the patients who took SU, the annual risk of having a registered diagnosis of any hypoglycemia event is of
1.8% (2% for patients over 65 years of age), and it is thought that these values are underestimated. The glibenclamide (gliburide) was the SU that was associated with a higher risk. According to this study, the number of registered events with gliclazide and glipizide were of 25 and 40% lower than with glibenclamide, respectively. It has been demonstrated that glimepiride, SU of third generation, causes less hypoglycemias than glibenclamide, but not the gliclazide of slow-release. It also seems that the hypoglycemia indexes are lower with metiglinides or glinides (repaglinide and nateglinide).

Table 4. Hypoglycemia incidence documented in several randomized clinical trials in the T2D with the different hypoglycemiant therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Serious hypoglycemia (% of events per patient/year)</th>
<th>Any hypoglycemia (% of events per patient/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Prospective Diabetes Study Group²⁵</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>De Fronzo et al.²⁶</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Kahn et al. (ADOPT study)²⁷</td>
<td>0.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Charbonnel et al.³⁴/Kahn et al. (ADOPT study)²⁷</td>
<td>0/0.1</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Brockley et al.³⁹</td>
<td>0</td>
</tr>
<tr>
<td>Inhibitors of the intestinal alpha glycosides</td>
<td>Chiasson et al.³⁵</td>
<td>0</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>UK Prospective Diabetes Study Group³⁵/Kahn et al.²⁷</td>
<td>0.6/0.6</td>
</tr>
<tr>
<td>Glycaccide MR</td>
<td>Schernthaner et al.³¹</td>
<td>0</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Schernthaner et al.³¹</td>
<td>0</td>
</tr>
<tr>
<td>Various</td>
<td>UK Hypoglycaemia Study Group³⁰/Donnelly et al.³²</td>
<td>7/0.8</td>
</tr>
<tr>
<td>Glinides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Rosenstock et al.³⁵/Moses³⁵</td>
<td>0/1.3</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Rosenstock et al.³²</td>
<td>0</td>
</tr>
<tr>
<td>Incretines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>Amori et al.³⁴</td>
<td>0</td>
</tr>
<tr>
<td>(−) DPP-4</td>
<td>Amori et al.³⁴</td>
<td>0</td>
</tr>
<tr>
<td>Regular insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Prospective Diabetes Study Group³²</td>
<td>2.3</td>
<td>36.5</td>
</tr>
<tr>
<td>Anderson et al.³⁶</td>
<td>2.2</td>
<td>41.7</td>
</tr>
<tr>
<td>Fast analogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>Anderson et al.³⁶</td>
<td>0.6</td>
</tr>
<tr>
<td>Aspart</td>
<td>Home et al.³⁶</td>
<td>0.88</td>
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<tr>
<td>Glulisine</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Basal insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>VA CSDM³⁷/Donnelly et al.³⁸</td>
<td>0.02/0.35</td>
</tr>
<tr>
<td>Gliargin</td>
<td>Rosenstock et al.³⁴</td>
<td>0</td>
</tr>
<tr>
<td>Detemir</td>
<td>Rosenstock et al.³⁴</td>
<td>0</td>
</tr>
</tbody>
</table>

Definition of serious hypoglycemia: disability condition that requires the assistance of another person in order to revert the clinical picture. Gliclazide MR: gliclazide of delayed release, NA: not available, NPH: neutral protamine Hagedorn.
nide) than with the SU. However, another 1-year extension, randomized, double-blind study performed in patients with T2D, concluded that glibenclamide and repaglinide have similar strength and hypoglycemia indexes. When a meal is left out and so the administration of repaglinide, less hypoglycemia take place than when glibenclamide has been taken. Therefore, repaglinide might have advantages in the treatment if the meal guideline of the patients is irregular. The nateglinide is less strong than the repaglinide and it does not produce hypoglycemia.

The data related to the serious hypoglycemia events in patients treated with insulin in T2D are dissenting according to the different studies, regarding to the duration of the DM and the treatment. The percentages of serious hypoglycemia found in the studies ACCORD, ADVANCE (The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and VADT, considering if the patients underwent an intensive or conventional therapy, have been as follows: 16.2 versus 5.1%, 2.7 versus 1.5% and 21 versus 10%, respectively. According to the database of Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit Collaboration (DAR-TS-MEMO), the index of patients/year was of 7.3% very similar to the one stated by the UK Hypoglycaemia Study Group of 7%. However, in the study UK Prospective Diabetes Study Group (UKPDS), the 2.3% of the patients treated with insulin showed one or more events of serious hypoglycemia per year, while the incidence of any event of hypoglycemia per year was of 36.5%. Donnelly et al. observed an average of 16 annual events of symptomatic hypoglycemia in patients with T2D. The hypoglycemia that pass unnoticed are more frequent than it is supposed in patients with both types of DM and the use of new techniques, as the CGMS, has stated this accordingly (figure 2).

Assessment measurements of hypoglycemia risk

The HbA1c is not the most complete markers of the glycemia level as it does not reflect the glycemic variability. It is known that the diabetic patients with the same HbA1c might show completely different glycemic patterns (figure 2). This parameter has a relevant correlation with the future hyperglycemia but not with the hypoglycemia, therefore it is advisable to use other parameters that inform about the glycemic variability of the patient.

Kilpatrick et al., after studying the data of the study DCCT (The Diabetes Control and Complications Trial), observed that the increase of 18 mg/dL in the mean plasmatic glycemia was associated to a reduction of 1.05 times the serious hypoglycemia risk, while the increase of 18 mg/dL in the standard deviation (SD) caused a risk increase of 1.07 times and this was kept after the adjustment by the HbA1c of the patients. These data suggest that the study of the DE in patients is a higher parameter regarding to the mean plasmatic glycemia and the HbA1c to estimate the serious hypoglycemia risk, both the night and the daytime ones. The study demonstrated also that only 7% of the serious hypoglycemia might be prevented from known variables in patients. Gold et al., could predict up to 18% of the serious hypoglycemia using a structural model in which they included serious hypoglycemia history and those that passed unnoticed, together with an alteration of the autonomous regulation in patients.

Kovatchev et al. have designed a mathematic model able to explain, prospectively, up to 40% of the serious events during the 6 months after the analysis of the glycemic data from the meters of capillary glycemia of their patients. It is the assessment of the LBGI Index (Low Blood Glucose Index) that comprises in a unique value the frequency and the extension or the magnitude of the glycemia in the “low range” of the patients, and represent the mean weight of all the low glycemia reading. In patients with serious hypoglycemia history an index of LBGI was obtained significantly higher than those who had not shown it (p <0.0005). The LBGI can be obtained by means of adapted systems for its estimation, as the Accu-Chek Smart Pix (Roche Diagnostics). Only approximately 130 capillary glycemia readings will be enough to perform a precise estimation of this index, which is achieved in 4-5 weeks carrying out a minimum of 3-4 controls daily of glycemia. Its quantification might help to predict prospectively a great number of imminent serious hypoglycemia events, which have clear clinical and educational implications. Cox et al. demonstrated that this parameter might help the physicians and the patients to promote certain changes in order to avoid hypoglycemia, as to increase the surveillance threshold, perform more self-analysis, be more attentive to the alarm signs, reduce the dose of insulin, and modify the therapeutic objectives, etc.
Consequences at long term
The potential complications of serious hypoglycémias, mainly those that develop with coma or epileptic crisis, have always been reasons of concern. The transitory reduction of the cognitive functions might affect certain relevant daily activities, as driving. The possibility of showing a brain lesion at long term has been observed and described in studies performed both in animals and in human beings. The anatomopathologic findings include gliosis and demyelination. A relation between mortality and serious hypoglycémias could be observed in some trials, therefore it has been indicated as the cause of mortality in 2-4% of the patients, and in others, as a cause of dementia. In the studies DCCT and DCCT/EDIT a neuropsychological assessment has been done, both at the beginning of the trial and in the years 2, 5, 7, 10 and 18 of the follow-up. The intensive therapy, with the increase associated to serious hypoglycémias, was not related to neuropsychological alterations. In a sub-analysis of the patients who had between 1 and 5 (n=314) or more than 5 events (n=23) of coma or epileptic crisis, no differences were found compared to the group who had no event (n=1,045). These findings were very reassuring and confirmed what has been stated previously in other studies. Thus, the secondary hypoglycémias to the intensive therapy do not cause neuropsychological alterations in adults (evidence B level). In spite of this assertion, it is necessary to make the best effort to minimize the serious and recurrent hypoglycémias.

As regards to the economical consequences, there are data that indicate that the persons with DM loose an average of 3 working days after having a serious event. The references of the DARTS-MEMO database state that 28% of the serious events end with the patients’s hospitalization and the indexes of hospital mean stay range between 4.4 and 9.5 days.

Prevention and treatment
The first point that has to be taken into account in the prevention of hypoglycémia in patients with DM is the individualization of the glycemic objectives, considering the type of diabetes, the years of evolution, the chronic complications, the work timetable, the life habits and the development of previous serious hypoglycémia pic-
Once the objectives are marked, it is essential to carry out an exhaustive education of the patients with a strict professional support, in order to achieve an excellent metabolic control with the minimum hypoglycemia risk. In the individuals under risk, several unnoticed hypoglycemias can be diagnosed and facilitate its prevention and treatment by means of the frequent diary record (5-7 measurements) of the capillary glycemia that has to include the night assessment. The individuals with unnoticed hypoglycemias or who have shown one or more serious hypoglycemia events have to raise their glycemic targets in order to reduce the risk of future events (evidence B level). We will not doubt in using the CGMS systems before the suspicion of unnoticed and/or night hypoglycemias (figure 3).

All the patients have to know the symptoms, the signs and the handling of the possible hypoglycemias that might appear. They will be warned that the hypoglycemia symptomatology might change with the time, and how to administer glucagon will be taught to their relatives. Other measures include not to sleep alone at home in order to be assisted in case of serious night hypoglycemia, avoid sleeping during the day if there is no person close to watch them and record the night glycemia in a scheduled manner.6

As regards to the therapeutic objectives of the metabolic control of the patients, the strategies have to be individualized. The young patients with DM not too developed might be benefited of a stricter glycemic control (HbA1c <6.5%) if it can be achieved safely. On the contrary, it is reasonable to set out more conservative objectives in patients with a hope of limited life, serious hypoglycemia history, relevant co-morbidity or manifested arteriosclerosis disease.

The uncontrolled intake of food or simple sugars without quantification is not recommended during the treatment because they tend to cause high values of plasmatic glycemia and might alter the metabolic control during several hours.13 When they appear in the interprandial periods or the symptomatology is florid, the recommendation is to take a quantity of glucose of 15-20 g whose effects shall be noted after 15 minutes (evidence A level).6 The test should be repeated after 15 minutes and 15 g shall be taken again if the glycemia rising objectives have not been achieved (evidence B level). Though the choice treatment is the pure glucose, any food that contains carbohydrates (the sucrose or the common sugar is recommended) will increase the glycemia level in blood. There are no evidences that support the administration of glucose gel by oral route, as the absorption through the mucous is very limited.5 The adding of proteins to the carbohydrates shall not affect the glycemic response or avoid the later onset of hypoglycemia. In turn, the adding of fat might delay first the glycemic response and then extend it. Since the glycemic response to the oral glucose is transitory (less than 2 hours in a model of hypoglycemia induced by insulin performed in patients

Figure 3. Unnoticed night hypoglycemia in a patient with T1D. Record with sensor of continuous glycemia monitoring (CGMS) Medtronic®
with T1D), after an event that required the intake of carbohydrates it is recommended the intake of a light mixed meal if the patients should not have one of the usual diabetic intakes (evidence E level).6

Conclusions
The present regimes of intensive treatments with insulin, oral antidiabetics or a combination of both, sometimes cause a relative or absolute excess of insulin in patients and give place to iatrogenic hypoglycemia. The assessment of incidence and prevalence of this entity is quite heterogeneous due to the lack of uniformity among the studies as they do not assess exactly the same premises. Sometimes it is the cut off point, others it is the definition of hypoglycemia itself that varies according to different authors. But this fact does not undermine the so high hypoglycemia indexes of our patients. Therefore, it is essential that the physicians carry out a good approach of the diabetology treatment of their patients, stating the glycemic objectives according to the metabolic condition, they should know well about the antidiabetic drugs they use and provide their patients the sufficient knowledge to avoid delicate situation as far as possible. ■

Declaration of potential conflict of interests
P. Martín Vaquero received fees for conferences, papers and/or consultancy from Abbott, GSK, Lilly, Medtronic, MSD, Novartis, Novo Nordisk, Roche, sanofi-aventis, Infocencia, Euromedic, Wolters Kluwer Health, Genetics Europe and Grupo ARS XXI de Comunicación. B. Barquiel Alcalá, M.A. Puma Duque and A. Lisbona Catalan state that there are no conflicts of interest in drawing up of this manuscript.

References

Practical considerations
• At present 70 mg/dL (3.9 mmol/L) are considered the value that defines the starting of a hypoglycemia, while 54 mg/dL (3.0 mmol/L) indicates the level from which a hypoglycemia with clinical relevance is considered.
• The frequency of hypoglycemias increase with the duration of the diabetes and its treatment, and it is inversely proportional to the HbA1c. In the follow-up of the diabetic patient it is advisable to use, besides HbA1c and the mean glycemias, other parameters that inform about the glycemic variability, as the standard deviation and the LBGI.
• It is extremely important to avoid serious hypoglycemias with the performance of more self-analyses, being more attentive to the alarm signs, reducing the insulin dose, modifying the therapeutic objectives, etc.


Hypoglycemia unawareness syndrome. Risk factors and treatment

Síndrome de falta de reconocimiento de la hipoglucemia. Factores de riesgo y tratamiento

F.J. Ampudia-Blasco
Reference Diabetes Unit. University Clinical Hospital of Valencia

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.

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.1,2 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
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 hypoglycemia (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, hypoglycemies are still the most important adverse effect of the insulin treatment.

When the hypoglycemies 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 symptomatology, 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 hypoglycemies, 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 hypoglycemies in patients with T1D and T2D? In the DCCT, the incidence of serious hypoglycemies 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 Trial.¹ The DCCT, the incidence of serious hypoglycemies 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 Trial.¹ Specifically, the incidence of serious hypoglycemies with loss of consciousness or convulsions was of 16.3 per 100 patients-year.¹ It has to be pointed out that most of the half of hypoglycemia events took place during the night, and up to a third part of those that took place during the day were asymptomatic.¹⁰ As regards to the T2D, the incidence of serious hypoglycemies in the UKPDS in patients under insulin treatment was high in those with a higher duration of insulin treatment.¹ Consequently, the
serious hypoglycémias 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 hypoglycémia and a retrospective analysis of serious hypoglycémia 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 hypoglycémia 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 hypoglycémia 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 hypoglycémia, since the oxidation of the glucose is the main energy source. Moreover, this organ is not able to synthesise 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 hypoglycémia, and trigger the release of contra-regulatory hormones and the onset of symptoms afterwards. If the neuro-endocrinous response is deficient, the hypoglycémia might be even longer and serious.

The physiologic neuro-endocrinous response versus the hypoglycémia 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 (autonomous 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.
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-endocrin 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-endocrin 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 regualtor 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 lose 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

- Dependent of the patient
  - T1D or T2D under insulin treatment
  - Advanced age
  - Longer duration of the diabetes
  - Presence of autonomous neuropathy
- Dependent of the treatment
  - Intensive treatment with insulin (versus conventional treatment)
  - Longer duration of the insulin treatment (T2D)
  - Therapeutic guidelines with regular insulin and/or NPH
  - Stricter metabolic control (lower levels of HbA1c)
  - Recurrent hypoglycemias, especially at night
  - Serious hypoglycemia history

*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 prevent and treat the chronic complications of diabetes in order to improve the clinical practice as it affects 1 over 4 patients.

However, in order to prevent the onset / progression of the chronic complications of 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 adequate programs of therapeutic education and to choose the most appropriate guideline versus a conventional treatment regimen.

Practical considerations

• The lack of recognition of the hypoglycemia is a very important limiting factor of 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.

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 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 adequate programs of therapeutic education and to choose the most appropriate guideline versus a lower hypoglycemia risks. To achieve this objective entails necessarily, at least in most of the cases, the use of therapy with basal bolus and the fast-acting insulin analogues (lispro, aspart, glulisine) and long acting (glargine, detemir), by means of multiple doses of insulin or CSII. The minimization of hypoglycemia risks helps to prevent / revert the HUS, contributing to increase the safety and life quality of the patients under insulin treatment.

Declarations of potential conflict of interests

F. J. Ampudia-Blasco received fees for conferences and/or consultancy of Abbott, Bristol-Myers-Squibb, GSK, LifeScan, Lilly, Madaus, MannKind Corp., Medtronic, Menarini, Merck Farma 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.

References


Postprandial reactive hypoglycemia: myth or reality?

F.J. Escalada, S. Laguna, S. Botella
Endocrinology and Nutrition Department, University Clinic of Navarra

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 posprandial 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 ingestas repartidas a lo largo del día. Sin embargo, algunos de ellos necesitarán tratamiento farmacológico. Los fármacos más utilizados son los inhibidores de las alfaglucosidasas, 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.

