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Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study

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Fear of hypoglycemia;
Quality of life;
Diabetes-related distress

Abstract *Background and aims:* Hypoglycemia represents a relevant burden in people with diabetes. Consequences of hypoglycemia/fear of hypoglycemia on quality of life (QoL) and behaviors of patients with T1DM and T2DM were assessed.
Methods and results: HYPOS-1 was an observational retrospective study. Fear of hypoglycemia (Fear of Hypoglycemia Questionnaire, FHQ), general health status (visual analog scale of EuroQol questionnaire, EQ5D-VAS) psychological well-being (WHO-5 well being index, WHO-5), diabetes related distress (Problem Areas in Diabetes 5, PAID-5), and corrective/preventive behaviors following hypoglycemia were compared between people with and without previous experience of severe and symptomatic hypoglycemia and by tertiles of FHQ scores. A multivariate analysis was performed to identify factors associated with the likelihood of being in the third tertile of FHQ score. Overall, 2229 patients were involved. Severe hypoglycemia had statistically significant and clinically relevant (measured as effect sizes) negative impact on EQ5D-VAS, WHO-5, PAID-5, and FHQ both in T1DM and T2DM. In T2DM, symptomatic episodes had similar impact of severe hypoglycemia. Moving from the first to the third FHQ tertile, lower scores of EQ-5D VAS and WHO-5, and higher levels of PAID-5 were found. Patients in the third tertile performed more frequently corrective/preventive actions that negatively impact on metabolic control. Previous hypoglycemia, insulin treatment, female gender, age, and school education were the independent factors associated with increased likelihood to be in the third tertile.

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Conclusion: Not only severe but also symptomatic hypoglycemia negatively affect patient QoL, especially in T2DM. Addressing fear of hypoglycemia should be a goal of diabetes education.

Introduction

Improved metabolic control is a goal of diabetes care, aiming to prevent or delay the development of micro-and macrovascular complications both in type 1 diabetes and type 2 diabetes [1]. However, therapeutic efforts necessary to maintain the values of glycated hemoglobin (HbA1c) within the target lead to an increased risk of hypoglycemia, especially when using insulin or secretagogues [2,3]. Hypoglycemia is generally perceived as an inevitable price to pay to achieve the HbA1c goal. Nevertheless, hypoglycemia is responsible for increased risk of cardiovascular events, fractures, cognitive impairment, and mortality [4–6]. Hypoglycemia is associated with high direct and indirect costs for healthcare systems and citizens [7–9]. It also exerts a negative impact on quality of life and can interfere with a wide range of daily activities [10]. People who have had experience of severe hypoglycemia tend to report a poorer quality of life and major concerns related to the disease [9]. Following hypoglycemia episodes, patients can develop fear of hypoglycemia that not only decreases their quality of life but also that of their family members [11–13].

The HYPOS-1 study represents the largest study on the burden of hypoglycemia in people with type 1 and type 2 cared for by diabetes outpatient clinics in Italy. Incidence, predictors, and costs associated with hypoglycemia were investigated and useful information derived for physicians and payers [14–16]. In the context of the HYPOS study, information on quality of life and patient behaviors associated with hypoglycemia was also collected. Aims were to investigate the role of hypoglycemia on general health status, psychological well-being, diabetes-related distress and fear of hypoglycemia both in type 1 and type 2 diabetes. The study aimed to evaluate the social implications not only of severe episodes but also of symptomatic episodes, taking into consideration that impact of symptomatic hypoglycemia on the lives of people with diabetes has been seldom investigated [17].

Furthermore, we investigated the role of the fear of hypoglycemia, measured through a new short instrument, as an explanatory variable associated with metabolic control and quality of life; this issue was assessed in a few studies [17] in spite of its importance in addressing educational interventions.

Methods

Study design and participants

HYPOS-1 is an observational retrospective study involving individuals with type 1 and type 2 diabetes (T1DM and T2DM) routinely referred to diabetes outpatients clinics (DOCs). Methods and part of results have been described in previous publications [14–16]. Eligibility criteria were: male or female gender, age $\geq$ 18 years, diabetes diagnosis at least 1 year before the recruitment in the study, unchanged diabetes treatment for at least 1 year, signed informed consent; the only exclusion criterion was the incapability to fill in the study questionnaire according to the investigator judgment.

