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SELF-REPORTED HYPOGLYCAEMIA IN PATIENTS TREATED WITH INSULIN: A LARGE SLOVENIAN RETROSPECTIVELY-PROSPECTIVE STUDY

HIPOGLIKEMIJE PRI BOLNIKIH, ZDRAVLJENIH Z INSULINOM: VELIKA SLOVENSKA RETROSPEKTIVNOPROSPEKTIVNA RAZISKAVA

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ABSTRACT

Introduction. Hypoglycaemia is the major barrier for glycaemic target achievement in patients treated with insulin. The aim of the present study was to investigate real-world incidence and predictors of hypoglycaemia in insulin-treated patients.

Methods. More than 300 consecutive patients with type 1 or type 2 diabetes treated with insulin were enrolled during regular out-patient visits from 36 diabetes practices throughout the whole country. They completed a comprehensive questionnaire on hypoglycaemia knowledge, awareness, and incidence in the last month and last six months. In addition, in the prospective part, patients recorded incidence of hypoglycaemic events using a special diary prospectively on a daily basis, through 4 weeks.

Results. At least one hypoglycaemic event was self-reported in 84.1%, and 56.4% of patients with type 1 and type 2 diabetes, respectively, during the prospective period of 4 weeks. 43.4% and 26.2% of patients with type 1 and type 2 diabetes, respectively, experienced a nocturnal hypoglycaemic event. In the same time-period, severe hypoglycaemia was experienced by 15.9% and 7.1% of patients with type 1 and type 2 diabetes, respectively. Lower glycated haemoglobin was not a significant predictor of hypoglycaemia.

Conclusions. Rates of self-reported hypoglycaemia in patients treated with insulin in the largest and most comprehensive study in Slovenia so far are higher than reported from randomised control trials, but comparable to data from observational studies. Hypoglycaemia incidence was high even with high glycated haemoglobin values.

Keywords:
hypoglycaemia, type 1 diabetes, type 2 diabetes, insulin treatment, Slovenia

IZVLEČEK

***Uvod**. Hipoglikemije so glavni omejujoči dejavnik varnega doseganja glikemičnih ciljev pri bolnikih s sladkorno boleznijo, ki se zdravijo z insulinom. Namen te raziskave je bil raziskati pojavnost hipoglikemij in napovedne dejavnike hipoglikemij v vsakodnevnem življenju bolnikov s sladkorno boleznijo.*

***Metode**. V raziskavo smo vključili več kot 300 zaporednih bolnikov s sladkorno boleznijo tipa 1 ali 2, zdravljenih z insulinom, iz 36 diabetoloških ambulant po državi. Bolniki so izpolnili natančen vprašalnik, ki je poizvedoval o znanju o hipoglikemijah, njihovemu zaznavanju in pojavnosti v zadnjem mesecu in v zadnjih šestih mesecih. V nadaljevalnem, prospektivnem delu raziskave, ki je trajal 1 mesec, so bolniki vsakodnevno beležili dnevnik hipoglikemij, kamor so sproti vpisovali, ali so doživeli hipoglikemijo.*

***Rezultati**. V raziskavo je bilo vključenih 84 bolnikov s sladkorno boleznijo tipa 1 in 227 bolnikov s sladkorno boleznijo tipa 2. Med enomesečnim prospektivnim delom raziskave je 84,1% bolnikov s sladkorno boleznijo tipa 1 in 56,4% bolnikov s sladkorno boleznijo tipa 2 poročalo, da so doživeli vsaj eno hipoglikemijo. Nočno hipoglikemijo je doživelo 43,4% bolnikov s sladkorno boleznijo tipa 1 in 26,2% bolnikov s sladkorno boleznijo tipa 2. Hudo hipoglikemijo je doživelo 15,9 % bolnikov s sladkorno boleznijo tipa 1 in 7,1% bolnikov s sladkorno boleznijo tipa 2. Nižji glikiran hemoglobin ni bil napovedni dejavnik za pojav hipoglikemij.*