Definition
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.¹ This entity has been widely questioned, mainly due to different criteria used to define hypoglycemia, the lack of clinical specificity, the scarce initial knowledge of its physiopathology and the inappropriate use of the oral glucose overload (OGO).² In fact, the terms applied to the PRH have been several (functional hyperinsulism, essential hypoglycemia, functional hypoglycemia, dysinsulinism, hypoglycemiac asthenia, insulinogetic hypoglycemia and relative hypoglycemia). Charles coined the term “idiopathic postprandial syndrome” for the patients with suspicion symptoms in whom no hypogly-
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 glucoseoneogenesis 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 counter-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 counter-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 cappation 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.
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{15} 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 hyperglycidic 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 glycemias 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 hyperglycidic 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

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**Table 1. Suspicion symptoms of reactive hypoglycemia*\textsuperscript{9}**

<table>
<thead>
<tr>
<th>Adrenergic symptoms</th>
<th>Neuroglycopenic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Anxiety</td>
<td>– Hunger</td>
</tr>
<tr>
<td>– Palpitations</td>
<td>– Dizziness</td>
</tr>
<tr>
<td>– Irritability</td>
<td>– Tingling</td>
</tr>
<tr>
<td>– Trembling</td>
<td>– Blurred vision</td>
</tr>
<tr>
<td>– Perspiration</td>
<td>– Difficulty to concentrate</td>
</tr>
<tr>
<td></td>
<td>– Unconsciousness</td>
</tr>
</tbody>
</table>

*Modified of Brun et al.\textsuperscript{9}*

**Table 2. Studies in patients with postprandial reactive hypoglycemia suspicion**

<table>
<thead>
<tr>
<th>Oral glucose overload</th>
<th>Test of hyperglycidic breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory capillary glycemia measurement</td>
<td></td>
</tr>
<tr>
<td>Continuous interstitial glucose monitoring</td>
<td></td>
</tr>
</tbody>
</table>
symptoms, the contra-regulatory response has already been triggered versus the hypoglycemia and no low values of glycemia are detected (false negative).9

Continuous interstitial glucose monitoring
The continuous interstitial glucose monitoring (CIGM) allows a practically constant measurement of the glucose concentration in the interstitial liquid,18,19 that shows a great parallelism with its blood concentration.20 This characteristic overcomes the problem of the false negatives commented in the case of using ACGM. Simpson et al.21 conclude in their study that most of the symptoms attributed to hypoglycemia where 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.21

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

Table 3. Pharmacological treatment in the reactive hypoglycemia

- Inhibitors of the alpha-glycosidases
- Biguanides
- Glitazones
- Anticolinergics
- Adrenergic antagonists
- Calcium antagonists
- Fenitoin
- Calcium gluconate
- Chromo
- Diazoxide
- Somatostatin analogues
- Adrenal extracts

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.23 The acarbose, an inhibitor of alpha-glycosidases, has proved that it prevents the hypersecretion of insulin and PRH.24 The biguanides have also been recommended: it has been suggested the taking of metformin in a dose of 500-850 mg in each meal.25 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.26

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.9 Some authors have proposed the surgical treatment with the reversion of a proximal jejunal segment.27

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/m². 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 the appearance of compatible symptoms in two occasions. Moreover, the ACGM necessary for the correct calibration of the CIGM did not objectify hypoglycemia at any moment during the study (values between 71 and 108 mg/dL). However, values under 60 mg/dL (56 mg/dL) have been observed during symptomatic events when the ACGM was performed outside the mentioned study.

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
The postprandial reactive hypoglycemia is characterized by symptoms compatible to the hypoglycemia during the 4 hours after intake. A secondary hyperinsulinism is admitted as cause to insulin resistance or to an excessive insulin response mediated by the previous secretion of incretins (GLP-1).

The tests used in the diagnosis are the ambulatory capillary glycemia monitoring (choice method), the continuous interstitial glucose monitoring, the oral glucose overload and the hyperglycemic breakfast.

The treatment consists of diet low in carbohydrates, with small intakes distributed throughout the day. Drugs can be used if the response is not the adequate one (acarbose, metformin).

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

Insulinoma. Diagnostic criteria and treatment

Insulinoma. Criterios diagnósticos y tratamiento

M. Diéguez Felechosa, M. Riestra Fernández, E. Menéndez Torre
Endocrinology and Nutrition Service. Central University Hospital of Asturias. Oviedo

Abstract
Insulinomas are rare islet cell tumors of the pancreas. Ninety percent are sporadic, usually single and small. The autonomous insulin secretion results in hypoglycaemia, mostly fasting hypoglycaemia, with neuroglucopenic symptoms. Biochemical diagnosis is established by demonstrating an endogenous hyperinsulinism pattern during a spontaneous or fasting-induced episode of hypoglycaemia. High resolution computer tomography and endoscopic ultrasonography are the preferred imaging techniques for diagnosis before surgery, localizing almost 100% of tumors. Other procedures are used only in selected cases. Surgery removal of insulinoma is the treatment of choice resulting in high overall cure rates. In cases of refractory hypoglycaemia medical management using drugs as diazoxide may be used. Currently, novel therapeutic approaches are being developed.

Keywords: hypoglycaemia, hiperinsulinism, insulinoma, pancreatic neuroendocrine tumors.

Resumen
Los insulinomas son tumores poco frecuentes derivados de las células beta de los islotes pancreáticos. En el 90% de los casos son esporádicos, únicos y de pequeño tamaño. La secreción autónoma de insulina da lugar a hipoglucemias, preferentemente de ayuno, con síntomas neuroglucopéneicos. El diagnóstico bioquímico se basa en la demostración de un patrón de hiperinsulinismo endógeno durante un episodio de hipoglucemia espontánea o inducida por el ayuno. La tomografía computarizada de alta resolución y la ecografía endoscópica constituyen los métodos de elección para el diagnóstico prequirúrgico, ya que localizan prácticamente el 100% de los tumores; otras técnicas se reservan para casos seleccionados. La cirugía es el tratamiento de elección, con la que se obtienen altas tasas de curación. Para el control de la hipoglucemia refractaria se utilizan determinados fármacos, como el diazóxido. Actualmente, se encuentran en fase de desarrollo nuevas estrategias terapéuticas.

Palabras clave: hipoglucemia, hiperinsulinismo, insulinoma, tumores neuroendocrinos del páncreas.

Introduction
The insulinoma is the most frequent functioning pancreatic endocrine tumor. It is characterized by the autonomous production of insulin by the beta cells of the pancreatic islets. Its incidence is of 4 cases per million of population and year, with a peak between the third and sixth decades of life, though it might be diagnosed at any age. Most of the series describe a slight predominance in women.

The 90% of the insulinomas are unique tumors, with a size lower than 2 cm and of benign nature. They are located in the same way in the head, the body and the pancreatic tail. They are sporadic, but in 6% of the cases they are part of the multiple endocrinous neoplasia type 1 (MEN 1), especially in young patients, with multiple tumors or that associate other endocrinous pathologies. The malignant insulinoma is less frequent (5-12% of the cases) and there are not anatomopathological criteria for its diagnosis. The diagnosis of the malignity is based on the demonstration of the existence of metastasis, in most of the cases of ganglionic or hepatic nature, which are present at the moment of the diagnosis.
Clinical report

The hypoglycemia diagnosis is based on the documentation of the triad of Whipple: low level of plasmatic glucose with symptoms and / or signs of hypoglycemia that are solved after the normalization of the glycemia. The insulinoma is, after the factitious hypoglycemia, the most frequent cause of hypoglycemia in the apparent healthy patient. It produces a fasting hypoglycemia of a characteristic way, usually at dawn, during fasting period and after physical exercise. It is important to remember that the patients with insulinoma might show also a postprandial hypoglycemia. The 75% of the patients show hypoglycemia only during fasting periods, 21% associates postprandial hypoglycemies and 6% only postprandial hypoglycemias.

The clinical expression of insulinoma is often unspecific and variable, even in a same patient, entailing, a mean delay in the diagnosis of 2 years together with the difficulty of documenting hypoglycemies. The adrenergic manifestations of hypoglycemia (perspiration, trembling, palpitations, hunger, diaphoresis...) might be absent. The picture is characterized by neuroglycopenic manifestations (changes in the mood state, behavior alterations, weakness, and visual symptoms, reduction of the conscious level and seizure disorders) and it is usual that the patient does not remember the event. It is frequent that the patients with insulinoma are wrongly diagnosed of neurological or psychiatric processes. The hypoglycemia shall be part of the differential diagnosis of the refractory epilepsy.

Biochemical diagnosis

The diagnosis of insulinoma is based on the demonstration of endogenous hyperinsulinism (EH) during a spontaneous hypoglycemia or induced by the fasting. The criteria for the diagnosis of EH have been modified during the last years. Classically, the criteria defined by Marks and Teale in 1996 and then by Service in 1999, are based on the existence of inappropriately high levels of insulin and C-peptide coinciding with hypoglycemia. Afterwards, other measurement parameters have been added, as the pro-insulin levels, considering the higher proportion of this substance secreted in patients with insulinoma, the beta-hydroxibutyrate, as marker of ketosis response during fasting period, and the response of the glycemia after the stimulation with glucagon. This last one allows determining the hepatic reserves of glucagon after the fasting period depleted in healthy individuals. The determination of the oral hypoglycemiant is added to this (sulphonylureas in urine) and the anti-insulin antibodies. These parameters have demonstrated a great diagnostic validity in order to determine the differential diagnosis of EH.

Since it is difficult to document a hypoglycemic event spontaneously or after night fasting, the hypoglycemia has to be induced by means of a controlled fasting in most of the patients. The fasting test of 72 hours is still the reference pattern for the insulinoma diagnosis. It is an expensive procedure that requires several days of hospitalization, but it is usually well tolerated by the patients. Though most of the patients experiment hypoglycemia before 72 hours (33% in 12 hours, 65% in 24 hours, 84% in 36 hours and 93% in 48 hours), a reduced number (7%) present insulinoma and negative fasting test after 48 hours. Moreover, a complete suppression of the beta cell in healthy individuals is achieved only after 72 hours of fasting. Therefore, with the aim of achieving the maximum diagnosis precision, the performance of the test of 72 hours is recommended. The negativity of the fasting test in a patient with insulinoma is exceptional. The protocol of the fasting test performance is detailed in table 1.

The fasting test is positive when a hypoglycemia is recorded with a EH biochemical pattern (insulin ≥3 μU/mL, C-peptide ≥0.2 nmol/L, pro-insulin ≥5 pmol/L, beta-hydroxibutyrate ≤2.7 mmol/L, glucose response after i.v. infusion of glucagon >25 mg/dL). The pro-insulin and the C-peptide are the most precise markers, with a sensitivity and a specificity close to 100%. The insulin levels and the ratio glucose/pro-insulin, pro-insulin/insulin and glucose/insulin have a lower diagnostic value, therefore its systematic use is not recommended at present. The development of hypoglycemia is not a sufficient criterion to give as positive the fasting test, due to the superposition with healthy individuals, especially in young women and children.

Differential diagnosis

The differential diagnosis of the insulinoma is performed with the other causes of hyperinsulinemic hypoglycemia (HH) in apparently healthy individuals. The factitious hypoglycemia produced an undistinguishable biochemical pattern by the abrupt determination of sulphonylure-
The C-peptide will be suppressed in the cases of exogenous administration of insulin (table 2).

The nesidioblastosis or islet cell hyperplasia is not so frequent due to HH in adults. It might be congenital (related to mutations in the insulin receptor) or induced by the abrupt determination of sulphonylureas or the surgery of gastric derivation. Unlike the insulinoma, the hypoglycemia is of postprandial presentation, and the fasting test is negative. The usual imaging techniques are negative; therefore one has to resort to more sensitive methods in order to determine the diagnosis. The non insulinoma pancreatic hypoglycemia (diffuse hypertrophy of the islets cells) and hypoglycemia of autoimmune origin are exceptional.12

Localization
At present we count with a multitude of techniques to determine the localization of the insulinoma. By means of the use of intraoperative ultrasounds and the pancreatic palpation by an experienced surgeon, 100% of the insulinomas are detected.13 The intraoperative echography has a sensitivity higher than 95% and it also provides anatomic information when localizing the duct system and the intra-pancreatic vessels, allowing to plan the type of surgery and reduce the number of complications. The 75% of the tumors are identified by means of pancreatic palpation (it shows limitations in the small tumors), of soft consistency and deep situation in the pancreas.14

Since the high precision of the intraoperative methods, the discussion is focused on the role of the pre-surgery diagnosis. Most of the authors support the pre-surgery localization as it allows planning the type of intervention, choosing a laparoscopic approach, shortening the surgi-

<table>
<thead>
<tr>
<th>Table 1. Fasting test of 72 hours10</th>
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<tbody>
<tr>
<td>• Record the 72 hours of fasting as from the last performed intake</td>
</tr>
<tr>
<td>• Suspend all the non-necessary medication</td>
</tr>
<tr>
<td>• The patient can drink water and teas</td>
</tr>
<tr>
<td>• Motivate the patient to keep himself active during the day</td>
</tr>
<tr>
<td>• Serial blood extractions each 6 hours, determining plasmatic glucose first until it decreases below 60 mg/dL and then analyze the insulin, the pro-insulin, the C-peptide and the beta-hydroxibutyrate sample and perform extractions each 1-2 hours</td>
</tr>
<tr>
<td>• End the fasting after 72 hours or when the glycemia is lower than 45 mg/dL, and the patient shows symptoms and/or signs of hypoglycemia. A low value of isolated glycemia without symptoms and/or signs of hypoglycemia are not an indication to interrupt the test. Should it be justified to interrupt it considering the presence of clinical hypoglycemia signs with glycemia values between 45 and 55 mg/dL</td>
</tr>
<tr>
<td>• At the end of the fasting, take a sample for the determination of glucose, insulin, pro-insulin C-peptide and beta-hydroxibutyrate and administer 1 mg i.v. of glucagon, recording the glycemia response after 10, 20 and 30 minutes</td>
</tr>
<tr>
<td>• To determine the concentrations of anti-insulin anti-bodies and sulphonylureas in urine during the test</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table 2. Biochemical pattern of insulinoma and differential diagnosis of the hyperinsulinemic hypoglycemia10</th>
</tr>
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<tbody>
<tr>
<td>Glucose (mg/dL)</td>
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<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Insulinoma</td>
</tr>
<tr>
<td>Nesidioblastosis</td>
</tr>
<tr>
<td>Factious hypoglycemia by insulin</td>
</tr>
<tr>
<td>Factious hypoglycemia by sulphonylureas</td>
</tr>
<tr>
<td>Non-insulinoma hypoglycemia syndrome</td>
</tr>
<tr>
<td>Autoimmune hypoglycemia</td>
</tr>
</tbody>
</table>
cal time and reducing the morbimortality.\textsuperscript{13-15} Moreover, the pre-surgical extension study by means of computed tomography (CT) or magnetic resonance (MR) allows performing the screening of the metastasis and its performance is indicated in all the cases with insulinoma. The pre-surgical diagnosis of 100\% of the patients can be achieved with the current methods (75\% though non-invasive methods).\textsuperscript{3} The diagnostic precision of the conventional imaging techniques (abdominal echography, CT) is limited, with a sensitivity of 50-60\%.\textsuperscript{15} These techniques detect preferably tumors >2 cm of easy intraoperative diagnosis. The new multi-cut helicoidal CT allow to diagnose 94\% of the cases,\textsuperscript{14} and are included within the option diagnosis methods (figure 1). The modern equipments of MR with the use of gadolinium, contrary to the other techniques, offer a better performance in the small and multiple tumors (<1 cm).\textsuperscript{14}

Among the invasive techniques, the endoscopic echography is the choice technique, recommended by most of the authors.\textsuperscript{3} It diagnoses 83-100\% of the tumors located in the head or the pancreas body, though it is less sensitive for the lesions in the tail (60\%). It allows the collection of biopsies and provides excellent anatomic information. The intraductal echography improves the diagnosis precision, but due to its complexity it is reserved for selected cases. The gammagrapy with octreotide has a limited value in the insulinoma study as less than 50\% of the cases express receptors of the somatostatine.\textsuperscript{11-16} The positron emission tomography (PET) with fluor-18-L-dihydroxyphenylalanine (\textsuperscript{18}F-DOPA) is a technique which is used in the diagnosis of neuro-endocrinous tumors. This technique localizes a great sensitivity of pancreatic tissue that produces the insulin in patients with insulinoma or hyperplasia of beta cells, due to the capacity of the endocrine pancreas to capture and descarboxilate L-DOPA. It has demonstrated a higher validity as regards to the CT or MR in small series and has a promising future in the functional study of the pancreatic tissue, but the study of greater series is necessary to validate its diagnostic precision.\textsuperscript{17} The arteriography is an invasive technique and not free from complications, with a variable sensitivity, in the region of 60\%, dependent on the tumor size and the level of vascularization, and its use is being abandoned as one disposes of other diagnosis methods.\textsuperscript{14}

The selective intra-arterial stimulation with calcium, by means of the measurement of insulinemia in the suprahepatic veins and the record of insulin secretion in specific territories is getting an increasing protagonism in the regional diagnosis of the insulinoma. Its sensitivity is of 90\%, clearly higher than the echography, the CT and the MR.\textsuperscript{18} The access is through the femoral route and the venous catheter is placed (Swan Ganz catheter) in the suprahepatic vein for the collection of insulinemia samples. Through the arterial catheter the stimulation takes place selectively with calcium gluconate in the arteries that irrigate the pancreatic head (gastroduodenal and superior mesenteric) the body and the tail (splenic artery) and samples are collected in venous blood of basal insulinemia, after 30, 60 and 120 minutes. The tumoral cells of an insulinoma have an exaggerated response to the calcium stimulation. When stimulating through the gastroduodenal or superior mesenteric artery, the insulinemia rises more than 2-folds over the basal level, the tumor will be localized in the body and the tail of the pancreas. If when stimulating the splenic artery the described effect is produced, the tumor will be localized in the body and the tail of the pancreas.