Procedures

On the occasion of a routine visit, a sample of consecutive cases was asked to fill in the study questionnaire. Sampling was stratified to reflect the distribution of patients with type T1DM and T2DM attending DOCs [18], i.e. 10% of patients with T1DM2 and 90% of patients with T2DM; T2DM patients were further stratified by classes of diabetes treatment (i.e. 60% treated with oral hypoglycemic agent/GLP-1 receptor agonists (OHA), 15% treated with OHA + insulin, 15% treated with insulin, and 10% treated with lifestyle interventions only) [18].

The patient questionnaire investigated the experience of severe hypoglycemia episodes in the past 12 months, and experience of symptomatic hypoglycemia episodes in the past 4 weeks. Severe hypoglycemia was defined as an episode of hypoglycemia that led to unconsciousness or requiring intervention of a third person; symptomatic hypoglycemia was defined as onset of one or more symptoms including palpitations, tremors, sweating, difficulty concentrating, dizziness, hunger, blurred vision, sense of confusion, difficulty in movement, resolved with the ingestion of sugar, food or sugary drinks. In addition, the questionnaire investigated a large set of socio-demographic and clinical characteristics (Table 1) and included standardized instruments for the evaluation of quality of life (QoL) dimensions, i.e:

- WHO-5 well-being index (WHO-5) to assess the psychological well-being, a core component of overall quality of life. It also represents a valid and reliable risk assessment measure for mild, moderate and severe depression. It includes 5 items with responses on a six-point Likert scale. A score <50 indicates poor psychological well-being, a score $\leq$ 28 indicates likely depression [19,20].
- Problem Areas in Diabetes -Short form (PAID-5) to evaluate the diabetes related emotional distress, i.e. specific worries and negative emotions related to diabetes. It includes 5 items with responses on a five-point

Table 1 Patient characteristics according to the type of diabetes.

	T1DM	T2DM
N	206	2023
Socio-demographic characteristics		
Male (%)	47.3	55.3
Age (years)	42.4 ± 14.0	66.3 ± 10.2
Employment status (%):		
Employed	59.6	20.9
Unemployed	21.7	19.1
Retired	11.3	60.1
Students	7.4	0
Highest level of school education (%):		
Primary school	8.3	40.3
Middle school	25.7	30.6
High school	47.6	22.8
University	18.5	6.3
Living status (%):		
Spouse/sons	61.3	77.8
Alone	9.3	15.8
Other family members	23.5	4.3
Other	5.9	2.1
Marital status (%):		
Not married	35.9	7.4
Married/cohabitant	56.8	75.2
Separated/divorced	5.3	4.3
Widower	1.9	13.1
Taking care of other people (%)	41.2	37.3
Clinical characteristics		
Body mass index (Kg/m^2)	24.9 ± 4.1	29.7 ± 5.7
Duration of diabetes (years)	19.0 ± 11.9	11.5 ± 8.9
Glycated Hemoglobin (%)	7.8 ± 1.2	7.1 ± 1.2
Glomerular filtration rate < 60 mL/min (%)	6.3	25.6
Diabetes complications (%):		
Cardiac/cerebrovascular	4.9	17.8
Lower limb complications	5.3	8.4
Retinopathy	30.6	21
Nephropathy	12.1	18.4
Sensory-motor neuropathy	8.0	11.9
Autonomic neuropathy	4.5	5.4
Neoplasms (%)	2.0	4.5
Self-monitoring of blood glucose (tests/week, N)	24.2 ± 13.2	6.9 ± 8.3
Number of drugs other than glucose-lowering ones (N)	1.4 ± 2.0	3.3 ± 2.6
Antihypertensive treatments (%)	27.5	70.7
Angiotensin Converting Enzyme Inhibitors (%)	18	29.1
Beta-blockers (%)	6.8	24.6
Lipid-lowering treatments (%)	29.5	56.4
Hypoglycemia		
Previous experience of severe hypoglycemia (before the last 12 months) (%)	38.8	10.0
At least one severe hypoglycemic episode in the past 12 months (%)	16.5	4.7
Mean number of severe hypoglycemic episodes in the past 12 months	0.5 ± 1.7	0.1 ± 0.7
At least one symptomatic hypoglycemic episode in the past 4 weeks (%)	78.6	28.1
Mean number of symptomatic hypoglycemic episodes in the past 4 weeks	4.5 ± 6.7	0.8 ± 2.1
Education		
% reporting has received practical guidance to recognize, prevent and manage hypoglycemia	91.7	71.0
Training on self-monitoring of blood glucose (%)	98.1	95.7
Having glucagon at home (%)	51.0	4.0

Likert scale. A score ≥40 indicates high diabetes-related distress. The Italian version of PAID-5 was validated in context of the BENCH-D study [20–22].

