New challenges in the clinical practice

Potential risks of hypoglycaemia in patients with type 2 diabetes

Riesgos potenciales de la hipoglucemia en pacientes con diabetes mellitus tipo 2

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Introduction

Diabetes mellitus type 2 (T2D) is responsible of 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\(_1c\)) 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 hypoglycemias, 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 hypoglycemias 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 hypoglycemias 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 hypoglycemias, 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 hypoglycemas 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 hypoglycemas:

• 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 hypoglycemas.
• 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 hypoglycemas 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 hypoglycemas 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 hypoglycemas 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.

References