To summarize, the performance of a pre-surgical study with multi-cut helicoidal CT and endoscopic echography allows the localization of the insulinoma with a sensitivity of 100\% and a specificity of 95\%.\textsuperscript{14} The PET with \textsuperscript{18}F-DOPA and the rest of the invasive procedures (arteriography and selective intra-artery stimulation with calcium), due to its high cost and its scarce accessibility, are reserved for patients with biochemical EH confirmation when the rest of the studies are negative,
and in patients with MEN 1 or with multiple tumors suspicion.

**Treatment**

The surgical extirpation of the insulinoma is the choice treatment and the only healing one, achieving remission rates of 75-98%. The surgery might be either open or laparoscopic. The enucleation and the pancreatic resection by laparoscopy have been performed with success at many sites and they offer all the advantages of a minimally invasive surgery, with a lower hospital stay and a faster recovery. Though the complications are relatively frequent as the pancreatic fistula (from 18 to 33%, according to the series), they do not entail neither increase of morbidity nor hospitalization days.

The intra-operative laparoscopic ultrasonography (US Lap) might facilitate the localization of the lesion and minimize the need of conversion to open surgery. The laparoscopy shall not be done in case of tumors localized in the pancreatic head, given the high risk of hemorrhage that it entails (up to 20-40% of the cases), so this route should be reserved for the patients with solitary lesions in the body and tail of the pancreas who have not undergone another pancreatic intervention previously and an experienced team should do it. The enucleation is indicated in small tumors located at least at 2-3 mm of the principal pancreatic conduct. The recent guidelines suggest that it is sufficient with the enucleation if the lesion is superficial and is clearly defined in the intra-operative process.

The widened resection is recommended when the tumor invades the pancreatic conduct or the big vessels, or when malignity is suspected by invasion of the peripheral tissues, dilatation of the pancreatic conduct or affection of the lymphatic ganglions. The different options of resection include the distal pancreatectomy (with or without splenectomy), the technique of Whipple or the almost total pancreatectomy, according to the localization of the insulinoma. The intra-operative determination of the insulinemia levels might be useful to ensure the complete resection of the tumor.

In patients with MEN 1 syndrome, the insulinomas are usually multiple up to 59% of the cases versus only 5% in the rest of the patients. Therefore, and considering the high index of post-surgical relapses, it is recommended to perform a subtotal distal pancreatectomy together with the enucleation of the tumors that are located in the pancreas head. A new localization diagnosis should be done in patients with persistent hypoglycemia after surgery and an intervention is recommended by means of the laparotomy. With the application of new techniques of pre-operation localization, especially the combinations of helicoidal CT and endoscopic ultrasonography (with sensitivity close to 100%), a few hidden insulinoma are left out. If the tumor cannot be identified, the “blind” pancreatic resection is not recommended and the patient shall be re-evaluated in order to verify the diagnosis.

The 91% of the intervened patients keep remission criteria 6 months after the surgery. From these ones, 11% experience a recurrent hypoglycemia during the follow-up. Relapses can occur up to 18 years after the intervention. The accumulated incidence of recurrences is of 6% after 10 years and 8% after 20 years. In patients with MEN 1, the recurrence index is higher, reaching 21% after 10 years.

The survival of the patients who underwent surgery is similar to the general population. However, it worsens significantly in advanced age patients and in the patients who show a malignant insulinoma, though it seems to have a long natural history in patients with metastatic disease and more than 20 years of follow-up.

**Treatment of the hepatic metastasis**

The liver is the most common place where the insulinoma metastasis are located, for which there are several direct therapeutic modalities. The hepatic resection is indicated in the absence of diffuse lesions in both lobules, previous hepatic failure and extensive extra-hepatic metastasis (pulmonary, peritoneal...), obtaining higher survival indexes, though the healing is only achieved in 15% of the patients. The therapeutic embolization of the hepatic artery causes necrosis of the tumoral tissue without damaging the healthy hepatic tissue. The selective embolization, with or without infusion of chemotherapeutic substances, is used as palliative techniques in patients with symptomatic hepatic metastasis who are not candidates to surgery. The radiofrequency and the cryoablation might be performed subcutaneously or by laparoscopic route, entailing a lower morbidity than the resection of the metastasis or the arterial embolization; there...
are no data available about the efficacy at long term. The hepatic transplant has been done in a few patients and the follow-up duration is insufficient to show data about the healing possibility. As regards to the chemotherapy, the traditional choice regime has been the streptozotocine and the doxorubicin, though its modest efficiency (achieves between 10 and 40% of tumoral remission) and its toxicity has promoted the development of new therapeutic agents, as the angiogenesis inhibitors.

Medical treatment

The medical treatment of the insulinoma has to be taken into account in patients with hidden insulinoma, in those who are not candidates to surgery or reject them, and in those who have a non-resectable metastatic disease. The therapeutic options to prevent the symptomatic hypoglycemia are as follows:

- The diazoxide (100-800 mg/day) increases the plasmatic concentration of glucose reducing the insulin secretion, and up to 50% of the patients achieve an improvement in the control of their hypoglycemas. The edema, the gastrointestinal disorders and the hypertriglyceridemia are described as side effects.
- The octreotide inhibits the secretion of the growth hormone, but it also inhibits the secretion of TSH, insulin and glucagon in high doses. Its efficacy is limited in the insulinoma. However, it is a reasonable alternative in patients with persistent refractory hypoglycemia as regards to the treatment with diazoxide.
- The lanreotide is another analogue of the somatostatin that seems to have a similar effect to the octreotide and offers the advantage of having a long-acting release form.
- The everolimus is an immunosupressor drug with anti-angiogenic effect, with promising results in the glycemic control and the tumoral reduction in patients with malignant insulinoma, even in clinical trials.25

Figure 2 shows the diagnosis algorithm that has to be followed before the suspicion of insulinoma.

Conclusions

The biochemical diagnosis and localization of the insulinoma is complex. It requires specific analytical and technical determinations, invasive some times. Almost the total diagnosis of the tumors is achieved with the current methods; therefore the hidden insulinomas are exceptional. The surgery offers high healing rates and the rest of the therapeutic options remain relegated to a second background.
**Declaration of potential conflict of interests**

M. Diéguez, M. Riestra and E. Menéndez state that there are no conflicts of interest as regards to this article.

**References**

Analysis of the results of continuous subcutaneous insulin therapy as an alternative to intensive treatment in type 1 diabetic patients

Abstract

Aim: To verify the efficacy of CSII treatment and determine patient’s clinical features that could have influenced the posterior metabolic control.

Methods: 37 patients; 21 males and 16 females, mean age of 36.2 ± 9.4 years. Mean duration of diabetes prior to CSII of 16.2 ± 7.4 years and previous year mean A1c of 8.1 ± 0.9%. Diabetic complications: 50% retinopathy, 19% nephropathy, and 11.4% neuropathy. Indications for CSII: poor metabolic control (33.3%), patient request (27.8%), frequent hypoglycaemia (22.2%), glycaemic variability (13.9%) and other (2.8%).

Results: Starting A1c was lowered significantly in the first year of CSII –0.71 ± 0.58% (p <0.001) and stable –0.9 ± 0.54% (p <0.001) after 36 months. Basal insulin requirements decreased and subsequently remained stable (start: 0.29 ± 0.08 U/kg/d; after 36 months: 0.32 ± 0.14 U/kg/d). The greatest reduction in A1c was found in patients with higher baseline A1c and longer duration of diabetes.

Conclusions: CSII resulted in a steady improvement in glycaemic control and reduction in insulin requirements. It could be considered a predictor factor of treatment effect.

Keywords: type 1 diabetes mellitus, insulin pump, multiple daily insulin injections, glycosylated haemoglobin.

Introduction

The continuous subcutaneous insulin infusion (CSII) was introduced for the first time in the 70s as a therapeutic option for the diabetes mellitus type 1 (T1D). At present, the CSII constitutes an alternative efficient treatment regarding to the multiple-dose insulin (MDI) in pa-
tients screened with T1D. In Spain, the implantation of CSII is estimated in 0.79% of the persons with T1D according to the data obtained by the Grupo de Trabajo de Nuevas Tecnologías de la Sociedad Española de Diabetes (SED), (Group of Work of New Technologies of the Spanish Diabetes Society). Pickup et al. made a revision of the studies that compared the use of therapeutic regimes of MDI based on long- and fast-acting insulin analogues versus the CSII and concluded that the long-acting insulin analogues have not yet replaced the treatment with CSII in patients with T1D and that at present the CSII constitutes the best therapeutic option for some of these patients. Zietlger et al. performed a parallel study of 2 years of follow-up, in which they compared the treatment with CSII in which regular insulin was used versus MDI with regular insulin/NPH, without observing relevant statistically differences in the glycemic control between both groups, with a glycosylated hemoglobin (HbA1c) of 8.7 versus 8.4%, respectively.

We have done this study with the aim of analyzing the results of the treatment with CSII in our environment, and in this way to verify the efficacy of this therapeutic modality during the follow-up and to determine the clinical characteristics of the patients who might have influenced in the later metabolic control. Actually, the characteristics of patients that could condition a better response to the treatment with CSII, are not well determined. Therefore, this study has the aim of determining the clinical characteristics of the patients that might have an influence in the later metabolic control.

**Material and methods**

For the performance of this study, we have included all the patients (47 diabetic type 1 patients) who underwent treatment with CSII in the Endocrinology Service of the Hospital of Navarra from 2005 to 2008. The exclusion criteria have been the starting of the treatment in another site (n= 4) and a duration of the treatment with CSII under 6 months (n= 6). Finally, the data of 37 patients have been analyzed.

The patients were screened to receive treatment with CSII following the indication criteria recommended by the SED. Considering the relevance of the therapeutic compliance and the therapeutic education as efficacious strategy for its obtaining, the candidate patients completed a program of diabetology education settled by the team of educator nurses of the Endocrinology Service of the Hospital of Navarra. Such program was carried out individually with an approximate duration of 5-6 sessions. The patients received daily classes of 1 hour of length about the knowledge related to the control of the diabetes: diet (diet per portions, ketosis diet), acute complications (hyperglycemia, hypoglycemia, ketonemia), modification of the treatment, physical exercise, trips and special situations (short length disconnection, extended, during weekend). Likewise, they got knowledge related to the handling and the terminology of the CSII: programming of the watch, programming and modification of the basal infusion, stop and restarting of the pump, recognition of the alarms and actions before them, preparation and placement of the cartridge and the catheter and maintenance of the CSII. Then, the patients received the pump and a simulation period of 2 days was carried out. Once this process came to an end, the infusion was placed in the patients and the first change of catheter was done at the nursing consultation. The first 2 days the intake was reduced to 3 main meals, and the patients received a unique basal index in order to be able to perform the necessary adjustments.

The estimation of the total dose in our patients was determined substracting 20% to the total of accumulated doses with T1D. The 50% of the obtained total determines the basal dose, and the bolus the outstanding 50%. The assignment of the insulin pump was done considering the cession. Moreover, the fungible materials, the catheters, the reservoir and strips of ketonic bodies were administered to the patients.

Finally, 37 patients were included in the study, 21 men and 16 women, who had a mean treatment time with CSII of 31.7 ± 19.3 months. As basal characteristics, the patients showed a mean age of 36.2 ± 9.4 years and an initial body mass index (BMI) of 24.9 ± 3.6. The 27.3% were smokers. When starting with the CSII, they had a mean evolution of the diabetes of 16.2 ± 7.4 years and 56.8% showed at least a complication: retinopathy (50%), nephropathy (19%) and neuropathy (11.4%). The metabolic control level of the previous year was estimated by means of the estimation of the mean value of the HbA1c, which was of 8.1 ± 0.9%. The reason of the main indication of the CSII was the inadequate metabolic control (33%) and the rest of the indications were the following ones: own request (27.8%), frequent hypoglycemias (22.2%), wide glycemic variability (13.9%) and
Combination of several indications could be offered (table 1). The evolution analysis of the glycemic control (HbA\textsubscript{1c}), the weight and the insulin requirements were performed comparing the mean values at the starting and after 12, 24 and 36 months of the treatment. The Student t test was used in the study of the changes in the quantitative variables for paired-off samples. The correlation coefficients were estimated. The multiple regressions (stepwise) were used in order to determine the possible variables associated to the improvement of the HbA\textsubscript{1c} (gender, age, mean of HbA\textsubscript{1c} of the previous year, evolution time and BMI). The confidence intervals (CI) were estimated of 95%. A value of p < 0.05 was considered a priori as statistically relevant.

**Results**

A relevant decrease was observed in the mean of the basal HbA\textsubscript{1c} of \(-0.71 \pm 0.58\%\) (p < 0.001) after 12 months of treatment. This improvement of the glycemic control was kept, and reductions of the HbA\textsubscript{1c} were observed of \(-0.9 \pm 0.72\%\) (p < 0.001) after 24 months compared to the basal hemoglobin and of \(-0.9 \pm 0.54\%\) (p < 0.001) after 36 months.

From the starting of the CSII, the requirements of the basal insulin were kept stable during the follow-up: at the beginning they were of 0.44 versus 0.29 U/kg/day; p < 0.001). The dose of insulin administered in bolus form could not be assessed given that many patients did not register it exhaustively.

As regards to the weight after 3 years of treatment, the patients increased 2.7 ± 4.8 kg. The highest weight gain (1.6 kg; CI of 95%: 0.45-2.75; p= 0.008) took place after 6 months and was not correlated to the change of HbA\textsubscript{1c} (coefficient of Pearson <0.27; p= 0.14).

The participants with worse glycemic control at the beginning of the CSII, or in other words, with higher basal HbA\textsubscript{1c}, and a longest diabetes evolution time, showed a higher decrease of HbA\textsubscript{1c} with this treatment modality. Thus, a reduction of 0.3% was observed for each increase of 1% in the mean HbA\textsubscript{1c} of the previous year (CI of 95%: 0.04-0.58) at the beginning of the treatment with CSII. Likewise, for each additional year of the diabetes evolution, before the beginning of the treatment, a reduction was observed in the HbA\textsubscript{1c} of 0.04% (CI of 95%: 0.01-0.08).

The treatment with CSII was not interrupted or abandoned in any case. Five patients showed ketoacidosis due in part to a failure of the catheter and the non admin-

### Table 1. Basal characteristics of the patients with T1D treated with CSII

<table>
<thead>
<tr>
<th>Basal characteristics</th>
<th>Total</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>37 (21 men, 16 women)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.2 ± 9.4</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>27.3</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>24.9 ± 3.6</td>
</tr>
<tr>
<td>Time of the diabetes evolution (years)</td>
<td>16.2 ± 7.4</td>
</tr>
<tr>
<td>Time of follow-up (years)</td>
<td>31.7 ± 19.3</td>
</tr>
<tr>
<td>HbA\textsubscript{1c} during the year pre-CSII (%)</td>
<td>8.1 ± 0.9</td>
</tr>
<tr>
<td>Basal dose of insulin (U/kg/day)</td>
<td>0.29 ± 0.8</td>
</tr>
</tbody>
</table>

### Table 2. Evolutive changes regarding to the basal values of HbA\textsubscript{1c} and requirements of the basal insulin

<table>
<thead>
<tr>
<th>Evolutive changes as regards to the basal values</th>
<th>12 months CSII</th>
<th>24 meses ISCI</th>
<th>36 months CSII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of HbA\textsubscript{1c} (%)</td>
<td>–0.71</td>
<td>–0.90</td>
<td>–0.90</td>
</tr>
<tr>
<td>Change of the basal insulin requirements (U/kg/day)</td>
<td>–0.13</td>
<td>–0.10</td>
<td>–0.11</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>1.7</td>
<td>2.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

HbA\textsubscript{1c}: glycosylated hemoglobin; CSII: continuous subcutaneous insulin infusion.
istration of a corrector bolus in ketosis situation; therefore they require the short duration admission in the hospitalization ward of endocrinology, with good evolution. A patient showed two or more events of serious hypoglycemia. There have been technical complications in 27.8% of the patients, caused by a catheter failure in most of the cases.