- EuroQol questionnaire (EQ-5D) as a generic measure of health status [23,24]. The EQ-5D questionnaire includes a visual analog scale (EQ5D-VAS). The respondent self-rates current health status on a thermometer-like scale ranging from 0 (“worst imaginable health status”) to 100 (“best imaginable health status”).
- Fear of hypoglycemia questionnaire (FHQ): FHQ is a 6-item questionnaire with responses on a six-point Likert scale, developed and validated in T2DM in a previous study [17]. The validation was repeated even in this study for both T1DM and T2DM. The FHQ questionnaire showed good psychometric properties: the Cronbach alpha was equal to 0.87 in T1DM and 0.90 in T2DM.
- The score ranges from 0 to 100, and the higher the score, the greater the fear of hypoglycemia.

Finally, information about patient hypoglycemia-related behaviors were collected through the questionnaire. Specifically, we asked how often patients ate something or drank sugary drink, checked their sugar levels, reduced next glucose-lowering drug dose, did not take next glucose-lowering drug dose, and increased SMBG frequency in the subsequent days after a symptomatic hypoglycemia. Responses were based on a 5-point Likert scale (1 = never, 2 = seldom, 3 = sometimes; 4 = often; 5 = always).

Investigators filled in a web-based clinical record form (eCRF) to collect clinical data (Table 1). Data was anonymous. Patients were identified by a unique ID number, representing the key linkage to merge data from patient questionnaires and eCRFs.

The study was approved by the local ethics committees of all participating centers.

Statistical analysis

Patient characteristics and QoL scores and behavioral items were expressed as mean and standard deviation (SD) or proportion. Between-group differences in QoL scores according to the previous experience of hypoglycemia were assessed through chi-square test for categorical variables and Mann−Whitney U-test for continuous variables. Differences were also expressed as effect sizes, which were calculated by dividing the between group difference in mean values of each QoL score by the SD of that score estimated on the entire group. The generally accepted benchmarks are 0.20 for a small effect size, 0.50 for a moderate effect size, and 0.80 for a large effect size [25].

The whole sample was divided by tertiles of fear of hypoglycemia score; HbA1c and mean QoL scores and behavioral items were compared among the three groups through the Kruskal−Wallis ANOVA test.

A multivariate analysis was finally performed to identify factors significantly associated with a higher likelihood of being in the upper tertile of FHQ score.

P-values <0.05 were considered statistically significant. All the analyses were performed using SAS Program (Release 9.4, SAS Institute, Cary, NC, USA).

Role of the funding source

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Results

Overall, 18 DOCs enrolled 206 (9.2%) patients with T1DM and 2023 (90.8%) patients with type 2 diabetes. Of patients with T2DM, 202 (10.0%) were treated with lifestyle intervention only, 1212 (59.9%) were treated with OHA, 306 (15.1%) with OHA + insulin and 303 (15.0%) with insulin alone. Clinical and socio-demographic characteristics of the study sample according to diabetes type are shown in Table 1. Overall, 16.5% of patients with T1DM experienced at least one severe hypoglycemic episode in the past 12 months (N = 33), while 78.6% of the sample reported at least one symptomatic hypoglycemic episode in the past four weeks (N = 162). Among patients with T2DM, 4.7% experienced at least one severe hypoglycemic episode in the past 12 months (N = 88), while 28.1% reported at least one symptomatic hypoglycemic episode in the past four weeks (N = 564).