***Zaključki**. Incidenca hipoglikemij, o katerih so poročali sami bolniki, zdravljeni z insulinom, je v doslej največji raziskavi o hipoglikemijah na Slovenskem višja kot v velikih randomiziranih prospektivnih raziskavah, a primerljiva kot v podobnih opazovalnih raziskavah iz vsakodnevnega življenja. Incidenca hipoglikemij je visoka tudi pri bolnikih z visokim glikiranim hemoglobinom.*

Ključne besede:
hipoglikemija, sladkorna bolezen tipa 1, sladkorna bolezen tipa 2, insulinsko zdravljenje, Slovenija

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1 INTRODUCTION

Intensive hyperglycaemia treatment reduces the risk of development of chronic diabetes complications. However, the main obstacle to attain tight glycaemic goals is the risk of hypoglycaemia (1). In addition, experiencing hypoglycaemia, especially a nocturnal one, decreases quality of life substantially (2). Moreover, severe hypoglycaemia, requiring external assistance for recovery, was associated with increased cardiovascular and overall mortality (3).

Data on hypoglycaemia incidence are variable, mainly because of the lack of a single threshold plasma glucose concentration that defines hypoglycaemia in diabetes. Typically, it is believed that hypoglycaemia incidence is high in type 1 diabetes, but not in type 2 diabetes. Yet, incidence of hypoglycaemia increases with type 2 diabetes duration (4, 5). Reported incidence of severe hypoglycaemia in retrospective observational studies in patients with longstanding type 1 diabetes was 320 cases per 100 patient-years (6). Of note, substantially lower incidence was established from a prospective randomised DCCT trial, with 62 cases per 100 patient-years (7). On the other hand, in patients with type 2 diabetes, severe hypoglycaemia incidence was 70 per 100 patient-years in observational studies (6), whereas it was only 3.1 per 100 patient-years in a multicentre, prospective, randomised ACCORD study (8).

Hypoglycaemia incidence in patients treated with insulin in Slovenia was never systematically studied. Therefore, the aim of the present study was to assess hypoglycaemia incidence in insulin-treated patients with type 1 and type 2 diabetes mellitus as patients report it, and to investigate factors, associated with hypoglycaemia risk.

2 METHODS

This was a multicentre, non-interventional study, designed to assess hypoglycaemia incidence in patients with type 1 and type 2 diabetes, treated with insulin. The study protocol, with hypoglycaemia classification and statistical analyses was in detail described elsewhere (9).

During the routine, out-patient visits with diabetologists, from 474 consecutive patients from 36 clinical sites in Slovenia invited to participate, 311 were enrolled in the study. The sites were quite uniformly distributed throughout Slovenia. The biggest number of patients was recruited from the north-western Slovenia, the only region without any patients included was the Slovenj Gradec region. The average number of patients per site was 8.6, per region 39. Minimal number of patients per region was 10 (Murska Sobota), maximal 75 (Gorenjska). Patients included were more than 18 years old, had type 1 or type 2 diabetes mellitus, with at least 12 months of insulin treatment experience, and had signed the informed consent. The exclusion criterion was the inability to complete a written questionnaire and a hypoglycaemia diary. Patients were not given any financial payment for the participation in the study.

Baseline characteristics of the patients analysed are presented in Table 1. More than two thirds of patients had type 2 diabetes mellitus.

Table 1. Baseline characteristics of patients included.

	DM type 1 N=84	DM type 2 N=227
Age (years)	49±13	64±10
Gender (male/female, %)	57/43	62/38
Diabetes duration (years)	21±11	16±9
Insulin therapy duration (years)	19±12	6 (3, 10)*
HbA1c (%)	9.2±2.7	9.3±2.8
Employed/unemployed/retired/other (%)	65/5/28/12	15/8/75/2
Diabetes treatment		
Short-acting insulin	85.7	48.9
Long-acting insulin	60.7	63.1
Pre-mixed insulin	1.2	35.1
Oral therapy	4.8	24.9
Injectable non-insulin therapy	3.6	10.2
Insulin pump	32.1	4.9
Self-measurement of blood glucose (%)	98.8	99.6
Continuous glucose measurement (%)	34.2	38.4
Hypoglycaemia experience (%)	98.8	89.2