**Discussion**

The treatment with CSII in our patients improves the glycemic control and keeps the improvement achieved during the treatment. The mean reduction of the HbA\(_1c\) compared to the basal is of \(-0.71\%\) after 12 months of treatment. The meta-analysis performed by Jeitler et al. included 12 studies that compared the effect of the CSII with the MDI in adults with T1D. Six of these studies used the HbA\(_1c\) as a measurement method, in which a mean difference in the HbA\(_1c\) of \(-0.4\%\) was obtained. (CI of 95\%: \(-0.65\) to \(-0.20\)) in favour of the patients treated with CSII.\(^6\) Retnakaran et al. compared the efficiency of the CSII and the MDI, proving the efficacy of the analogues of fast insulin in both treatments, and observed that the CSII was associated to an adequate metabolic control compared to MDI; the therapeutic effect was estimated comparing the percentage of the reduction in the HbA\(_1c\) obtained with CSII and MDI, that was of 0.35\% (CI of 95\%: \(-0.10\) to 0.80; p= 0.08).\(^7\)

In the patients of our series, the requirements of the basal insulin decreased since the starting of the treatment and were kept stable throughout the follow-up, in a similar manner than the one observed in several studies performed in patients treated with CSII. In a study carried out by Hoogma et al., a relevant reduction was observed of the total dose on insulin at the end of the study. 0.53 IU/kg/day in the group treated with CSII versus 0.71 IU/kg/day in the group treated with MDI.\(^8\) Hanaire-Broutting et al. obtained similar results, with a total final dose of insulin of 38.5 IU/kg/day with CSII versus 47.3 IU/kg/day with MDI.\(^9\) However, due to the lack of insulin used in the bolus, we cannot assess the change of the total dose of insulin in our series.

We observe a weight gain of 2.7 ± 4.8 kg after 3 years of treatment with CSII. The increase was of 1.6 kg (CI of 95\%: 0.45–2.75; p= 0.008) after 6 months and no relevant correlation was obtained with the change of HbA\(_1c\) (coefficient of Pearson: p= 0.14). Ziegler et al. observed a relevant weight gain, with a higher BMI at the end of the study in the group treated with CSII (24.2 versus 22.5 with MDI).\(^3\) In another study that compared both therapeutic modalities, a not relevant gain determined by means of the final weight could be observed (98.1 kg with CSII versus 97.6 kg with MDI).\(^10\)

A finding that we consider important in our study was the obtaining of a better response to the treatment with CSII in the individuals with a worse glycemic control at the beginning of the treatment and a higher diabetes evolution time. This finding has also been described in other studies and this subgroup of patients has been included (those with the worst glycemic control in conventional therapy) has been considered a candidate group to receive treatment with CSII. The benefit of the passage to CSII increases when the basal HbA\(_1c\) is higher.\(^11\)

A model derived from the meta-analysis performed by Retnakaran et al. predicts that in a patient with basal HbA\(_1c\) of 10\%, the CSII would reduce the HbA\(_1c\) in an additional 0.65\% compared to the MDI in a patient with a basal HbA\(_1c\) of 6.5\%.\(^7\) No relation was found between the reason of the indication and the later evolution.

Five of our patients showed ketoacidosis due in part to a catheter failure and not to the administration of a corrector bolus in ketosis situation. In fact, Hoogma et al. observed a lower number of adverse events in a group of patients treated with MDI compared to a group treated with CSII.\(^6\) Ziegler et al. observed that the onset of ketoacidosis per each 100 patients-year was higher in the group of CSII, but this difference was not relevant.\(^3\) The results available for the performance of the meta-analysis of Jeitler et al. indicated that there have not been differences in the adverse events between the groups treated with CSII and MDI.\(^6\)

The hypoglycemia is the greatest barrier to improve and achieve a strict glycemic control. In our series, a 2.7\% of the patients had more than two events of hypoglycemia, and none of them was serious (loss of consciousness, need of help by a third person, administration of glucagon, convulsions, admission at emergency wards, etc.). Recently, Pickup and Sutton have demonstrated in a meta-analysis of randomized trials that the serious hypoglycemia index was lower during the CSII compared to the MDI, with a index ratio of 2.89 (CI of 95\%: 1.45–5.76;
p <0.001). The reduction was higher in patients with initial index of serious hypoglycemas with MDI and in patients with a longer duration of diabetes. There have not been differences according to the used fast-acting insulin analogue.

There have been technical complications in 27.8% of the patients, caused mostly by a catheter failure without any relation to the different characteristics of the mentioned device. Some recent publications determine that certain events occur with a seldom frequency, as the pump dysfunction, the catheter infection, the irritation or the local uneasiness, though in other studies different results were found. Since our study is observational, it is not possible to determine a cause-effect relation in the found associations. We have not either measured the parameters of the life quality.

Conclusions
In our experience with this modality of intensive therapy, a sustained improvement of the glycemic control in the evolution could be observed as well as the need of basal insulins as from the beginning of the treatment with CSII and during the follow-up.

The greatest decrease of HbA1c was associated to a longer time of evolution of the diabetes and a worse initial glycemic control.

A weight gain after the beginning of the treatment with CSII was observed.

Declaration of potential conflict of interests
C.M. Causso, M.J. Goñi, M. García, M. Toni, P. Munárriz and F.J. Basterra-Gortari state that there are no conflicts of interest as regards to the content of this article.

References
Knowledge of insulin treated diabetic patients about food carbohydrate content. Results of a survey

Conocimiento del contenido de hidratos de carbono de los alimentos en pacientes con diabetes tratados con insulina. Resultados de una encuesta

I. Ramos, J. Girbés


Abstract
Medical nutritional therapy is an essential piece of diabetes treatment. Our objective was to investigate, with a survey, the knowledge about carbohydrates of a group of insulin treated diabetic patients, and the relationship between this knowledge and individual and treatment factors. A survey was made to obtain a score to measure the knowledge about carbohydrates. In the univariate analysis we observed some influences: age, general education, type of diabetes, diabetes education and insulin regime; sex didn’t showed any influence. In the multivariate analysis only general education and diabetes education showed influence on the score, being the diabetes education the more influential factor on the patient knowledge about carbohydrates. Our results emphasize, so, the importance of the diabetes education to improve the quality of our care to the patients with diabetes.

Keywords: survey, diabetes education, carbohydrate, nutrition therapy.

Introduction
The medical nutrition therapy (MNT) is an essential element in the treatment of the diabetes mellitus and is part of the “education for the self-management” that each patient with diabetes has to achieve throughout his lifetime. In the MNT standards of the American Diabetes Association they are recognized with an evidence A level, that the control of the carbohydrates (by means of the count, conversion or estimation of volumes based on the experience) constitute a key strategy to achieve an adequate glycemic control. An individual diet plan based on the quantification and distribution of carbohydrates (CH) is valid for all the diabetic patients, and indispensable in those who undergo treatment with multiple insulin doses.

The MNT, as the diabetological education (DE) in general, has evolved during the last decades as from a didactic-theoretical approach towards a more practical one, customized and based on active learning techniques to achieve the self-management. The first step of the diet education of the diabetic patient comprises the differen-
iation between the food groups and the identification of the CH.\textsuperscript{5} The initial level of instruction might be carried out in basic diabetes attention units and in primary care.\textsuperscript{6}

An adequate nutritional therapy has to start considering the individual reality of the subject.\textsuperscript{5} Taking into account this premise; the patient’s nutritional knowledge should be assessed before starting the learning process. Moreover, since the DE is a continuous process, a periodical evaluation of such knowledge should be convenient. The DKQ\textsuperscript{2} questionnaire is usually used in the therapeutic education programs in order to evaluate the general knowledge of the diabetic patient about the disease. It is made up of 16 questions of multiple answers; six of them are about food and one is focused on the identification of CH. However, specific tests have not been issued about the nutritional knowledge.

The objective of this work is to estimate the knowledge level about the CH identification in a sample of diabetic patients treated with insulin and to analyze its relation with factors linked to the subject and the treatment.

**Material and method**

**Study field and subjects**

The study population is constituted by diabetic patients seen at the Diabetes Unit of the Health Department 8 of the Community of Valencia. Such Department comprises a population, of rural and semi-urban type, of approximately 70,000 people. The Diabetes Unit has a basic attention function, placed in an extra-hospital office and in this case, is made up of a specialist physician in endocrinology and nutrition.

In order to carry out the study, a sample has been screened that included diabetic patients undergoing insulin treatment who attended consecutively during a period of 3 months to the control medical consultation and who accepted to take part voluntarily. The exclusion criteria were: 1) recent insulinization (less than 6 months), 2) insufficient understanding capacity (according to the interviewer’s opinion) and 3) gestational diabetes.

**Survey**

A survey was done to each patient, without previous notice, during the medical control visit at the Diabetes Unit. All the surveys were conducted by the same interviewer: the physician of the Diabetes Unit.

The survey format consisted of a first introduction question followed by a multiple answer test. The initial question was asked orally: “Do you know what carbohydrates are?”. In case of an affirmative answer, the person passed directly to the test. A brief explanation was given to the patient in case of a doubtful or negative answer (“It is the food that contains sugar, flour, starch...”) and the test was done afterwards.

The test of multiple answers was in writing in capital letters of great size. The patients filled them out alone, unless there was certain difficulty in writing and reading, receiving the help of the interviewer in this case. The wording of the test coincides with the one of question No. 5 of the DKQ2 questionnaire: “Which of the following foods contain carbohydrates?”. There appeared below a list of 20 usual foods in our diet and pertaining to the different food groups (table 1). The score of the test is expressed as absolute number of correct answers.

**Socio-demographic and clinical variables**

The following variables have been collected: age, gender, cultural level, diabetes type, diabetes duration, received diabetological education and current guideline of insulin. For each of the following five variables and as regards to the data analysis, the patients have been grouped in three categories:

- **Age:** under 51 years of age, between 51 and 65 years and older than 65 years of age.
- **Cultural level:** “high” (university studies), “middle” (professional formation or secondary school) and “low” (primary studies or without studies).
- **Type of diabetes mellitus** (according to the classification of the World Health Organization):\textsuperscript{8} T1D, T2D and other specific types of diabetes (“Others DM”).
- **Diabetological education:** “advanced” (specific learning program about carbohydrates), “basic” (standard program of diabetological education of primary care) and “none”.
- **Insulin guideline** (associated or not to the oral antidiabetics): “bolus-basal” (1-2 doses of slow- or intermediate action insulin and 1-4 doses of fast-acting insulin), “mixed” (2-3 doses of premixed insulin) and “basal” (1-2 doses of slow-intermediate acting action insulin).

**Statistical analysis**

The data are processed with the information program SPSS, version 11. The variable “score” (number of cor-
Identification of carbohydrates. I. Ramos, et al.

Rect answers of the test) was considered that it was an estimation of the knowledge about CH, and it was proved that it did not fail to keep with the normality requirement by means of the test of Shapiro-Wilk. The mean scores of the groups of subjects were compared by means of the Student t test or the one way ANOVA test. Multiple post hoc comparisons were done with the procedure of Bonferroni if the ANOVA model was relevant. When it had to do with an ordinal independent variable (age group, cultural level, received diabetological education) and in order to assess the effect lineal tendency, a polynomial contrast of lineal order was also carried out. Finally, the interaction and the effect of the category variables were studied in the dependent variable “score” by means of a univariant general lineal model. A value of p <0.05 was accepted as bilateral statistical meaning level.

Results

From 196 diabetic patients under treatment with insulin who attended the consultation, 44 were excluded due to recent insulinization and 32 due to insufficient understanding capacity. The others (n= 120) took part in the study. The characteristics of our studied population sample are depicted in table 2.

To the introduction question (“Do you know what the carbohydrates are?”), 67 patients (55.8%) answered affirmatively. In a whole, the score obtained in the test was of 12.15 ± 2.66 (mean ± SD). Twelve (12) subjects exceeded the level of 15 correct answers (10% of the total).

The score of the different groups or categories of patients are collected in table 3. In all the variables, except in sex, the mean scores of the groups were relevantly different. When comparing the groups by means of the contrasts, the results were different for the groups <51 years of age and >65 years, T1D as regards to T2D, and the middle and high cultural levels compared to the low level. As regards to the diabetological education, the score of the group with advanced SD was higher than the one of the group with basic SD and of the group with no SD; in turn, there was no difference between these two last ones. Finally, among the insulin guidelines, the group with bolus-basal guideline was different compared to the group with basal guideline, while the mixed guideline did not show differences compared to the basal. A relevant lineal tendency was observed in the variables of the age group (F= 7.07; p= 0.009), cultural level (F= 25.86: 28.96; p= 0.000), and received diabetological education (F= 38.64; p= 0.000).

Table 1. Carbohydrates identification test

<table>
<thead>
<tr>
<th>Food</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bread</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prawns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macaroni</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artichoke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cookies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sardines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchego cheese</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banana</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cucumber</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured ham</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almonds</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Socio-demographic and clinical characteristics of the sample (n= 120)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1 (15.0)*</td>
</tr>
<tr>
<td>&lt; 51 years</td>
<td>36 (30)**</td>
</tr>
<tr>
<td>51-65</td>
<td>42 (35)**</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>42 (35)**</td>
</tr>
<tr>
<td>Gender</td>
<td>Women / Men</td>
</tr>
<tr>
<td>Cultural level</td>
<td>High / middle / low</td>
</tr>
<tr>
<td>Diabetes type</td>
<td>T1D / T2D / Others</td>
</tr>
<tr>
<td>Duration of the diabetes (years)</td>
<td>15.8 (9.8)*</td>
</tr>
<tr>
<td>Diabetological Education</td>
<td>Advanced / basic / none</td>
</tr>
<tr>
<td>Insulin guideline</td>
<td>Bolus-basal / mixed / basal</td>
</tr>
</tbody>
</table>

*Data expressed as mean (and standard deviation). **Data expressed as number of subjects (and percentage).
p <0.0001) and diabetological education (F= 75.86; p <0.0001).

No relevant interaction in variables combination was found when the univariant general lineal model was used. The only variables that showed a relevant effect in the score of the test was the SD and the cultural level of the patient. The summary of the results is depicted in table 4.

**Discussion**

The characteristics of the studied sample (ratio 1:2 of T1D:T2D, mean age 57 and mean-low cultural level) fit with the population usually assisted in a diabetes basic unit, which supposes a intermediate step between the primary care and the mentioned specialized units. However, due to the heterogeneity of the assistance organization of the health departments, these data cannot be extrapolated to other geographic areas.

The global results state the scarce knowledge about the CH by the diabetic patients of this assistance unit: almost half of them did not know the meaning of the term “carbohydrates” and only 10% reached an “acceptable” or “sufficient” score (more than 15 correct answers).

The statistical analysis reveals that having followed a specific education program is the main determining factor in the knowledge on CH identification, influencing also the individual’s cultural level. The fact that the advanced program is precisely more applied among young subjects, with T1D, high cultural level and with bolus-basal guideline would explain mostly the better scores of these groups of patients. It is also logical that if the patient has a higher instruction he might assimilate better the specific knowledge. There are a few studies that assess the factors related to the diabetological instruction level. Zafra et al. observed that the young patients had a better diet knowledge and that the frequency to the nursing consultations was the main factor related to these knowledge. A recent North American study observes that a worse score in the “numeral skill related to the diabetes” is associated to an older age, low socio-cultural level and less time of diabetological education.

As regards to the therapeutic education programs in this attention unit, the study shows, better results in the specific advanced program as it is logical. The scarce effi-
efficiency of the basic program as regards to the supply of knowledge about the CH explains why such program has focused more on the promotion of a Mediterranean diet low in saturated fats than on the identification of CH.

On the other hand, a high percentage of patients of this sample treated with multiple insulin doses have not received specific instruction about CH. In other words, in many cases we are carrying out a “pharmacology intensification” of the diabetes treatment that is not accompanied by a “diet intensification”. There are multiple barriers to fully develop the MNT in the attention of the diabetic patient: lack of attention to the physician regarding to the MNT, lack of nursing staff specialized in diabetes and lack of nutritionists, attention overload that conditions the limited times, complexity of the own MNT, scarce compliance of the education program by the patient, etc.

The principles of a DE program have to be the transmission of information and the promotion of attitude changes to achieve an adequate autonomy of the diabetic person. This study reflects that we are far from reaching such objective in most of the patients.

Finally, we think that the specific questionnaires about the identification and quantification of the CH might be useful in the clinical practice. They allow evaluating objectively and in a fast way the patient’s knowledge and detecting mistakes that otherwise might pass unnoticed, therefore they represent an adequate complement to the current education tools. Thus, the design and validation of these questionnaires supposes an interesting work line in the diabetology clinical investigation.

Declaration of potential conflict of interests

I. Ramos and J. Girbés state that there are no conflicts of interest as regards to the content of this article.

References

The impact of obesity and glycemic control on birth weight in gestational diabetes

Obesidad y control glucémico: efecto sobre el peso del recién nacido en la diabetes gestacional

Endocrinology and Nutrition Service. University Hospital “La Paz”. Madrid

Abstract
The aim was to evaluate the effect of glycemic control and obesity on birth weight in 1,960 women with gestational diabetes. Different birth weight parameters were considered: macrosomia, large-for-gestational-age (LGA) and foetal ponderal index. Foetal ponderal index was higher in obese and poor-glycemic-control groups. The LGA rate was higher in obese women compared to non-obese (OR=2.16; CI of 95%: 1.44-3.25%) and in patients with poor glycemic control compared to good-glycemic-control group (OR=1.88; CI of 95%: 1.35-2.63). In the latter, an increase in foetal ponderal index and LGA rate was observed in obese women. The LGA attributable risk percentage was 53.7% for obesity and 46.8% for bad-glycemic-control. In conclusion, obesity and poor glycemic control are associated with a higher foetal ponderal index and a higher risk of LGA newborn in gestational diabetic women. There is an increase in the foetal ponderal index of the obese subgroup independently of glycemic control. And obesity could explain the excess of LGA newborns despite mother’s good glycemic control during pregnancy.

Keywords: obesity, birth weight, gestational diabetes.