Figure 1 shows quality of life scores by diabetes type and by previous experience of severe or symptomatic hypoglycemia. In T1DM, statistically significant poorer scores of EQ-5D VAS, WHO-5, PAID-5, and FHQ were found in patients with vs. those without previous experience of severe hypoglycemia, while no statistically significant differences were found stratifying by symptomatic episodes. In T2DM, all QoL scores were significantly lower in patients with vs. those without previous experience of severe and symptomatic hypoglycemia. In terms of impact of severe hypoglycemia, between-group differences in QoL scores were associated with moderate/large effect sizes both in T1DM and T2DM; for symptomatic hypoglycemia, no effect sizes were evaluable in T1DM, while moderate effect sizes were found in T2DM associated with the between group differences in WHO-5, PAID-5 and FHQ scores.

The proportion of patients with high diabetes-related distress (PAID-5 score >40) and likely depression (WHO-5 score ≤ 28) was markedly higher in individuals with T1DM with a previous experience of severe hypoglycemia as compared to those without previous severe hypoglycemia (69.7% vs. 43.8%, and 25.0% vs. 11.7%, respectively). Among patients with T2DM, a previous experience of both severe or symptomatic hypoglycemia was associated with significantly higher proportions of patients with diabetes related distress or likely depression (Fig. 2).

Table 2 shows the association between tertiles of FHQ and mean levels of metabolic control and other QoL dimensions. Patients in the worst tertile of FHQ had poorer metabolic control and lower scores of EQ-5D VAS and WHO-5, and higher levels of PAID-5. Furthermore, the table shows the increasing frequencies of corrective/preventive actions that could negatively impact on metabolic control moving from the first to the third tertile of FHQ.

Table 3 shows that after adjustment for patient case mix, some factors were independently associated with the likelihood to be in the highest tertile of FHQ score: experience of at least one severe hypoglycemic episode in the previous 12 months was associated with a twofold risk of being in the third tertile and represented the strongest correlate; having had a severe episode before the past 12 months or having had a symptomatic episode in the past 4 weeks were associated with an about 50% increased risk. Furthermore, treatment with insulin increased the risk by 88% vs. treatment schemes not including insulin. Among

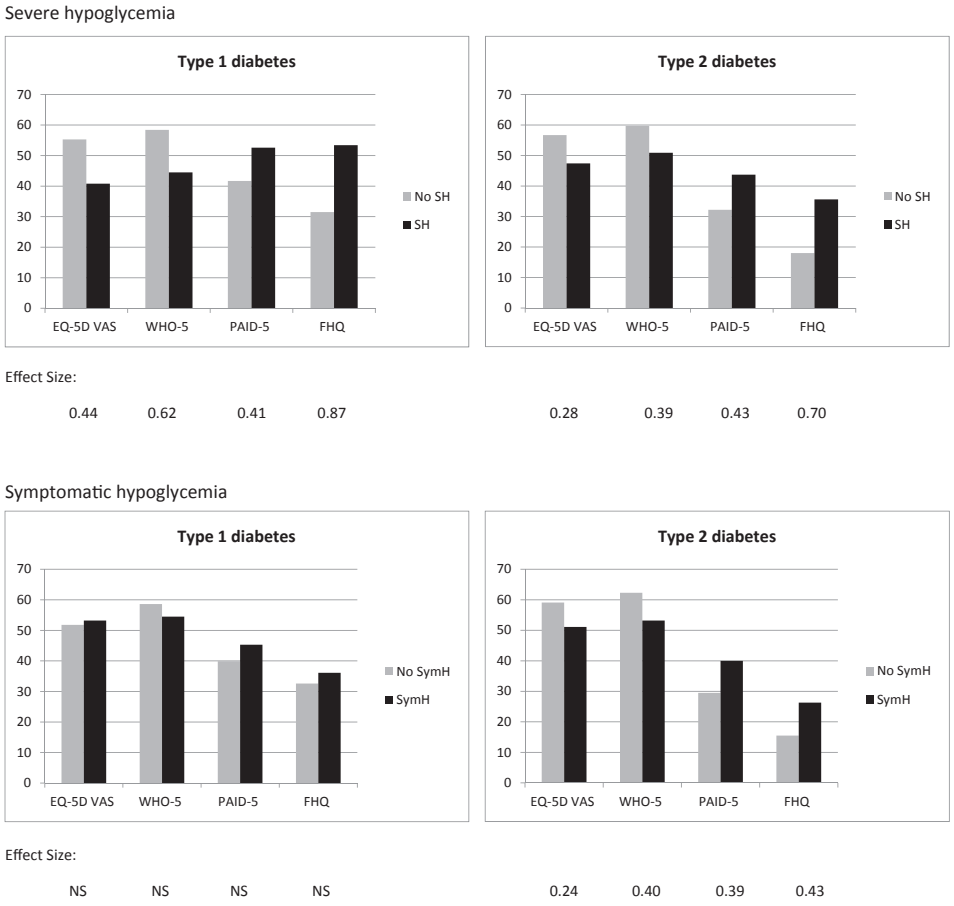

Figure 1 Between-group differences in quality of life scales according to the experience of hypoglycemia.