*Non-normally distributed variables are represented as median (25th, 75th percentile)

The study was comprised of two parts: a retrospective 6-month period and a prospective 4-week period. In the retrospective part, patients were asked to recall a 6-month history of severe hypoglycaemia and a 4-week history of non-severe and severe hypoglycaemia. In the prospective period, they were asked to complete a special diary of hypoglycaemia on a daily basis.

The primary endpoint of the study was the percentage of patients experiencing at least one hypoglycaemic event during the 4-week follow-up period. The majority of statistical analyses were prepared on data from the prospective part, in order to avoid a recall bias.

The study was performed from March to September 2013. It was conducted in accordance with the Declaration of Helsinki and was also approved by the Slovenian Ethics Committee.

2.1 Statistical Analyses

The majority of analyses were descriptive in nature. All statistical tests were two-sided. A p-value of less than

0.05 was considered as statistically significant. Univariate binomial regression models were used to examine the relationship between hypoglycaemia and factors, including age, gender, HbA1c at baseline, diabetes duration, duration of insulin therapy, type of insulin therapy, frequency of blood glucose monitoring, knowledge of hypoglycaemia, hypoglycaemia unawareness, fear of hypoglycaemia, period, and diabetes type. Differences in retrospective versus prospective data reporting were assessed using a paired t-test.

Definitions used: non-severe hypoglycaemia was defined as a hypoglycaemic event managed by the patient alone, whereas severe hypoglycaemia was defined as any hypoglycaemic event that requires external assistance for recovery. Nocturnal hypoglycaemia was defined as a hypoglycaemic event occurring between midnight and 6 in the morning. Documented symptomatic hypoglycaemia was defined as any event reported by the patient as a symptomatic hypoglycaemia, regardless of the glucose level. Patients who answered the question 'Do you have symptoms when you have a low blood sugar measurement?' with 'never' or 'occasionally,' were said to have 'severely impaired' or 'impaired' hypoglycaemia awareness, respectively.

3 RESULTS

Ninety-nine % of patients with type 1 diabetes and 89% of patients with type 2 diabetes reported that they had experienced hypoglycaemia in their life. In addition, 30% of patients with type 1 diabetes and 27% of patients with type 2 diabetes reported impaired or severely impaired hypoglycaemia awareness.

At least one hypoglycaemic event (with or without measured glucose value) was self-reported in 84.1% and 56.4% of patients with type 1 and type 2 diabetes, respectively, during the prospective period of 4 weeks. 43.4% and 26.2% of patients with type 1 and type 2 diabetes, respectively, experienced a nocturnal hypoglycaemic event. In the same time-period severe hypoglycaemia was experienced by 15.9% and 7.1% of patients with type 1 and type 2 diabetes, respectively.

Estimated annual incidence rate of documented symptomatic hypoglycaemic events (with blood glucose 3.9 mmol/l or less), calculated from patient diaries in the prospective follow-up was 48 events (95% CI 43 to 53) and 11 events (95% CI 9 to 13) per patient-year in type 1 and type 2 diabetes, respectively. Also, estimated annual incidence rate of severe hypoglycaemia was 6 events (95% CI 4 to 8) and 1 event (95% CI 1 to 2) per patient-year in type 1 and type 2 diabetes, respectively. There were altogether 62 episodes of severe hypoglycaemia documented in 4 weeks period in 29 patients with type 1 and type 2 diabetes. Compared to type 2 diabetes, the percentage of patients experiencing severe hypoglycaemia was more than double in type 1 diabetes. Nocturnal hypoglycaemia was reported with an estimated annual rate 12 (95% CI 9 to 15) and 8 (95% CI 5 to 8) patient-years in type 1 and type 2 diabetes, respectively.