Introduction
At present, the obesity and gestational diabetes (GD) are highly prevalent in women in fertile age. The exponential increase of both pathologies in this group is a reality that is being proved globally. In Spain, the obesity affects the 8% of the women between 25 and 44 years of age,¹ and the prevalence of GD increase up to 12%.²

In the pregnant women, the obesity and the hyperglycemia cause common deleterious effects that affect the mother and the newborn. At short-term, the obesity and the hyperglycemia entail a wide range of pre/perinatal complications. The hypertensive stages of pregnancy and the excessive number of caesarean sections are the most common obstetrics complications. In the peripartum period, the obese mother has a higher risk of throm-
boembolism, hemorrhage and surgical wound infection.\textsuperscript{3} The recurrence of GD in successive gestations is more frequent after delivery, as well as the persistence or development of glucose intolerance, T2D and several components of the metabolic syndrome.\textsuperscript{4}

Moreover, both factors suppose a higher risk of abortions, fetal and neonatal mortality and congenital malformations, and points out the highest frequency of large weight of the newborn with the consequent dystocic and associated metabolic disorders.\textsuperscript{3,5,6} Additionally, the inadequate increase of weight during the fetal period seems to imply a higher risk of children obesity and metabolic syndrome in the descendant.\textsuperscript{4,5,7}

The confluence of obesity and GD is more and more frequent. The pregestational obesity and the GD are implied in the large weight of the newborn. Multiple studies are focused on the negative effect of obesity in mothers on several perinatal variables.\textsuperscript{3,6,8-10} However, the contributions are scarce as regards to the impact of the obesity in the specific group of women with diabetes during pregnancy.\textsuperscript{11,12}

The aim of this study is to assess the repercussion of the glycemic control and the obesity on the weight of the newborn in women with GD.

Material and methods

A study of historic cohorts has been started, in which 1,960 women with GD were included according to the criteria stated by the National Diabetes Data Group, followed at the Diabetes Unit between 1987 and 2006, whose mean age was of 33 ± 4 years, with a mean body mass index (BMI) previous to the gestation of 24.8 ± 4.7. We define the obesity as a BMI ≥30 kg/m\textsuperscript{2}. We obtained the mean of the glycosylated hemoglobin (HbA\textsubscript{1c}) of at least two determinations in the third quarter, measured by high resolution liquid chromatography (HPLC BioRad, Richmond, CA). We consider an adequate metabolic control an HbA\textsubscript{1c} <5.4% (range: 4-6), corresponding to the P\textsubscript{70} of the distribution for the sample. The ponderal variables evaluated in the newborn have been: macrosomia (weight ≥4 kg), large weight for the gestational age (LGA) (weight ≥P\textsubscript{90} of the Spanish tables)\textsuperscript{13} and fetal ponderal index (FPI) (weight of the newborn/ P\textsubscript{50} of the weight according to the gestational age). We compare the ponderal variable of the newborn among the non-obese and obese mothers, among pregnant women with an adequate and inadequate control, and finally among four groups (adequate control non-obese, adequate control obese, inadequate control non-obese and inadequate control obese) compared two by two according to the presence of obesity. For the LGA frequency it has been estimated the percentage of attributable risk (AR%) to the obesity and to the inadequate metabolic control in the group exposed to the respective factors. The data have been analyzed by means of SPSS version 11.0 for Windows. The t Student tests have been applied in the statistical analysis for the comparison of means applied to independent samples and the $\chi^2$ for the comparison of validity conditions. We consider the statistically relevant association with a value of p <0.05.

Results

The demographic characteristics of the pregnant women and the newborns are depicted in table 1. The characteristics of the subgroups stated according to the obesity and the glycemic control are depicted in table 2. The age was similar in the considered subgroups. The ponderal gain was lower in previously obese women and the gestation term was earlier.

The FPI was higher both in the obese pregnant women compared to the non-obese (1.02 ± 0.14 versus 0.98 ± 0.12; p=0.000) as well as in the pregnant women with an inadequate glycemic control compared to the ones with an adequate control (1 ± 0.14 versus 0.98 ± 0.12; p=0.005). The mean FPI in the four defined groups is depicted in table 3. The LGA frequency was higher in

| Table 1. Epidemiological characteristics of pregnant women and newborns |
|------------------|------------------|
| n | 1,960 |
| Age (years)* | 33 ± 4 |
| Body mass index (kg/m\textsuperscript{2}) | 24.8 ± 4.7 |
| Gestational age at term (weeks)* | 38.8 ± 1 |
| Obesity (n/%) | 236/12 |
| Inadequate glycemic control (n/%) | 584/28.9 |
| Macrosomia (n/%) | 53/2.7 |
| LGA newborns (n/%) | 430/22.1 |
| Weight of the newborn (g)* | 3,127 ± 417 |
| Fetal ponderal index* | 0.98 ± 0.13 |

*Mean ± SD. LGA: newborn large weight for gestational age.
obese women than in the non-obese (12.2 versus 6.1%; odds ratio [OR] = 2.16; confidence interval [CI] of 95%: 1.44-3.25). The AR% of LGA was of 53.7% for the mothers’ obesity (figure 1). The LGA frequency was higher in the pregnant women with inadequate control versus the pregnant women with an adequate control (10.5 versus 5.9%; OR= 1.88; CI of 95%: 1.35-2.63). For the inadequate glycemic control, the AR% of the LGA was of 46.8% (figure 1). The comparative LGA frequency in the four defined groups is depicted in table 3. In women with an adequate control, the obesity increased the FPI significantly and the frequency of the LGA (OR= 2.03; CI of 95%; 1.08-3.79). In women with an inadequate control, the obesity increased the FPI and there have not been relevant differences in the LGA frequency among obese and non-obese women (OR= 1.71; CI of 95%; 0.92-3.16).

**Discussion**

The pregestational obesity and the GD are implied in the large weight of the newborn. To elucidate which is the relative contribution of obesity and diabetes on the neonatal result it is important regarding the efficient prevention of the inadequate ponderal increase during the fetal period and its complications derived at short and long-term.

This present analysis stands out the impact that supposes the obesity in the mother added to the GD in the women of our environment. We observe an excess of LGA newborns of mothers that were obese, in spite of the adequate maintained glycemic control. Likewise, there has been an increase of FPI in all groups with obesity, regardless of the glycemic control. Similarly, the results of Langer at al.\textsuperscript{11,12} revealed an increase of newborns with macrosomia and LGA among the women with GD that also had a high BMI previous to gestation, especially when exceeding 30 kg/m\textsuperscript{2}, depending on the glycemic control. However, it is difficult to extrapolate the results of such study to the Spanish population, as the referred population showed highly marked indexes of overweight and obesity. In the same way, the inadequate glycemic

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**Table 2. Basal characteristics of the subgroups stated according to the presence of obesity and mother glycemic control**

<table>
<thead>
<tr>
<th></th>
<th>Non-obese, adequate control</th>
<th>Obese, adequate control</th>
<th>Non-obese, inadequate control</th>
<th>Obese, inadequate control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1,239</td>
<td>135</td>
<td>476</td>
<td>108</td>
<td>0.125</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33 ± 4</td>
<td>32 ± 5</td>
<td>33 ± 4</td>
<td>33 ± 4</td>
<td>0.000</td>
</tr>
<tr>
<td>Ponderal gain (kg)*</td>
<td>10.1 ± 3.8</td>
<td>6.2 ± 4.5</td>
<td>10.8 ± 4</td>
<td>6.3 ± 4.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Gestational age at term (weeks)*</td>
<td>38.9 ± 1.1</td>
<td>38.7 ± 1.4</td>
<td>38.8 ± 1</td>
<td>38.6 ± 1.1</td>
<td>0.042</td>
</tr>
</tbody>
</table>

*Media ± desviación estándar.

**Table 3. Mean FPI and frequency of newborn LGA according to the presence of obesity and mother glycemic control**

<table>
<thead>
<tr>
<th></th>
<th>Non-obese</th>
<th>Obese</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adequate control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPI</td>
<td>0.97 ± 0.12</td>
<td>1 ± 0.13</td>
<td>0.048</td>
</tr>
<tr>
<td>LGA</td>
<td>5%</td>
<td>9.6%</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>Inadequate control</strong></td>
<td></td>
<td></td>
<td>0.112</td>
</tr>
<tr>
<td>FPI</td>
<td>0.99 ± 0.13</td>
<td>1.03 ± 0.15</td>
<td>0.009</td>
</tr>
<tr>
<td>LGA</td>
<td>9.2%</td>
<td>14.8%</td>
<td>0.112</td>
</tr>
</tbody>
</table>

FPI: fetal ponderal index (mean ± standard deviation); LGA: large weight for gestational age.
control was more frequent among the patients included in the mentioned study. On the other hand, a previous analysis carried out to the Spanish population explained a higher risk of perinatal complications associated to the increasing prevalence of mother obesity.6 

The ethnic group and the maternal age seem not to predict different results in the study of Langer.12 There have not been differences in our sample among groups as regards to the age. The birth weight is also conditioned by other factors, as the ponderal gain during pregnancy.5 

The ponderal gain was lower in the subgroup with previous obesity, and the gestation term of these women was slightly early. However, should they have an effect in the results; these differences would underestimate the impact of the obesity on the weight of the newborn. Additionally, it is worth mentioning that the patients included in the several sub-groups did not show differences compared to the follow-up jointly performed by the obstetrician and the diabetologist.

The pregnant woman with obesity and/or GD has a higher risk of showing adverse mother-fetal results. In the GD context, we prove the impact both of the glycemic control and the mother obesity on the weight of the newborn. Though what is more outstanding was the relative influence of the pregestational BMI, which expressed in the form of attributable risk has even exceeded the one exerted by the GD inadequate control. The therapeutic intervention on the GD has probably performed a role, but not the obesity control previous to the gestation. However, Ricart et al.6 considered this explanation insufficient. In fact, these authors pointed out the relevance of the pregestational BMI in women with or without concomitant GD on the risk of perinatal complications in our population.

Another known matter is the insufficient efficiency of the adequate glycemic control of the GD to reduce the newborn overweight indexes up to values comparable to the described ones in the general population.8 In this sense, the maternal obesity would be responsible, at least partially, of such risk excess notwithstanding the adequate control.

It has to be pointed out that the exposed preliminary data are subject to revision and consideration of potential confusion factors that should be taken into account in further analysis.

To summarize, both the obesity and the inadequate control of the GD increase the FPI and the LGA risk, though the impact of the obesity might be higher. The FPI in the newborns of obese mothers is higher, regardless of the glycemic control, and the obesity might explain the LGA of the newborns as regards to the pregnant women with an adequate control. Therefore, the obesity supposes an added risk to the risk inherent to the GD for the large weight of the newborn.

At present, the evidence about the risk associated to the ponderal excess and the increasing impact on the population generate the precise need of a preventive approach. During the pre-conception phase, an approximation would include adequate information for women in fertile age, the evaluation of the overweight determinations and the diet advice added to the usual supplementation of folic acid. Complementary, it would be desirable to perform a follow-up of these women by means of a physical activity program, and provide psychological assistance in the cases of associated diet behavior disorders. Additionally, the performance of a careful follow-up of weight is required during gestation, as well as of blood pressure, glycemia and fetal biometry. A post-delivery evaluation is recommended to be carried out with the aim of preventing and detecting the ponderal gain and the onset of T2D.14 Therefore, this clinical approach of the obesity during the reproduction age would contribute to minimize the risk both in women and in the descendants during the gestation and peripartum delivery periods, as well as at long-term.

Declaration of potential conflict of interests
B. Barquiel, L. Herranz, P. Martín-Vaquero, I. Castro, J.A. Rosado, M. Jáñez, A. González and L.F. Pallardo state that there are no conflicts of interest as regards to the content of this article.

References
Perioperative mortality in diabetic patients after non traumatic lower extremity amputations in Madrid from 1997 to 2005

Abstract
Introduction: Chronic diabetic complications greatly affect the cost in health, economic productivity, with an emphasis on diabetic foot. Objectives: Analysis of mortality trends and related factors associated with LEA. Material and methods: A retrospective observational study of LEA in Madrid between 1997 and 2005. Documentary source: MBDS (discharge minimum basic data set). We selected cases that included an 84.1X procedure and 250.XX diagnosis (ICD-9-CM). Minor amputation was defined as distal to the ankle joint and a perioperative death that occurred during hospitalization. The trend of mortality was assessed using joinpoint regression analysis and expressed as percentage of annual change (PAC). We studied the risk of death by multivariate logistic regression using the independent variables age, sex, type of amputation and diabetes. Results: During the study period there were 278 deaths (7.3%) in diabetic patients. Mortality trends: PAC 1.99% (–2.7 to 6.9) was not significant. Risk of death (OR; 95%CI), patients over 65 years old (3.16; 2.03-4.91; p= 0.0001) and major LEA (2.75; 2.08-3.64; p= 0.0001). Conclusions: The perioperative mortality of LEA remains high and showed no downward trend during the study period with an increased risk of death for adults over 65 years and major LEA.

Keywords: mortality, amputation, diabetes.
Introduction
The diabetes mellitus has been named the epidemic of the XXI century due to the large number of affected individuals and the sanitary and socio-economical consequences. It is the most frequent endocrinopathy, with effects in almost all the systems and organs of the body, placing itself in most of the developed countries among the ten first causes of death, with worrying projections. This increase in the incidence and prevalence of the diabetes might suggest an increase in the number of diabetic persons with chronic complications, and it is foreseeable that it occurs at earlier ages. The prevalence of the foot ulcer is of 4-10% in diabetic patients, and 40-60% of all the non traumatic lower extremity amputations (LEA) occur in diabetic persons followed with ulcer in 85% of the cases. The diabetic foot affects more than 2 million of individuals per year in the United States and supposes a huge social and economic cost both for the health systems and for the patient and family. The polyneuropathy, the peripheral vascular disease and the infections are the factors that condition the diabetic foot in different proportions; all of them very frequent complications in diabetes and responsible of the foot ulcer, that does not heal, leading to the amputation in the worse of the cases and to death in some occasions. Objectives and declarations have been stated worldwide leading to reduce the amputations rates, and the declaration of Saint Vincent of 1989 was left behind. First, the efforts have to be directed to the optimization of the metabolic control and of the associated cardiovascular risk factors, to the health education of the patient and persons who take care, and to the adoption of specific measures addressed towards the prevention of the amputation, in other words, towards comprehensive programs on the diabetic foot assistance. The basis of these programs has to be the monitoring of the indicators by means of the development of adequate and feasible information systems. In this sense, the evolution of the rates of amputations or mortality due to amputation are indicators that have been incorporated in many health services as it has to do with sentinel events of great clinical-epidemiological interest and accessible by means of non-specific record systems, as it takes place under hospitalization regime.

In view of the above, it seems to be of great interest to know which has been the trend of the hospital mortality related to the LEA in diabetic patients in the environment of the Community of Madrid during the last decade, as well as the related factors.

Material and methods
An observational and retrospective study has been designed in which all the recorded admissions at public hospitals of the Community of Madrid have been analyzed regarding to the period comprised between January 1st 1997 and June 30th 2005, with the aim of identifying all patients who underwent a LEA. The file of the Minimum Basic Data Set (MBDS) has been used as source, which has been delivered to the central services of the extinct Insalud by all the hospitals appointed to its network and after the transfers as regards to health matter to the Health Counsel of the Community of Madrid. Such files contain up to 13 diagnosis fields and up to 21 related to surgical procedures, codified by means of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The records that included the procedural codes 84.1X have been chosen and the subgroup of diabetic patients have been included if the code 250.x was in any of the diagnosis fields. Moreover, the traumatic and neoplastic amputations have been excluded. The methodology of Global Lower Extremity Amputation Study Group has been used in the definition of amputations: lower LEA has been considered the distals to the tarsometatarsian and the rest greater LEA. The trend of the mortality in the studied period was evaluated with segmented regression models of Poisson by means of the software Jointpoint of the Surveillance Research Program of the US National Cancer Institute. For the evaluation of the association among category variables, the test of the $\chi^2$ has been used considering the statistically relevant differences by an alpha mistake lower than 5%. The mortality risk was analyzed through logistics regression models, considering the death as dependent variables and being older than 65 years of age as independent variables as well as the sex, the type of amputation (higher or lower) and the presence of diabetes (codified as dichotomy variables). A multivariate model has been designed with the mentioned variables that showed a statistically relevant association with the dependent variable (p <0.05) in the bivariant analysis and the interaction terms >65 years/diabetes and higher/diabetes LEA, through the statistical package SPSS® version 12.0; those that did not show statistical relevance were excluded.

Results
Table 1 depicts the casuistry description. During the study period, 555 deaths occurred in patients who underwent LEA (9%), 278 occurred in diabetic patients (7.3%)
versus 277 (11.8%) in non-diabetic persons (p <0.0001), 221 (11.2%) in women versus 334 (8%) in men (p <0.001), 485 (10.7%) in persons older than 65 years of age versus 70 in persons under 65 years of age (4.3%) (p <0.001) and 434 (12.7%) in those who underwent upper LEA versus 121 (4.4%) of those submitted to lower LEA versus (p <0.001). In the patients who underwent upper LEA, the mortality was of 11.3% in the diabetic patients versus 14.4% in the non-diabetic patients (p <0.001), and in case lower LEA the mortality was of 3.7 versus 6.3%, respectively (p <0.005). Table 1 depicts the evolution of the mortality by LEA in diabetics patients, in the non-diabetics and in the total of patients: the change annual percentage was of 0.22% (confidence interval [CI] of 95%: –5.47 to 6.26) for the total LEA, of 1.99% (CI of 95%: –2.7 to 6.9) for the LEA in diabetic patients and –0.47% (CI of 95%: –8.98 to 8.84) for the LEA of the non-diabetics (differences not statistically relevant), that is to say, no trend in the studied groups could be proved.