socio-demographic characteristics, women showed a 26% increased risk of being in the highest FHQ tertile compared to men; the risk increased by 4% by each additional year of age; patients with high school/university degree had a 27% increased risk of being in the upper tertile of the FHQ score vs. those with primary/middle school level.

Discussion

This analysis of the HYPOS-1 study shows two key findings: first, not only severe hypoglycemia but also symptomatic hypoglycemia has a negative impact on general health status, psychological well-being, and fear of hypoglycemia, especially in T2DM. In T1DM, symptomatic episodes were reported by the vast majority of participants (78.6% of the patients reported at least one episode in the previous 4 weeks), thus suggesting that symptomatic episodes are very common among these patients, who probably perceive mild hypoglycemia as a normal occurrence they are able to manage. However, despite statistical significance was not reached, even patients with T1DM reporting at least one episode of symptomatic hypoglycemia in the previous 4 weeks showed lower psychological well-being, higher diabetes related distress and higher fear of hypoglycemia as compared to patients without symptomatic hypoglycemia.

Second, the HYPOS-1 study shows that fear of hypoglycemia is associated with poorer metabolic control, higher diabetes-related distress levels, poorer psychological well-being and general health status. It is also associated with corrective behaviors following hypoglycemia in both diabetes types.

The second Diabetes Attitudes, Wishes and Needs (DAWN2) study, which assessed psychosocial outcomes in people with diabetes across 17 countries, found that proportion with likely depression (WHO-5 score $\leq$ 28) was 13.8%, while high diabetes-related distress (PAID-5 score $>$ 40) was reported by 44.6% of participants (17.2–67.6%) [26]. The BENCH-D study found that among people with type 2 diabetes, 15.0% had WHO-5 $\leq$ 28 while 60.2% had PAID-5 $>$40 [27]. HYPOS-1 study shows that in people with type 1 diabetes severe hypoglycemia is associated with high distress in 70% of the cases, and with likely depression in 25% of the cases, while no association with symptomatic hypoglycemia was documented. On the other side, in people with type 2 diabetes both severe and symptomatic hypoglycemia are associated with markedly higher proportions of patients suffering from high distress or likely depression.

In the recent nine-country cross-sectional PANORAMA study [11], worry about hypoglycemia emerged as a frequent and relevant issue for type 2 diabetes, representing a barrier for therapy intensification and adherence

