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Impaired awareness of hypoglycaemia in subjects with type 1 diabetes. Results of an online survey in a diabetes web site

Ignacio Conget[a,*], Dalia Ávila[b], Marga Giménez[a], Carmen Quiros[a], Vanesa Salaverria[c], Belen Dueñas[c]

[a] *Diabetes Unit. Endocrinology and Nutrition, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), Hospital Clínic i Universitari, Barcelona, Spain*
[b] *Endocrinology and Nutrition Department, Health Services Center, University of León, León, Spain*
[c] *Fundación para la Diabetes, Madrid, Diabetes Unit, Spain*

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KEYWORDS
Hypoglycaemia;
Hypoglycaemia unawareness;
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Abstract
Objective: To assess the frequency of impaired awareness of hypoglycaemia (IAH) using a specific questionnaire (Spanish version) in a free access diabetes-related web site.
Methods: Data from a free access Spanish version of the Clarke test previously uploaded to the website of the *Fundación para la Diabetes* (March 2014–January 2015) were assessed. In addition to the eight questions in Clarke's questionnaire, information on type of diabetes, age, and disease duration was obtained. The Clarke test divided participants into three categories: normal awareness, uncertain and IAH.
Results: Of the 418 participants with type 1 diabetes, 51.2% were aged 36–55 years. In 34.7%, diabetes had been diagnosed >15 years before, while disease duration was <2 years in 11%. According to Clarke categories, 23.4% had IAH, 15.3% uncertain awareness, and 61.3% normal awareness. The longer the duration of diabetes, the higher the Clarke test score. According to the Clarke test, 14.1% of participants had experienced at least one episode of severe hypoglycaemia in the previous year, and half of these (7.4%) had suffered severe hypoglycaemia two or more times. All but one of the participants with two or more episodes of severe hypoglycaemia had IAH.
Conclusions: Our study shows that the rate of IAH using an online survey is similar (25%) to that previously reported in other geographical areas, increases with diabetes duration, and identifies subjects prone to severe hypoglycaemia.

* Corresponding author.
E-mail address: iconget@clinic.ub.es (I. Conget).

PALABRAS CLAVE
Hipoglucemia;
Hipoglucemia desapercibida;
Diabetes mellitus tipo 1

Hipoglucemia desapercibida en personas con diabetes tipo 1. Resultados de una encuesta ''on line'' en una Web de diabetes

Resumen
Objetivo: Determinar la frecuencia de hipoglucemia desapercibida (HD) en una amplia cohorte de pacientes adultos con diabetes tipo 1 (DT1) a través de un cuestionario específico disponible para ser rellenado en la Web de manera voluntaria.
Metodología: Desde marzo de 2014 a enero de 2015 se recogieron los resultados del cuestionario en lengua española de percepción de la hipoglucemia para adultos con DT1 (Test de Clarke versión en castellano) disponible *on-line* en la página Web de la Fundación para la Diabetes. Además, la encuesta *on-line* incluía datos sobre el tipo de diabetes, la edad y el tiempo de evolución de la enfermedad. La puntuación final del cuestionario cataloga a los pacientes en 3 categorías: percepción normal, indeterminada y anormal-HD ante una situación de hipoglucemia.
Resultados: De los 418 participantes con DT1 el 51,2% tenía una edad entre 36-55 años. En el 34,7% la DT1 la diabetes tenía una duración > 15 años y en el 11% menos de 2 años. De acuerdo con el resultado del cuestionario de Clarke, un 23,4% de los pacientes presentaba una HD, un 15,3% una percepción indeterminada y en el 61,3% el resultado fue normal. A mayor duración de la DT1, mayor puntuación del cuestionario. El 14,1% de los participantes había tenido una hipoglucemia grave durante el año anterior y la mitad de ellos (7,4%) había presentado ≥ 2 episodios. De estos últimos todos, excepto uno, presentaban HD.
Conclusión: Como en estudios precedentes realizados en otras áreas geográficas, nuestro estudio demuestra que casi una cuarta parte de los pacientes con DT1 tiene alterada la capacidad para percibir los síntomas de hipoglucemia. Esta anomalía es más frecuente conforme aumenta la duración de la enfermedad, e identifica las personas en riesgo de presentar hipoglucemia grave.

Introduction

Hypoglycaemia is the most relevant adverse event related to insulin treatment.[1,2] Repeated episodes of hypoglycaemia in subjects with type 1 diabetes (T1D) may result in failure to recognize hypoglycaemia symptoms and signs at a physiologically normal threshold.[3] Impaired awareness of hypoglycaemia (IAH) may occur in up to 20–25% of individuals with T1D and the lack of warning symptoms places them at high risk for severe hypoglycaemia (SH).[4,5] In addition, both IAH and SH represent the main limiting factor to achieve optimal beneficial glycaemic control precluding its beneficial effects.[6]

In order to identify IAH, different questionnaires and self-report measures are being used in clinical practice.[7,8] Among these, despite some limitations, the Clarke test is one of the most frequently used, providing detailed assessment of IAH.[7] This test encompasses eight questions regarding exposure to hypoglycaemia and a subjective estimation of the glycaemic threshold for the generation of symptoms and signs. The use of the Clarke questionnaire which was conceived in English requires its validation in a different language before its use in clinical practice and research purposes in non-English speaking populations.