In the bivariant logistics regression analysis, the death risks (odds ratio [OR]: CI of 95%) with statistical relevance have been for the presence of diabetes of 0.59 (0.5-0.7; p= 0.0001), for the age over 65 years of 2.69 (2.08-3.47; p= 0.0001), for the female of 1.45 (1.21-1.74; p=0.0001) and for the LEA over 3.16 (2.56-3.89; p= 0.00001).

In the multivariant analysis, a model has been obtained with the variables age over 65, larger amputation and absence of diabetes, as prognosis factors of mortality; the gender has been excluded due to the loss of statistical meaning (table 2). In the final model, the interaction over 65 years and diabetes has been included as well as the interaction greater AMI and diabetes due to statistically meaning.

In any case, as it can be observed at the bottom of the table, the explaining power of the logistics model is very limited (determination coefficient). When analyzing exclusively the discharges of the diabetic patients we obtain regression equations with identical variables (gender is also excluded), though in the diabetic patients the OR for the age and the type of amputation is greater, in other words, the association between >65 years of age and suffer a greater amputation and die during admission is greater (table 3). Consider that in table 2 the last interaction or effect modification has been excluded (higher/diabetes LEA) when losing the statistical meaning in the multivariant model (p >0.05).
Discussion

The diabetic patients who underwent LEA show a high mortality related to the great associated comorbidity (brain vascular disease, heart disease, chronic renal disorder, etc.). The amputation is a good marker of the advanced microvascular and macrovascular diabetes disease and, therefore, an unfavourable prognosis sign.

Among the works that study the hospital mortality due to LEA in diabetic patients in our environment we point out the Alcalá Martínez et al.15 (Murcia), with a mortality of 2% for lower LEA and 10% in case of greater LEA (global mortality of 5.8%) or the one of Almaraz et al.16 (Malaga) with a 3.6% of total LEA. The mortality in the diabetic patients of our study was of 7.3% of 11.3% for greater LEA and 3.7% for the lower LEA, slightly greater than in the two mentioned studies.

In the study about the mortality performed at Tayside (Scotland)17 between the years 1992 and 1998, a mean survival is described after the LEA of 27.2 months for the diabetic patients, and after 12 years the survival was of 25%; the values for the non-diabetic patients was of 46.7 months and 7.4% respectively. In both cases, the greater amputations are analyzed. Greater perioperative mortality has been reported when the amputation is proximal. Thus, Subramaniam et al.18 (Boston, United States) obtained between 1990 and 2001 mortality after 30 days of a LEA over the knee of 17.5% and below the knee of 4.2%, with a total mortality of 7.4%. The diabetes mellitus in the logistics regression study was not related to a higher risk of perioperative death nor to a lower survival after 3 years, though in fact after 10 years. Our work is not designed for the survival study after the patient’s discharge; in fact, the follow-up is circumscribed to the admission events and all the deaths occurred outside admission that includes amputation, though the obtained perioperative mortality (intra-event) is practically identical to the one analyzed in the article of Subramaniam, with an equal methodology. Our diabetic patients shown a death OR of 0.4 (CI of 95%: 0.24-0.67) lower than 0.76 and the same occurs with the amputation level, with an OR of 2.64 (CI of 95%: 2.13-3.26) for greater LEA versus 4.35 in the work that we compare, though such authors consider proximal amputation the one practiced over the knee, which might explain these differences. Probably we might have obtained similar results as regards to the mortality at mean term if we could have studied it, but what is stated in the high perioperative mortality for the greater amputations. It has to be considered that the number of lower LEA exceeds the greater one in men but exactly the opposite happens in women, which together with the distribution explains its highest mortality (it has to be reminded that the gender variable is excluded from the regression equation in the multivariant adjustment). The age is also an independent death risk factor, which also modifies the diabetes effect, which seems logical when preventing a higher prevalence of the comorbidities, as the cardiovascular and renal disease. In Europe, different observational studies of similar design, as the one performed in Greece19 and in the United Kingdom,20 obtained perioperative mortalities of 14.7% in diabetic patients versus 21.3% in non-diabetic in the first one and 5.9 versus 9.1% in the second one, without the differences resulting statistically relevant and likewise a higher death risk associated to the amputation level and the age.

However, we could not demonstrate any trend to the mortality reduction in the study period; probably, the intervention point has to be looked after in the prevention of the amputation.

The outstanding fact that the mortality is lower in the diabetic patients than in the non-diabetic might be attributed considering that the first LEA occurs at earlier ages in diabetic patients and that in them the diabetes control as well as the modifiable cardiovascular risk factors is stricter during the last decade;21 moreover, the differences attributable to a different comorbidity and etiological composition of amputations in diabetic patients cannot be excluded. The limitations of our observational and retrospective design, as well as the used document

### Table 3. Death risks (multivariant logistics regression). Diabetic and non-diabetic patients

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>OR</th>
<th>CI of 95% of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: &gt;65 years old</td>
<td>0.0001</td>
<td>3.16</td>
<td>2.03-4.91</td>
</tr>
<tr>
<td>LEA: greater</td>
<td>0.0001</td>
<td>2.75</td>
<td>2.08-3.64</td>
</tr>
<tr>
<td><strong>Non-diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: &gt;65 years old</td>
<td>0.0001</td>
<td>1.8</td>
<td>1.3-2.52</td>
</tr>
<tr>
<td>LEA: greater</td>
<td>0.0001</td>
<td>2.34</td>
<td>1.68-3.25</td>
</tr>
</tbody>
</table>

CI: confidence interval; LEA: non traumatic lower extremity amputations; OR: odds ratio or advantages reason.
source, difficult the evaluation of certain factors, as the associated morbidity, mainly the cardiovascular disease and the nephropathy, or the presence of infections of ulcers related to the mortality, as well as the death cause. As we have already mentioned, the neuropathy and the vasculopathy are the main causes of amputation and the prevention should be the intervention point to reduce the high number of associated deaths.

To conclude, we believe that the use of general systematic records, as the MBDS might be useful as basis with a low cost, for the record of the events of great impact in diabetology as the LEA and the mortality due to LEA; fact that will be also useful to improve the quality of such records.

Conclusions
We have to conclude that the rates of mortality related to the hospitalization due to LEA are high in the Community of Madrid, higher than the ones reported by other groups of our environment, and have not shown a decreasing trend during the 9 years of study. The advanced age and the proximal association are associated to a higher mortality.

Declaration of potential conflict of interests
Á.M. Molino, P. de Miguel, A. Albarracín, R. Patiño and A. Fernández-Cruz state that there are no conflicts of interest as regards to the content of this article.

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Flow cytometry and platelet activation markers

Flow cytometry

It is an analytical technique that allows assessing different parameters in individualized cells that flow through a sensor point. Thanks to the technology of the monoclonal antibodies and to the use of different fluorochromes, the density and the distribution of several cell antigens can be studied. The application of the flow cytometry has experienced during the last years a great development, allowing studying several cell subpopulations simultaneously.

At the beginning of the 70s the argon laser started to be used for the fluorescence measurements. Multiple commercial flow cytometers were developed during the following decade (Coulter Cytometry, Ortho Diagnostics, Becton Dickinson, Bio-rad Laboratories Inc, Cytomation Inc., Partec AG, Sysmex Corporation, etc.) which have been incorporating the technology developed dur-
ing the last years in several fields, therefore more versatile, accurate and fast flow cytometers have been commercialized.

At present, there are cytometers able to measure multiple cell parameters of dispersed light and conjugated fluorescence with specific antibodies as from a cell suspension or particles (cores, organelles, chromosomes). These systems, unlike other analysis techniques that measure the mean population of a determined property, are able to measure, store, process and represent the parameters of thousands of cells in a customized manner. Basically, these systems collect the dispersed light and the one emitted by such particles, as the radiation from the argon laser with a wave length of 488 nm affects them.

The critical essential step in flow cytometry is to count with a suspension of individual cells, representative of the original population. Such suspension is marked with conjugated antibodies with fluorescent colors and after an optimal incubation period, it is injected into the cytometer, in which the sample is focused hydrodynamically in the flow chamber. In such chamber, the cells interact with the monochromatic light shaft, causing diffraction. Once the cell interacts with the radiation, the system measures several parameters and relate them with determined cells characteristics. Such cytometric parameters are as follows:

- Frontal dispersion (forward scatter): related to the cell size.
- Lateral dispersion (side scatter): related to the density and cell rugosity.
- Fluorescence intensity: related to the amount of conjugated antibodies with a fluorochrome, bound to a specific antigen.

In order to obtain this information, the optics of the cytometer is placed in such a way to allow collecting the dispersed light in the same direction than the incident light (forward), the dispersed light with an 90° angle as regards to the other one (side) and the light emitted by fluorescence with this same angle. From the light collected from the side, through dichroic mirrors, the different wave lengths, which reach the corresponding detectors with a determined intensity. In these detectors, the light signal turns into an electric signal; it is amplified conveniently and processed in a computer with software able to transform the electric signals in graphic and numerical results.

Especially in the platelets, the flow cytometry is able to assess the in vivo activation condition of the circulating platelets. Besides being able to determine the natural condition of the platelet function, the inclusion of an exogenous activator allows assessing the platelet reactivity in vitro or the ex vivo action of a drug. The main advantages of the flow cytometry of total blood for the analysis of the platelet activation are depicted in table 1.

The principal inconveniences of this technique are the high cost of the equipment and the antibodies, and the need of counting with well-qualified staff, making its use difficult in a standard clinical laboratory.

### Activation markers

It is well known that the platelets are essential cells in the normal hemostatic process. The lesion of the vascular wall originates the exposure and release of several agonists that activate platelets. Such activation consists mainly of the exposure of binding sites for adhesion molecules – as the fibrinogen and the Von Willebrand factor – and of the secretion of the intracellular granules content, that ensure the growth of platelet aggregates, with which the formation of the hemostatic clot starts.

It is known that the glycoprotein complex IIb/IIIa (GPIIb/IIIa) of the platelet membrane plays an essential role in the process of platelet aggregation, interacting with the plasmatic fibrinogen when the conditions of the blood flow are of low shearing speed, and with the Von Willebrand factor when the shearing speed is high. The platelet at rest does not adhere itself neither to the vascu-
lar endothelium nor to the leucocytes, but when it is activated, the adhesion to both increases due to the morphologic and functional change, in a first step, which the GPIIb/IIIa experiences, that will be represented as GPIIb/IIIa in the activation process. Another glycoprotein that is only expressed in the surface of the activated platelet is the P-selectin (CD62) that regulates the platelet adhesion to the neutrophils and monocytes and to the endothelium, stabilizes the initial interaction GPIIb/IIIa-fibrinogen and allows the formation of big platelet aggregates and the possible development of a thrombo. At the same time, the platelet-monocyte complex and platelet-endothelium, measured by the CD62 induces the activation of the tissue factor and stimulates the deposition of fibrin at the vascular lesion site. On the other hand, the expression of CD62 is correlated positively with the thickness and rigidity of the arterial wall, and is associated to the pathological changes that can be observed. These findings suggest that the CD62 expressed in the surface of the activated platelets, is involved in the initial process of the in vivo atherosclerotic lesions. Another indicator of degranulation reaction is the exposure of the liposome CD63 antigen on the platelet surface, which constitutes also a sensitive marker of platelet activation.

It is known that the circulating platelets might get stimulated spontaneously inside the vessels, forming platelet micro aggregates (PMA) with potential to form major thrombos, able to occlude vessels. Therefore, the detection of the PMA turns out to be relevant as first step indicator of the platelet aggregation, which is a phenomenon that constitutes a thrombosis risk factor. Besides the indicated processes, another response of the platelet in the activation process is the exposure in the membrane of the phospholipid phosphatidylserine (PS), which provides an adequate catalytic surface for the formation of the calcium-binding- depending prothrombinase complex, which transforms the prothrombin in thrombin. This exposure of PS in the external hemilayer of the platelet membrane is associated, when caspase family is activated, to the formation of micro particles or micro vesicles from the platelets, that are released to the environment and that present also a pro-coagulant activity due to the formation of prothrombinasa complex on the surface, thanks to the exposure of PS on it.

It is well determined that if the platelet is at rest, membrane turns out to be impermeable to the Ca$^{2+}$ ion, which can be found in a higher concentration in the external environment than in the intraplatelet environment. During the activation process, the concentration of cytosolic free calcium increases due to the diffusion of such ion from the external milieu, through specific calcium channels, and the mobilization of the internal intraplatelet stores, mainly of the dense tubular system. The mobilization of the Ca$^{2+}$ is fundamental regarding to the platelet response to the activation process and proceeds to other changes experimented by platelets: morphology, aggregation, secretion and expression of the pro-coagulating activity.

As we can observe in this revision, the platelet parameters indicated up here (GPIIb/IIIa*, CD62, CD63, PS, Ca$^{2+}$ mobilization, micro particles and micro aggregates) are useful to assess the condition of platelet activation and function, and all of them can be determined by means of flow cytometry.

**Application of flow cytometry to the record of antiplatelet therapeutics**

The platelets play a critical role in patients with cardiovascular disease, as they increase the risk of thrombosis events. It is known that the antiplatelet drugs might reduce the incidence of ischemic cardiovascular events, therefore it is interesting to register with the aim of stating the most adequate customized doses in each case, and reduce the risk of hemorrhage and thrombosis recurrence. Since the acetylsalicylic acid (ASA) has an inhibitory effect on the platelet only through the cyclooxygenase route 1 (COX-1), whose inhibition impedes the generation of thromboxane A$_2$, it has been observed that a great number of patients, in spite of being treated with this drug, show recurrence of thrombosis events attributable to the platelet activation through different routes than the one inhibited by the ASA, or because of patients who respond badly or have developed a resistance to such drug. In these cases, the thrombosis events might be due to the in vivo exposure of the platelets to strong concentrations of agonists, as collagen or thrombin or adenine diphosphate (ADP) released by the platelets themselves or by the thromboxane A$_2$ of non platelet origin, that might cause its activation. It has been communicated that the expression of GPIIb/IIIa, CD62 and...
CD63 in circulating platelets, or in platelets activated with ADP or thrombin, is not modified with the ASA, therefore several working groups have studied the efficiency of the combined therapy of ASA with other drugs, as ticlopidine and clopidogrel, that exert their action through a different mechanism, consisting of the blockade of the P2Y12 receptor of the ADP. In this type of analysis, the flow cytometry allows assessing, as platelet activation markers, the expression and induction through ADP of CD62, CD63 and GPIIb/IIIa*, it can be proved that in patients who respond adequately, clopidogrel prevents the expression of such markers of activation after the stimulation with ADP or thrombin, and that the addition of ASA improves its inhibitory effects ex vivo. With the use of the flow cytometry it can also be determined the minimum doses of ASA that is necessary to potentiate the effect of clopidogrel in each patient, as well as the detection of patients who do not respond adequately to the treatment with this drug.

The post-surgery thromboembolic ictus is frequently associated to a hyperactivity of the platelets to the ADP, which might be detected by means of flow cytometry and ictus, providing, in general, an immediate antiplatelet action, higher than the combination of ASA and clopidogrel. However, the antagonists of GPIIb/IIIa are expensive and they also require the administration of an intravenous bolus followed by the continuous infusion of the drug during certain period of time, therefore, before implanting them, it would be convenient to study their efficiency compared to ASA, clopidogrel or ticlopidine and their possible combinations. The efficiency of the anti-IIb/IIIa drugs depends to a great extent to their dosage, which might be based in measuring the inhibition of the platelet aggregation. Though it is not well determined, it is accepted that an optimal level of platelet inhibition has been achieved for an efficacious prevention of thrombosis events after coronary surgery when the inhibition of 80% of the aggregation induced by the ADP is achieved. However; this inhibition depends on certain factors, as the concentration of used agonist, the number of platelets, the intake of food, the concomitant medication and the inter-individual variation. Thus, the aggregometry is not recommended in order to undertake a follow-up of this group of drugs as it turns insensitive to the extreme values of GPIIb/IIIa receptor activity by the drug and to the small inter-individual variations. On the contrary, the flow cytometry allows registering the treatment with these measurements, without the inconveniences of the aggregometry, when quantifying directly, through the antibodies. LYP18 and 4F8, the total and free number of sites of the, GPIIb/IIIa receptors, in the steady phase of the treatment. Knowing these data, the number of sites occupied by the drug can be estimated. An optimal therapeutic dose is considered the one that produces an 80% of activity by the drug of the 50,000-80,000 GPIIb/IIIa sites that are on the platelet surface. With this level of activity, the aggregation of the platelets is inhibited, as it remains only 20% of sites free, suitable to bind to the fibrinogens. With this dose, the intention is to obtain the maximum inhibition without inducing an excessive risk of bleeding in the patient. This therapeutic range, relatively narrow, together with the great variability of inter-individual response, makes the follow-up of these drugs advisable in order to avoid the hyper/hypo treatment risk as possible.