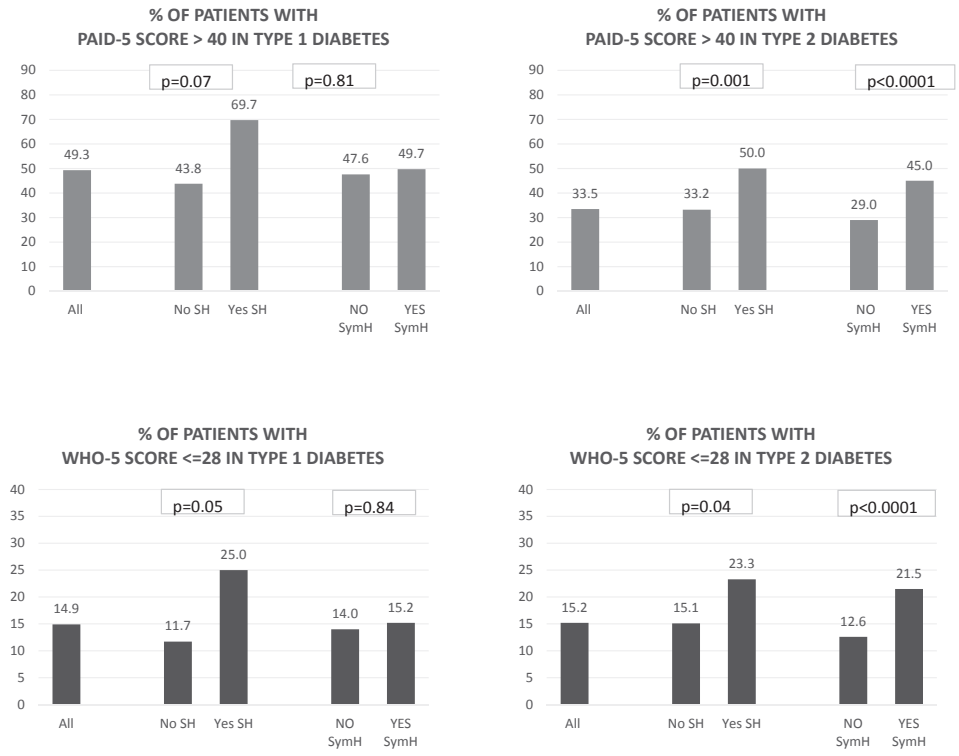

Figure 2 Proportion of patients with high diabetes-related distress (PAID-5 score >40) and likely depression (WHO-5 ≤ 28) by diabetes type and experience of hypoglycemia.

with treatment. Lower mean scores of the EQ-VAS and EQ-5D and higher fear of hypoglycemia score [31] associated with hypoglycemia occurrence were found in previous studies [28–30], as well as the risk of counterproductive behaviors due to hypoglycemia [30], then suggesting the need of incorporating screening for symptoms of hypoglycemia and fear of hypoglycemia into the routine health assessment of all patients with diabetes [31]. In the HYPOS-1 study, the fear of hypoglycemia was measured through a new, short questionnaire, which could be easily integrated in clinical practice for the regular monitoring of this important parameter. Furthermore, characteristics of patients more likely to have high levels of FHQ have been identified: previous experience of severe or symptomatic hypoglycemia, insulin treatment, female gender, older age, and high school education level (i.e. being aware about hypoglycemia) are the most important correlates for FHQ.

Table 2 Mean HbA1c, quality of life scores, and behavioral items by tertiles of fear of hypoglycemia (FHQ) scores in type 1 and type 2 diabetes.

	FHQ score			*p*-value
	1st tertile 0	2nd tertile 0.1–25.0	3rd tertile >25.0	
N	736	783	625	
FHQ score	0	15.3 ± 7.6	49.8 ± 17.0	<0.0001
HbA1c	7.0 ± 1.1	7.2 ± 1.2	7.3 ± 1.3	<0.0001
EQ-5D VAS	62.3 ± 30.3	58.3 ± 29.4	47.2 ± 31.8	<0.0001
WHO-5	64.2 ± 24.2	60.9 ± 24.5	51.5 ± 24.4	<0.0001
% with WHO-5 ≤ 28	11.3	14.9	20.5	<0.0001
PAID-5	18.8 ± 21.9	31.9 ± 22.6	52.8 ± 24.5	<0.0001
% with PAID-5 >40	13.8	28.6	67.5	<0.0001
% of patients who, after a symptomatic hypoglycemia:				
Ate something or drank sugary drink	3.5 ± 1.6	3.8 ± 1.4	4.0 ± 1.2	0.05
Checked their sugar levels	3.6 ± 1.7	3.7 ± 1.6	4.1 ± 1.2	0.004
Reduced next antidiabetic drug dose	1.6 ± 1.2	1.8 ± 1.2	2.3 ± 1.5	<0.0001
Did not take next antidiabetic drug dose	1.2 ± 0.8	1.4 ± 0.8	1.6 ± 1.1	<0.0001
Increased SMBG frequency in the days after	2.2 ± 1.6	2.5 ± 1.4	3.0 ± 1.5	<0.0001

Results are expressed as means and standard deviations.
*p values are based on Kruskal–Wallis test.
Abbreviations: QoL quality of life, FHQ Fear of hypoglycemia questionnaire, HbA1c Glycated Hemoglobin, EQ-5D VAS visual analog scale of EuroQol questionnaire, WHO-5 WHO 5 well being index, PAID-5 Problem Areas in Diabetes 5, SMBG Self-monitoring of blood glucose.