We recently conducted and published the psychometric validation of the Clarke questionnaire in two different languages, Spanish and Catalan.[9] In our study, we sought to evaluate the frequency of IAH using the Spanish version of the Clarke test in a free access diabetes-related web portal.

Patients and methods

We collected (March 2014–January 2015 inclusive) anonymous data from a free access Spanish version of the Clarke test previously uploaded in the website of the *Fundación para la Diabetes* (http://www.fundaciondiabetes.org/encuestas/box_encuesta_clarke.htm). This is a free access web portal for patients and health care professionals. In addition to the eight questions included in the questionnaire, on a previous page we asked for information regarding the type of diabetes (T1D, T2D, other types of diabetes, I do not know), age (four categories: 18–35; 36–55; 56–65 and >65 years old), and duration of the disease (five categories: <2; 2–5; 5–10; 10–15 and >15 years). In the Clarke Test a score <3 designates normal awareness; 3 indicates uncertain awareness and >4 designates IAH (Table 1). According to the Clarke test, severe hypoglycaemia is defined as episodes where the patient is unconscious or had a seizure and needed glucagon or intravenous glucose.

Results are presented as mean $\pm$ SD or %. Comparisons were performed using the Student's *t*-test or an ANOVA for repeated measurements. Comparisons between proportions were made with a Chi-square test. A p value <0.05 was considered statistically significant. All statistical calculations

Table 1 Spanish version of the Clarke test.[9]

1. Escoja la categoría que mejor le describe (sólo una)
   (a) Siempre tengo síntomas cuando mi azúcar en sangre está bajo.
   (b) Algunas veces tengo síntomas cuando mi azúcar en sangre está bajo.
   (c) Ya no tengo síntomas cuando mi azúcar en sangre está bajo.
2. ¿Ha perdido alguno de los síntomas que solía presentar ante una bajada de azúcar? (hipoglucemia)
   (a) Sí (b) No
3. En los últimos seis meses, ¿Con qué frecuencia ha tenido episodios de HIPOGLUCEMIA GRAVE SIN PERDIDA DE CONOCIMIENTO? (episodios en los que se ha sentido confundido, desorientado, cansado y sin posibilidad de tratar usted mismo la situación de hipoglucemia).
   (a) Nunca (b) Una/dos veces (c) 1 vez cada 2 meses (d) Una vez al mes (e) Más de una vez al mes.
4. En el último año, ¿Con qué frecuencia ha tenido episodios de HIPOGLUCEMIA GRAVE CON PÉRDIDA DE CONOCIMIENTO? (episodios acompañados de pérdida de conciencia o convulsiones que hayan requerido la administración de glucagón o glucosa intravenosa).
   (a) Nunca (b) 1 vez (c) 2 veces (d) 3 veces (e) 5 veces (f) 6 veces (g) 7 veces (h) 8 veces (i) 9 veces (j) 10 veces (k) 11 veces (l) 12 veces o más
5. En el último mes, ¿Con qué frecuencia ha tenido lecturas inferiores a 70 mg/dl con síntomas?
   (a) Nunca (b) de 1 a 3 veces (c) 2 ó 3 veces/semana (d) 4 ó 5 veces/semana (e) Casi cada día
6. En el último mes, ¿con qué frecuencia ha tenido lecturas inferiores a 70 mg/dl sin síntomas?
   (a) Nunca (b) De 1 a 3 veces (c) 2 ó 3 veces/semana (d) 4 ó 5 veces/semana (e) Casi cada día
7. ¿Hasta cuánto ha de bajar su azúcar en sangre para notar síntomas?
   (a) 60–69 mg/dl (b) 50–59 mg/dl (c) 40–49 mg/dl (d) inferior a 40 mg/dl
8. ¿Hasta qué punto puede decir por sus síntomas que su azúcar en sangre es bajo?
   (a) Nunca (b) Casi nunca (c) Algunas veces (d) Casi siempre (e) Siempre

Cálculo de la puntuación:
Preguntas 1: b ó c = R
Pregunta 2: a = R
Pregunta 3: b, c, d, e (cualquiera de ellas) = R
Pregunta 4: b, c, d, e, f, g, h, i, j, k, l (cualquiera de ellas) = R
Pregunta 5 y 6: respuesta pregunta 5 < respuesta pregunta 6 = R
Pregunta 7: c ó d = R
Pregunta 8: a, b ó c = R

La suma total de R determina el grado de percepción del paciente frente a la hipoglucemia:
1-2 R = percepción normal;
3 R = percepción de categoría indeterminada;
>3R percepción anormal ante una situación de hipoglucemia (hipoglucemia desapercibida)

were performed using the Statistical Package for Social Science (SPSS, v 19.0) for personal computers.