It has been described that the patients with an acute myocardial infarction, who underwent thrombosis with reteplase, show an increase in the expression of GPIIb/IIIa* 24 hours after the thrombolysis. Said phenomenon...
is not observed in patients treated with alteplase. These data that have been obtained by means of cytometry, indicate objectively the convenience of administering an anti-GPIIb/IIIa to the patients treated with reteplase in order to avoid the reocclusion of the rechanneled arteries. This clinical usefulness of the flow cytometry is not offered by any of the other preconized techniques at present in order to evaluate the platelet function (optical aggregometry, PFA-100, Verify Now, etc.).

Circulating activated platelets in pathologies with a high atherothrombotic risk

It is known that the platelet activation plays an important role in the mechanisms of the arterial disease which includes the myocardial infarction, the ictus and the peripheral artery disease.34

In the acute coronary syndrome and in the myocardial infarction, the presence of circulating activated platelets and platelet hyperactivity have been described,35-36 as well as the increase of monocytes-platelet circulating aggregates and circulating micro-particles.17 The presence of such circulating aggregates has been reported in patients with stable and unstable angina,38,39 and in those who underwent percutaneous coronary interventions. Other authors have communicated that the expression of glycoproteins of platelet membrane in circulating blood is associated to the increase of risk of suffering an ischemic event after the angioplasty and the stent implantation.40

A relevant increase is observed in the ictus of the circulating activated platelets,41 as well as changes in the morphology and increase of circulating GPIIb/IIIa platelets.42 Other work groups describe a higher number of circulating micro-particles in the patients than in the control group.43 However, it is interesting to point out the great variation of platelet activation response in patients with ictus, that paradoxically might show even a lower activation than the control group.44

In the peripheral vascular disease, an increase has been described in the percentage of positive circulating CD62 and in the positive GPIIb/IIIa platelets,45 as well as in the number of micro-aggregates and micro-particles of platelet origin,45 confirming the platelet hyper-activity in these patients by means of flow cytometry.

Diabetes, hyperlipemia and blood pressure

Several authors have suggested that diabetes, hyperlipemia and the blood pressure have a relevant influence on the platelet function, increasing the reactivity of such cells.46-51

The diabetes mellitus is one of the most frequent chronic diseases in the developed countries.52 It is known that the diabetes increases the risk of coronary heart disease, ictus and peripheral arterial disease, as consequence of the greater incidence of blood pressure, obesity, dyslipidemia compared to the non diabetic patients.53 These risk factors associated to the diabetes are closely related to the atherosclerosis and thrombosis processes, which are so frequent in these patients,54 so the basic objectives in the treatment of diabetes should be the control of the blood pressure and plasmatic lipids besides the normalization of the glycemia level.

There is a tendency to associate the microvascular risk to the T1D and the macrovascular risk to the T2D, but both types of complications are frequent in both types of diabetes; thus, the cardiac disease appears also frequently in the T1D.55,56

It is well determined that in the angiopathic complications associated to diabetes, the platelets exert a key role57 and that platelet function might be altered through several mechanisms, among which the hemorrhagic disturbances that these patients show frequently should be pointed out.58 Such rheological disturbances depend to a great extent on the changes in the lipid situation of the red blood cells membrane, reducing the deformability and increasing the shearing tension of the circulating blood in certain areas of the circulatory system,59 causing a greater platelet activation. Thus, diabetes is associated to multiple metabolic, cellular disturbances and to the blood flow, which might lead to vascular complications. The activated platelets form circulating micro-aggregates that might contribute to the development of angiopathy by micro-embolization of the capillaries of the in vivo micro-circulation60 and to the development of great sized thrombosis.61

Notwithstanding that several studies suggest a direct association between platelet aggregation and vascular and atherosclerotic complications in diabetes, the role of platelets in such complications are not clearly deter-
mained. On the other hand, the studies published to determine increased platelet aggregation in diabetes, use, in general, unable methods to detect the presence of sub-populations of platelet aggregates formed spontaneously in the circulating blood. Most of the used methods require the addition of high concentration of stimulating agents, they use plasma rich in platelets as sample and measure the changes produced in the light transmission during the aggregation process. With the addition of agonists, the capability of platelets of being stimulated by an external agent is assessed, but the spontaneous activation that the platelets experience in the circulation cannot be assessed. On the other hand, the platelet response is more physiological when it is assessed in whole blood, in the presence of the rest of blood cells, than when it is isolated, as in the cases in which it is used for the analysis of the plasma rich in platelets. Finally, the changes in the transmitted light are only noticeable when the platelet aggregates are bigger, but they do not allow detecting the presence of small platelet aggregates or micro-aggregates. All these reasons, among others, support the performance of studies that use the flow cytometry of whole blood as technique.

The presence of platelet-leukocyte circulating aggregates has been reported in diabetes, but the presence of platelet-platelet aggregates is not described, either its formation is related to the spontaneous platelet activation or to the level of glycemia control. It has either been described if the changes in the distribution of phospholipids of the platelet membrane— with exposure to the phosphatidylserine and formation of the consequent prothrombinase complex that transforms the prothrombin in thrombin— are involved in the formation of PMA in diabetic patients.

Diabetic patients are characterized for showing a higher number of GPIIb/IIIa receptors, a higher percentage of positive platelets CD62, CD63 and GPIIb/IIIa* and more circulating micro-particles and the control group, constituting a risk situation of suffering acute vascular events. It has also been communicated that diabetic patients show an postprandial increase of the platelet reactivity. Since platelets have insulin receptors in the membrane and the hormone increases platelet activation, it might be speculated that the beneficial effects that the insulin exerts on platelet function are more related to the improvement of the metabolic control than with the direct normalizer effect on the platelets. In this sense, it has been reported that an adequate metabolic control of the disease reduces the activation of platelet markers.

With the aim of reducing the risk of suffering thrombosis events, it would be convenient to determine adequate anti-platelet strategies in these patients. Even after the dual treatment with ASA/clopidogrel, the diabetic patients show a greater residual activity in some markers of platelet activation than the normo-glycemic patients, and are benefited to a great extent of the anti-thrombosis prevention with ASA. The greater platelet activation and the greater response to the agonist action in diabetic patients have been attributed to the high glucose levels that cause a greater osmolarity leading platelets to be more reactive through different mechanisms.

In the hypercholesterolemia, platelet activation increases in a parallel way to the high levels of the low density lipoprotein-cholesterol (LDL-C). In spite of the interest of this study regarding to platelet activation in hyperlipemia, the available information about these aspects is scarce and frequently contradictory. For example, it has been reported that the patients with high levels of LDL-C show a higher percentage of circulating platelets with the GPIIb/IIIa in its active form. Moreover, the platelets of such patients are more sensitive to the ADP action. It seems that there exists a correlation between the reduction of the plasmatic cholesterol concentration and the expression of CD62. In general, the observed impairments in platelet activation of hyperlypidemic patients are normalized by means of the treatment with certain drugs, as the atorvastatin.

The lypemia induced by the diet makes the percentage of platelets expressing CD62 in the membrane to increase significantly during the postprandial period, both in vivo and after the stimulation with ADP. It is known that the hypertriglyceridemia is a cardiovascular risk factor associated to a hypercoagulability condition; although, the relation with platelet activation has not been determined. The available information in this sense is very scarce; thus, it has been described that the patients with hypertriglyceridemia show a higher percentage of positive CD63 platelets. However, such patients do not express CD62 more than the control group, which becomes difficult to understand, since CD63 is a platelet degranulation marker and the CD62 should also be expressed in this process.
The presence of a higher number of circulating micro-particles has been described in the hypertension, whose membranes have a pro-coagulating nature due to PS exposure. The results of several studies indicate that the hypertensive patients constitute, at baseline, a population under atherothrombosis risk, characterized by the presence of circulating platelets activated spontaneously \textit{in vivo}, and by relevant changes in the kinetics of the intra-platelet free calcium. Both parameters constitute important thrombosis risk factors and are assessable by means of flow cytometry. Many of the impairments described about platelet function, in hypertension, are normalized through an adequate antihypertensive treatment.

**Conclusion**

The platelet function is not yet assessed systematically in the clinical practice due to the workload that its performance suggests, because it is expensive and requires adequate instrumentation and space and the training of qualified staff. Besides these difficulties, the application of specific techniques, as the platelet aggregation in patients with cardiovascular disease is very arguable. However; the results of the consulted literature allow confirming that the flow cytometry is a well-determined powerful analysis technique, whose clinical application is increasing progressively. The cytometric parameter that have proved to be useful, both in the diagnosis and in the follow-up of antiplatelet treatments are depicted in table 2.

In conclusion, at present flow cytometry offers an important range of possibilities for the study of a great number of platelet activation markers in several pathologies, therefore it is expected to constitute not only an investigation tool but also of application in the usual clinical practice in the future.

**Table 2. Cytometric parameters with demonstrated clinical usefulness**

- Expression of GPIIb/IIa complex in its active form (GPIIb/IIa*)
- Exposure of P-selectin (CD62) in the platelet surface
- Exposure of phosphatidylserine (PS) in the platelet surface
- Exposure of CD63 lisosomal in the platelet surface
- Changes in the kinetics of the cytoplasmatic free calcium
- Formation of micro-particles and platelet micro-aggregates
- Formation of mixed aggregates platelet-leukocytes
- Quantification of the activity for anti-GPIIb/IIa drugs

**Practical considerations**

- The flow cytometry uses whole blood directly and in this way it allows to detect several antigens simultaneously in different well identified cellular sub-populations.
- This methodology allows studying the in vitro and ex vivo effect of several drugs on platelet function in several pathologies as diabetes, hyperlipemia and hypertension.
- The principal inconveniences of this technique are the high cost of the equipment and of the antibodies, as well as the need of well-qualified staff, therefore its use is quite difficult in a routine clinical laboratory.

**Declaration of potential conflict of interests**

M. Labiós Gómez, M. Martínez Silvestre and F. Gabriel Botella state that there are no conflicts of interest as regards to the content of this article.

**References**


Case report discussed by experts

Insulin treatment in an obese patient and a secondary diabetes due to pancreatectomy

Tratamiento con insulina en un paciente obeso y con diabetes secundaria a pancreatectomía

Male aged 41, obese, with secondary diabetes to pancreatectomy, which is not able to control it adequately. He is professor of religion and has never done physical exercise.

Personal history
In the year 2003 part of the pancreas was extirpated since it showed a neuroendocrine carcinoma which produced gastrin, which was later treated with lanreotide. He received the last dose before his arrival to our center, and in the record it mentioned that the patient found himself with radiological stability and with a decrease of markers. Generalized epilepsy since he was ten years old with a treatment of sodium valproate and carbamazepine.

Actual disease
As consequence of the pancreatic intervention, which left him only a rest of the pancreas head, the patient developed diabetes that was treated with insulin from the beginning. When arriving at our site, he was under treatment with insulin glargine 88 IU/day and insulin glulisine 6 IU before each meal, with adjustments according to pre-prandial capillary glycemias, together with metformin (2,550 mg/day) and pioglitazone (30 mg/day). He rarely carried out postprandial glycemias. When asked about his metabolic control, he did not know the HbA1c value and said not knowing what this parameter is about. He submits a report from his physician corresponding to the month previous to his arrival, in which a value of 8.3% can be observed in the HbA1c. The patient had already attended our site a year before an in his analytics an HbA1c of 8.5% could be appreciated as well as a C-peptide of 0.7 ng/mL, as well as hyperlipidemia and hyperuricemia, with normal hepatic and renal function. He undergoes treatment with bromozepan, omeprazol, fenofibrate and lanreotide 120 mg in autogel (1 ampule each 28 days), besides his hypoglycemiant treatment, of valproic acid and carbamazepine.

The exploration stresses a weight of 111.9 kg, height 171 cm. blood pressure (BP) 150/85 mmHg and abdominal perimeter 118 cm. Neither peripheral vascular disorder nor peripheral neuropathy signs can be observed.

Answer of Dr. Ezequiel Arranz Martínez

Introduction. Therapeutic objectives in this patient
The diabetes resulting from the pancreatectomy is according to the mechanism, the prototype of the second-
of glucagon, the glucose turnover and the considerably reduced glycogenesis, as well as the adrenalin release in response to the altered hypoglycemia, and c) impairment of the insulin resistance, that might worsen with the administration of glucagon. All this obliges the preference to a less strict metabolic control than in patients with a functioning pancreatic tissue.

The high concentration of islets in the pancreas tail suggests that a distal pancreatectomy would be worse tolerated in terms of endocrine secretion of the gland. In fact, resections of 90% are requested to produce endocrine deficit, in spite of the hypertrophy and the increase of the physiological activity of the remaining islets, what would oblige a strict insulin cover and more than a daily dose would be necessary. However, neither the intake nor the absorption of nutrients would be affected. Hormones and enzymes should be replaced after a total pancreatectomy.

The gastrinoma is a tumor that secretes gastrine, responsible of the great hypergastrinemia of the Zollinger-Ellison syndrome, characterized by refractory peptic ulcer, diarrhea and steatorrea. Of very low prevalence (1-4 per 1 million of people); it appears between 50 and 60 years of age, usually in women more than in men (3:1). It is localized in the pancreas in 40% and in the duodenal wall in the other 40%. It can be associated to the MEN-1 syndrome (20-25%) and it is then frequently malignant. In our case, the patient is obese on whom it can be considered an insulin peripheral resistance condition and other factors of cardiometabolic risk, as the dyslipemia

The level of the C-peptide is useful to have an idea of the insulin reserve, considering that the exogenous insulin inhibits the production of endogenous insulin by the conserved pancreatic tissue.

**Which are the modifications you would do in the hypoglycemiant treatment?**
**Do you consider adequate to keep the insulin-sensibility drugs in this patient?**
**Which are the most adequate glycemic controls?**

There is a marked resistance to the action of the insulin in the obese patient closely related to the adipose tissue and, especially, to the abdominal deposit or centripetal.

In the postabsorptives phases, the exogenous load of glycemia is not captured adequately by the insulin-dependent tissues (adipose and muscular) and the main mechanism of the hyperglycemia is postprandial. This alteration suggests a stimulus for the release and the hepatic synthesis of glucose as of the glycogenolysis and the glycogenesis.

The thiazolidinediones improve the glycemic control when acting as sensitizing agents to the insulin and as reducers of the hepatic glyconeogenesis. Its clinical efficiency is in clear relation to the presence of a conserved insulin reserve; therefore it is only useful in patients with functioning pancreas. So, it would be feasible to withdraw the pioglitazone in this case.

The biguanides improve the sensitivity to insulin and reduce the hepatic production of glucose when reducing both the glyconeogenesis and the glycogenolysis. Moreover, they have also demonstrated that they reduce the concentrations of triglycerides in 20-25% and the LDL (c-LDL) cholesterol in a 5-10%; while the levels of HDL (c-HDL) cholesterol do not vary or increase discretely. Finally, it has been proved that the treatment with biguanides comprises loss of weight, especially if compared with the patients treated with sulphonylureas or insulin. The characteristics guarantee the maintenance with metformin in our case report. A 85% of the patients achieve the maximum reduction of the glycosylated hemoglobin (HbA1c) (2%) with doses of 2,000 mg, without obtaining additional reductions when reaching the dose of 2.500 mg.

In our case, the patient is with a very high dose of slow analogue and does not know what is HbA1c, so the controls up to date have exclusively been based in the preprandial values of glycemia. It is logical to think that such values are close to normality. When the treatment has to be intensified in a diabetic patient, it is necessary to perform capillary controls with 6 determinations, 3 preprandial and 3 postprandial. The value of HbA1c of 8.3% has to be very influenced by the postprandial glycemia, whose values we do not know about.

After the performance of the profiles, we will encounter probably one of the following assumptions:

- **High basal and postprandial glycemies.** We could keep the same type of insulin or, what is more logical, due to the high units of insulin glargine that are admin-
istered, to use a slow analogue that allows two daily shots (as the insulin detemir), distributing the total dose to 50% in each one, and increasing the units until keeping reasonable basal glycemias. We should add fast analogue considering the postprandial peaks and we would keep the metformin for the already mentioned reasons. A second alternative would be to use the mixture 30/70 with rescue of fast analogue in the midday meal. The total dose of the mixture should be reduced a 20-30% as regards to the dose of the total basal analogue and then adjust according to the later profiles. This guideline would be of easy application if the patient keeps a stable life rhythm, with adequate food and scheduled as regards timetables.

• Normal basal glycemias with high postprandial peaks. We would keep the same slow analogue and adjust only with the fast analogues. This a useful technique if we encounter a patient with irregularities regarding to the number of intakes a day and their timetable.

Which other therapeutic modifications would you carry out?

This patient shows a blood pressure (BP) of 150/85 mm-Hg. The diabetic patients are considered of high risk as from the BP values over 130/80 mmHg. For the reduction of the pressure values in a patient with diabetes, the blockade of the rennin-angiotensin system should be always placed in the first therapeutic step, though the need to associate drugs in most of the cases is recognized.11 The intense reduction has beneficial and consistent effects in the reduction of the global mortality and cardiovascular cause, as well as the ictus incidence, coronary disease, cardiac disorder and cardiovascular events in general. The ADVANCE study proved in the same way that the reduction of the systolic blood pressure up to values of 134 mmHg with the use of a combination with angiotensin-converting enzyme inhibitors (ACEI) and an added diuretic to the usual treatment, had beneficial effects in preventing the cardiovascular morbimortality, with a reduction even in the global mortality that reached the 14%.12

A key aspect should be added to the medical treatment that might consolidate the adequate metabolic control: the diabetological education with nursing support. It would allow obtaining basic knowledge about the diet, about the techniques of insulin injections, the recognition of alarm symptoms regarding to possible hypoglycemias and how to neutralize them, about the use of glucagon and the action in relation to the punctual hypoglycemias.