Table 3 Factors significantly associated with a higher likelihood of being in the upper tertile of the fear of hypoglycemia questionnaire (FHQ). Data are Odds Ratios with their 95%Confidence Intervals (OR and 95%CI).

	OR (95%CI)
Age	1.04 (1.00–1.09)
Previous experience of severe hypoglycemia (before the last 12 months)	
NO	1.00
YES	1.59 (1.18–2.14)
Experience of at least one severe hypoglycemic episode in the past 12 months	
NO	1.00
YES	2.17 (1.43–3.29)
Experience of at least one symptomatic hypoglycemic episode in the past 4 weeks	
NO	1.00
YES	1.55 (1.24–1.95)
Gender	
M	1.00
F	1.26 (1.03–1.55)
Glucose-lowering therapy	
No Insulin	1.00
Insulin	1.88 (1.51–2.35)
School education	
Primary/middle school	1.00
High school/university	1.27 (1.01–1.61)

Multivariate models (with backward selection) adjusted for age, gender, diabetes duration, type of diabetes, insulin treatment, presence of microvascular complications (retinopathy or nephropathy), macrovascular complications (cardiac or cerebrovascular or lower limb complications), neuropathic complications (sensory motor and/or autonomic), school education (primary/middle school vs. high school/university), living status (with spouse/sons vs. alone/other), previous experience of severe hypoglycemia (before the last 12 months), experience of at least one severe hypoglycemic episode in the past 12 months, experience of at least one symptomatic hypoglycemic episode in the past 4 weeks, having received practical guidance to recognize, prevent and manage hypoglycemia, number of drugs other than glucose-lowering ones.

The study has important implications, since it clearly documents that even symptomatic episodes of hypoglycemia exert a negative effect on quality of life. These findings are particularly important considering the elevated frequency of such episodes, despite we documented a lower incidence as compared to the existing literature. A recent meta-analysis of 46 studies (n = 532,542) [32] conducted in Europe, USA, Asia, and Australia showed that the rates for mild/moderate and severe episodes in people with T2DM were 19 (95%CI 0.00, 51.08) and 0.80 (95%CI 0.00,2.15) per patient-year, respectively, as compared to 9.3 (95%CI 8.8, 9.7) and 0.09 (95%CI 0.08, 0.11) in the HYPOS-1 study.

The study has strengths and limitations. The main strength of the study was the opportunity to assess in a largely representative population the impact of both severe and symptomatic hypoglycemia on a large set of patient-centered outcomes and to investigate the role of the fear of hypoglycemia as outcome and as mediator. Sampling of the study population was made to reflect as much as possible the distribution of treatment groups under routine clinical practice conditions. This allowed to obtain quality of life scores truly representative of the whole population of patients with T1DM and T2DM attending diabetes clinics.

Main limitation is the cross-sectional design, which implies the unavailability of information about cause-effect relationship between fear of hypoglycemia and clinical and QoL outcomes; in addition, the relatively small sample of people with type 1 diabetes may have hidden statistical significance of some comparisons. Furthermore, the definition of symptomatic hypoglycemia in the current paper was based on symptoms, independently from the measurement of blood glucose. A confirmation of hypoglycemia through blood glucose measurement would have provided more reliable information. However, SMBG is not common practice among T2DM patients not treated with insulin, and some patients may adopt compensative behaviors to counteract hypoglycemic symptoms without a confirmation of the actual blood glucose levels. Nevertheless, study results show a strong correlation between symptomatic hypoglycemia and worse quality of life/increased fear of hypoglycemia, thus supporting the reliability of the definition applied.

In conclusion, both severe and symptomatic hypoglycemia negatively affect patient quality of life. Developing educational programs targeted on reduction of fear of hypoglycemia, in addition to effective and safe therapeutic strategies, may represent a specific and effective intervention to minimize the impact of hypoglycemia on the lives of people with diabetes.

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Conflicts of interest

We declare no competing interests.

Author contributors

CG and AN conceived and designed the study. GL, MCR, AN conducted the statistical analyses. MCR and CG wrote the first version of the manuscript. CG, AO, SG, AA, AC, FB, MMG, FR collected data. AO, SG, AA, AC, FB, MMG, FR contributed to the discussion. CG is the guarantor of accuracy and integrity of any part of the work.

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Appendix

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