Results

Only those with T1D diabetes (418) were included in the analysis, with 51.2% being in the 36–55 years of age range. Regarding disease duration, 34.7% had had T1D for more than 15 years; 20.6% between 11 and 15 years; 17.2% between 2 and 5 years; 16.5% between 6 and 10 years and in only 11% subjects, T1D had been diagnosed less than 2 years before. We found the presence of IAH in 23.4% of questionnaires. Uncertain awareness was found in 15.3% and normal awareness of hypoglycaemia was found in 61.3% of the participants. There was a significant positive relationship between the duration of T1D and the Clarke test score (<2 years 1.86 ± 1.30; 2–5 years 1.83 ± 1.62; 6–10 years 2.07 ± 1.73; 11–15 years 2.23 ± 1.79; >15 years 2.68 ± 2.13; $p < 0.03$). The longer the duration of T1D, the higher the score in the Clarke test (Fig. 1). According to the Clarke test 14.1% of the participants had had at least one episode of severe hypoglycaemia in the previous year and half had done so (7.4%) on 2 or more occasions. All but one of the participants with 2 or more episodes of severe hypoglycaemia had IAH.

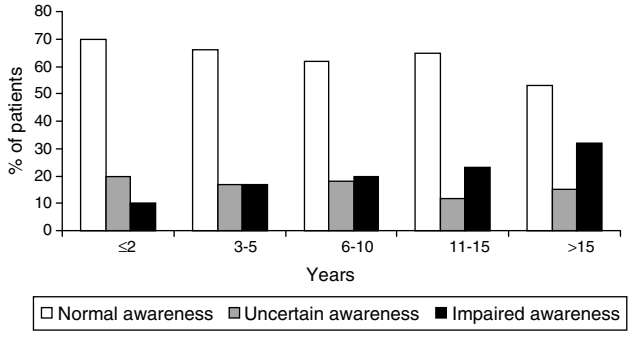

Figure 1 Clarke test results by duration of T1D.

Discussion

According to an online survey using the Spanish version of the Clarke questionnaire we found that up to ~25% of adult participants with T1D have IAH and that the prevalence of this condition increases with the duration of the disease.

Data regarding the prevalence of IAH in Spain are still very scarce in comparison with other countries. This is probably due, at least in part, to the infrequent use of specific questionnaires dedicated to the detection of IAH mainly because of the lack of translated versions to Spanish. In 2014 we performed a psychometric analysis of the Spanish version of the Clarke questionnaire[9] and described that the Spanish version of Clarke Test displays good psychometric properties and could be considered a useful tool for evaluating IAH in patients with T1D using Spanish as the native language. With the use of this test in our routine clinical practice we detected IAH in 16% of an adult population with T1D (average of 20 years of T1D duration, unpublished data) and in 9% of young adults transferred from paediatric to adult Diabetes Units (average of 8 years of TD1 duration, data published only in abstract form).

We report here information regarding the prevalence of IAH in a large group of individuals with T1D based on a survey performed using a anonymous free access online questionnaire with the Spanish version of the Clarke Test. Our results are similar to those of other authors and surveys and confirm the relationship between the presence of IAH and disease duration.[10,11] In addition to this, 7% of the participants in the present study fulfilled the very recent definition of problematic hypoglycaemia and were designated as IAH by the test.[10] Thus, despite modern patient education and improvements in the insulin therapy, severe hypoglycaemia and IAH are still far from being solved in T1D. Repeated non-severe and severe episodes of hypoglycaemia, and the presence of IAH are major barriers to achieving normoglycaemia over a lifetime of using intensive insulin therapy and thereby preclude the long-term benefits of euglycemia.[6,12,13] In addition, hypoglycaemia and its consequences have a very negative impact on the perceived quality of life of individuals with T1D.[14–16] Considering our results, evaluation and review of the presence of risk factors for severe hypoglycaemia should mandatorily include screening for the presence of IAH using adequate versions of specific questionnaires.

Our study has limitations. The most important limitation is inherent to the study design. We relied on data from an anonymous, free access on-line survey, and therefore cannot totally guarantee the truthfulness and accuracy of the results. In addition to this, it is possible that mostly those patients with T1D affected by recurrent episodes of hypoglycaemia or specially interested in that subject answered the questionnaire. However, the large number of participants, as well as, the fact that our findings can be extrapolated to previous reports on the same subject, could be considered a significant strength of our work.

In summary, at least 25% of T1D participants in an online survey using a Spanish version of a currently used questionnaire showed impaired awareness of hypoglycaemia. The presence of this condition increases with the duration of the disease and allows the identification of subjects prone to severe episodes of hypoglycaemia.

Conflict of interest

The authors declare no conflict of interest regarding the manuscript.

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