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Declaration of potential conflict of interest

Ezequiel Arranz received feed for conferences about the use of the DPP-IV inhibitors in type 2 diabetes mellitus by the MSD laboratories.

References

Which are the therapeutic objectives you would indicate for this patient?
In an oncological patient, a determining factor when deciding the therapeutic objectives is the vital prognosis at long term. There are several factors that condition the survival of the sporadic gastrinoma. From these, probably the most important one is the magnitude of the metastatic disease at hepatic level and its growth speed before starting the treatment. The survival at 5 and 10 years of the patients with metastatic hepatic disease of slow growth might reach approximately 100% and 80%, respectively.

On the other hand, even in patients with progressive metastatic gastrinoma and with worse prognosis, the somatostatin analogues, as the lanreotide, have demonstrated to be able to stabilize the tumor growth and, in some cases, to reduce its volume. Thus, in a study of patients with more aggressive tumors, a survival of 75% could be observed for a follow-up period between 4 and 8 years in those patients with a good response to the octreotide.

Therefore, for our patient, the possibilities of an extended survival are considerable. So, it seems to be reasonable to mark a glycemic control objective with glycosylated hemoglobin (HbA1c) of 7-7.5% (mean glycemia estimated between 150-160 mg/dL). This objective allows balancing the therapeutic, psychological, economical and self-management effort with the possible clinical benefits, in a patient with certain comorbidity. On the contrary, we could mark less strict objectives in case of progression evidence of inadequate prognosis during the follow-up. In the same way, we could set out a stricter glycemic control in young patients with pancreateogenic diabetes, without evidence of residual disease and without other comorbidities. In this sense, in spite that there is no data in patients with secondary diabetes, but the evidences in patients with T2D indicate clear benefits derived from a multifactorial intervention regarding to the different risk factors. The study of Gaede et al. is remarkable, where a reduction of approximately 50% of cardiovascular and microvascular risk events in patients with high risk T2D after a multifactorial intervention with a mean follow-up of 7.8 years. Therefore, I would mark the following objectives: BP <130/80 mmHg, LDL cholesterol (c-LDL) <100 mg/dL, HLD cholesterol (c-HDL) >40 mg/dL, triglycerides <150 mg/dL and a loss weight over 5%.

Which are the modifications you would do in the hypoglycemicant treatment? Do you consider adequate to keep the insulin-sensibility drugs in this patient?
The diabetes secondary to pancreatic resections comes together with hormonal impairments that depend on the type of intervention, the extension and the location (distal or proximal). These alterations confer differential characteristics as regards to T1D and T2D. In wide resections, besides the insulinopenia, the deficit of glucagon might contribute to the iatrogenic hypoglycemia and the deficit of the pancreatic polypeptide contributes to the persistent hyperglycemia due to insulin-resistance at hepatic level. The impairments, on occasions, cause labile diabetes of difficult management. Likewise, in those costs, in turn of an uncertain benefit in terms of cardiovascular risk reduction. In the same way, the analysis of these studies does not predict great benefits in a uniform manner in terms of microvascular risk. A possible exception to these affirmations would be the youngest patients, with recent starting diabetes and without complications.

On the other hand, we are facing a patient with high cardiovascular risk, since, besides diabetes, the patients shows a level 2 obesity (body mass index [BMI]: 38.3 kg/m²), a high waist perimeter (>102 cm), hyperuricemia, hyperlipidemia and an inadequately controlled blood pressure (150/85 mmHg). In this case, there is no data in patients with secondary diabetes, but the evidences in patients with T2D indicate clear benefits derived from a multifactorial intervention regarding to the different risk factors. The study of Gaede et al. is remarkable, where a reduction of approximately 50% of cardiovascular and microvascular risk events in patients with high risk T2D after a multifactorial intervention with a mean follow-up of 7.8 years. Therefore, I would mark the following objectives: BP <130/80 mmHg, LDL cholesterol (c-LDL) <100 mg/dL, HLD cholesterol (c-HDL) >40 mg/dL, triglycerides <150 mg/dL and a loss weight over 5%.

List of acronyms quoted in the text:
ACEI: angiotensin-converting enzyme inhibitors; ARA II: angiotensin-II receptor antagonists; BMI: body mass index; HbA1c: glycosylated hemoglobin; T2D: diabetes mellitus type 2.
cases that comprise intestinal resection, an impairment of the incretin secretion occurs that also has a considerable effect in the homeostasis of the glucose. On the other hand, it has to be considered the influence of the disease that motivates the pancreatectomy. For example, in patients with pancreas cancer, the clearance of the cytokine secretion by the tumor might improve the peripheral sensitivity to insulin and glucose homeostasis.

In case of distal resection, the incidence of diabetes is low, ranging between 9 and 32% considering the magnitude of the resection, the disease that motivates it and the presence or not of previous intolerance to the glucose. In this sense, it is estimated that it is sufficient to keep 20-25% of the residual pancreas to keep a clinically normal glucose homeostasis. For a pancreatectomy of the same magnitude, the most important prognosis factors of postsurgical diabetes are obesity and the pre-surgical glycemía. This indicates that factors as the previous impairment of the beta-cell function and the insulin-resistance that the obese patients show facilitate the hyperglycemia, so its correction is important. In this sense, almost 40% of the patients with distal postpancreatectomy diabetes keep an acceptable metabolic control level with oral antidiabetics (table 1).

As regards to the insulin guideline, it is interesting to assess and discuss with the patient the possibility of simpler regimes. A recent publication shows how the simplification of insulin treatment in insulinized patients with T2D and detectable C-peptide allows reducing the hypoglycemia risk without engaging the metabolic control level. Perhaps in our patient we could consider the use of 2 or 3 doses of prefixed mixtures as alternative to the bolus-basal treatment.

Another interesting aspect refers to the use of insulin glargine. It has been described that glargine induces the proliferation of osteosarcoma cell lines. In spite of the lack of data available regarding to neuro-endocrine tumors, a recent study could not objectify any effect of glargine in the growth of pancreas carcinoma cell lines nor in the survival of the patients with this disease. Probably, from this point of view, should the glargine not raise concern.

In models of diabetic animals due to pancreatectomy, exendine-4 has demonstrated to have capacity to stimulate the regeneration of the pancreas and the beta-cell expansion, through its effect on the GLP-1 receptor. Therefore, it is interesting to think about the use of treatments based on incretin in pancreatectomized patients. Moreover, the addition of vildagliptin to insulin in T2D has demonstrated a glycemic control improvement with less hypoglycemias. In our environment, this association is not authorized. On the other hand, in my opinion, it would be imprudent to use it in our patient. In this sense, it is known that there is an over-expression of GLP-1 receptors in several human tumors that might have an influence in the tumoral biology.

### Table 1. Approximate prevalence of postpancreatectomy diabetes considered the resection time

<table>
<thead>
<tr>
<th>Different pancreatic resections and post-surgical diabetes</th>
<th>Post-surgical diabetes prevalence (%)</th>
<th>Diabetic patients treated with insulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure (resection %)</td>
<td>Total pancreatectomy (100%)</td>
<td>100 (75% with labile diabetes)</td>
</tr>
<tr>
<td></td>
<td>Almost total pancreatectomy (80-95%)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Distal pancreatectomy (40-80%)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Pancreatoduodenectomy (50%)</td>
<td>26</td>
</tr>
</tbody>
</table>

The percentages might vary in the different series, basically influenced by the basal disease that motivates the pancreatectomy and by the pre-surgical prevalence of alterations of the carbohydrate metabolism. Modified in Slezak and Andersen.

Which is the type and number of glycemic controls you consider appropriate for this patient?
The patients with multiple insulin doses should undergo 3 or more daily controls. Moreover, it is recommendable to perform postprandial controls to achieve the postprandial glycemia objectives (initially, I would recommend 1 to 2 weekly profiles). Obviously, during the follow-up we should be sure that the technique is appropriate and that it has capacity to adjust the treatment according to the results.

Which other therapeutic modifications would you perform?
I would indicate therapeutic changes in the lifestyle, with exercise and hypocaloric planned diet. I would also start an hypotensive treatment with an antagonist of the
angiotensin-II receptor antagonists (ARA II) or angiotensin-converting enzyme inhibitors (ACEI) in case of confirming a BP >130/80 mmHg during a new visit. As regards to the lipids, I would assess the possibility of adding a statin or replace the fibrate by a statin, as a preferable strategy for the control of lipids in patients over 40 years of age and one or more factors of cardiovascular risk. Moreover, I would indicate 100 mg/day of acetylsalicylic acid as a primary care prevention strategy.\(^\text{16}\)

Finally, due to the antiepileptic carbamazepine and valproate have been related to weight gain and insulin-resistance, I would ask for a new specialized assessment to consider its replacement by other drugs with a more beneficial metabolic profile (for example, topiramate, zonisamide or lamotrigine).\(^\text{17}\)

**Declaration of potential conflict of interest**

Ll. Masmiquel received feed for conferences and/or consultancy from Abbott, GSK, MSD, Lilly, Menarini, Novartis, Pfizer, Novonordisk, Sanofi-Aventis and Roche. He took also part in clinical trials sponsored by Novartis, Novonordisk, Lilly, Abbott and MSD.

**References**

Introduction
Diabetes mellitus type 2 (T2D) is responsible for the arousal of microvascular and macrovascular complications, which increases the use of health resources, and has become an important cause of premature mortality.\(^1\) Approximately 27% of the deaths in subjects from ages ranging between 35-64 can be attributed to diabetes.\(^2\) The strict glycemic control has shown to reduce the risk of complications in T2D,\(^3\) in spite of which there still exists an important distance between the advice of the different Consensus and the attainment of the control objectives.\(^4\) In a recent European study, 50% of the patients with T2D showed a glycosylated hemoglobin (HbA\(_1\)C) below 7% and only a 25.5% below a 6.5% (a 29.9% in Spain).\(^5\) Among the different reasons which have been related with the insufficient metabolic control, hypoglycemias constitute one of the habitual factors mentioned as the most outstanding, and it has been described as the fundamental limiting factor to reach an adequate glycemic control.\(^6\)

Impact of the problem\(^7\)
In general the hypoglycemia rates with insulin sensitizing medication (metformin and glitazones) oscillate between the 0.5 and the 10% in the ADOPT study, but the rate of severe hypoglycemia’s is inferior to 0.1%. This risk can increase when the combination of secretagogues is used with insulin. The sulfonylurea and insulin secretagogues oscillate around a 30% of events/year, with a severe hypoglycemia rate of around a 0.8-2% of events/year, but with important differences compared to the type of medication. The glibenclamide is responsible for a higher rate of hypoglycemies, while the glimepiride, gliclazide or glipizide show inferior rates of hypoglycemia. Insulin on the other hand, shows values of events of hypoglycemia/year around a 30% with a 1-2% of severe events. But important variations exist according to the guideline of insulin used, the patients’ age, the years of duration of the diabetes and the treatment with insulin. The new medications potentiators of the incretin hormones do not seem to entail risk of hypoglycemia when they are used in monotherapy or with insulin sensitizing medications, but entail risk when used associated with sulfonylureas, due to the underlying risk.

Various studies have analyzed the effects of hypoglycemia in different aspects in the management of T2D. The problem is that the different criterions used when defining and classifying the hypoglycemic events has made it difficult to be able to carry out systemic or meta analysis revisions which evaluate this concrete aspect in T2D. Certain consensus exists when a severe hypoglycemia is defined, due to the need of the intervention of third parties during the assistance of the event, while the mild hypoglycemia would comprehend the rest of the events, identified and treated by the patient himself. The absence of consensus in this point makes difficult the comparison of the rates of hypoglycemia and the different drugs. Besides, many studies tend to undervalue the real rate of hypoglycemies, especially the ones of mild character, since a few patients register or communicate the professionals responsible about such events. It has been
described that only a 15% of the patients whom suffer an event of mild or moderate hypoglycemia report it to their doctors in the next visit.\(^8\)

**Risk factors of hypoglycemia in T2D**

The main cause of hypoglycemias in patients with T2D continues to be iatrogenic,\(^9\) in reference to the medications which increase the insulinemia not conditioned to glucose, in other words, the secretagogues and the insulin. Immediately afterwards we enumerate the factors related to the increase of the rate of hypoglycemias:

- Iatrogenic factors: treatment with secretagogues and insulin medications.
- Behavioral factors: dietetic transgressions because of omission or irregularity during the meals, alcohol consumption, inadequate exercise or incorrect use of the hypoglycemiant medication.
- Physiological factors: advanced age, duration time of diabetes, presence of concomitant diseases, kidney failure, unbalances of the perception of the hypoglycemias.
- Factors related with the intensive treatment, the strict objectives control, and the type of insulin guideline.

**Potential consequences of the hypoglycemia in T2D**

Among the possible consequences associated with hypoglycemias in patients with T2D, the following are accepted:

1. Increase of the death rate. The severe hypoglycemia entails an increase in mortality which has been calculated around a 9% of the global increase in the case of monotherapy with sulfonylureas, especially due to its capacity to trigger cardiovascular, ischemic coronary, and cerebrovascular events.\(^10\)\(^-\)\(^11\) Recently the interruption of the group of glycemic intensive treatment in the ACCORD study has revived the controversy around the possible effect of severe hypoglycemias in an advanced age population, with an important comorbidity associated to an established cardiovascular disease.\(^12\)

2. Decrease in the quality of life related to the health of the patients whom experiment a greater rate of hypoglycemic events.\(^7\)

3. Increase in the sanitary costs related both with the lack of productive activity as well as the induced social services expenses due to the management of the hypoglycemias and secondary hospital admittance.\(^7\)

4. Alterations in the emotional sphere, which increase the psychological suffering and, or occasionally, favor the trigger of adaptive disorders in relation with the fear of suffering new events of hypoglycemia.\(^7\)

5. Difficulties in the adequate compliance of the treatment. Some studies have determined that the direct relation among the number and severity of hypoglycemia with the degree of satisfaction with the treatment and adequate therapeutic fulfillment.\(^13\) In such a way, the patients with a greater number of events or greater severity in these show a lesser satisfaction with their treatment and a worst therapeutic compliance, that at the same time is directly related and inversely with the consecution of the more adequate objective controls.

**Conclusions**

The effects of the hypoglycemia in T2D are various and they are linked to the morbidity and mortality of patients with diabetes, their quality of life, psychological suffering, the socio-sanitary costs, and a lesser therapeutic carrying out. Definitively, to reach an adequate glycemic control will depend on the capacity of obtaining such objectives in the best security conditions for our patients, reducing to the lowest hypoglycemias through the strategies or the adequate medication, with the minimum possible secondary effects.

**Declaration of potential conflict of interests**

F. Álvarez Guisasola has taken part in consultancy from Bayer, Bristol Myers Squibb-AstraZeneca, Novo-Nordisk and Sanofi-aventis. In the same way he has taken part in courses and given conferences receiving fees from Bristol Myers Squibb, GSK, Merck, Novartis, Novo-Nordisk, Lilly and Sanofi-aventis.

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New challenges in the clinical practice

Risks of hypoglycaemia. F. Álvarez Guisasola

Diabetic patient with breastbone painful mass

*M. Fallas-Wahrmann, J. Gutiérrez-Ramos, B. Hasbum-Fernández*


**Case report**

Male aged 57 years old, hypertensive and with T2D, under treatment with insulin, metformin, enalapril, acetylsalicylic acid and lovastatin. He attends the emergency service incidentally due to a serious hypoglycemia. The hypoglycemia is stated during the initial approach and the examiner describes an indurated and painful mass in the upper third part of the breastbone of 10 cm of transversal diameter and 7 cm of longitudinal diameter (figure 1). According to the relatives who came with him, the patient showed dyspnea of small efforts since some weeks before, as well as anterior thoracic pain that exacerbated during the deep inhalation and asthenia. The initial examinations evidenced the presence of anemia (hemoglobin of 10.1 g/dL), renal failure (plasmatic creatinine of 1.61 mg/dL, creatinine clearance of 73.4 mL/min, proteinuria of 9,650 mg/24 h), hyperkalemia (10.8 mg/dL), hypergammaglobulinemia (8.5 g/dL) and high globular sedimentation speed (90 mm/h). A 40% of anaplatic plasmatic cells could be observed in the bone marrow aspiration. The electrophoresis of plasmatic proteins showed the presence of a monoclonal peak in the gammaglobulines. The test of Bence-Jones for the proteins in urine was positive. An expansive process in the breastbone manubrium could be observed in the thorax computerized tomography, associated to multiple osteolytic lesions in the rib cage and the dorsal column.

**Comment**

The multiple myeloma is a malignant disease of the plasmatic cells. Usually, it appears as a disseminated bone disease, though sometimes it is associated to the presence of focal accumulations of anaplastic cells, known as plasmacytomes. It is a special aggressive disease. Only 33% of the patients survive after 5 years, no greater incidence of this disease can be observed in the diabetic patients, though it appears frequently in the obese subjects.

**Declaration of potential conflict of interest**

The authors state that there are no conflicts of interest as regards to the content of this article.

**References**