When asked about their definition of hypoglycaemia, only 40% of type 1 and of type 2 diabetes patients define hypoglycaemia depending on both, blood glucose measurement and symptoms, whereas 33% of type 1 and 37% of type 2 diabetes patients define hypoglycaemia only depending on the presence of symptoms. The mean blood glucose value below, which patients considered a glucose value to be a marker of hypoglycaemia, was 3.18 ±0.64 mmol/l and 3.41±0.83 mmol/l in type 1 diabetes and type 2 diabetes, respectively.

Differences on hypoglycaemia recall were noted when data on hypoglycaemia from the prospective and retrospective part of the study were compared, depending on diabetes type (Figure 1). Specifically, a large difference in recall was noted in the case of mild hypoglycaemia in type 1 diabetes patients, with significantly less hypoglycaemias reported by the patients from the past 4 weeks compared to prospective 4 weeks (37 vs.77 cases, p<0.001). There was a much smaller, but still statistically significant difference seen in type 2 diabetes, and mild hypoglycaemia reporting, with lower reporting for the past 4 weeks, compared to the prospective reporting (18 vs. 24 cases, p=0.027). Of note, in type 2 diabetes, there was also a difference in nocturnal hypoglycaemia reporting, but in the opposite direction, reporting more nocturnal hypoglycaemia in a retrospective time period (12 vs.6 cases, p=0.007).

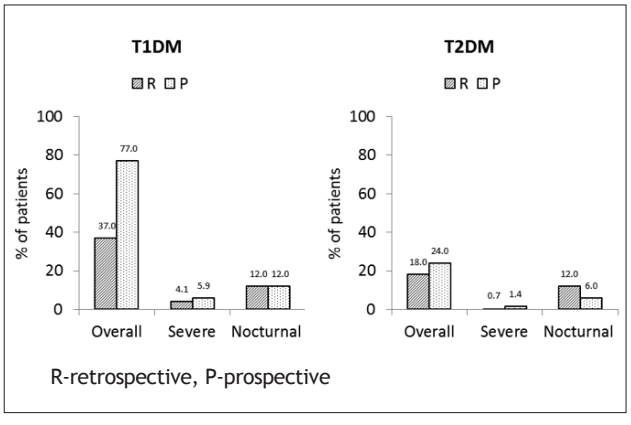

Figure 1. Hypoglycaemia incidence depending on the retrospective or prospective recall by patients.

Using a negative binomial model, adjusted for several factors, including duration of diabetes, age, hypoglycaemia awareness, and type of insulin therapy, we studied possible predictors of hypoglycaemia incidence. From all the variables studied, only fear of hypoglycaemia predicted severe hypoglycaemia incidence. Neither HbA1c, age, diabetes duration nor hypoglycaemia awareness were predictors of severe hypoglycaemia (Figure 2, Table 2).

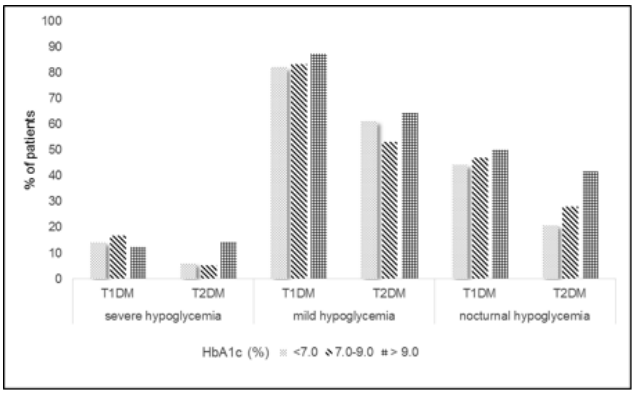

Figure 2. Hypoglycaemia incidence and HbA1c.

Table 2. Predictors of severe hypoglycaemia in a fully adjusted negative binomial model.

VARIABLES	HR	95% C.I.	P-VALUE
Age (years)	0.99	0.96, 1.02	0.556
Female gender	0.80	0.36, 1.78	0.585
HbA1c (%)	1.01	0.98, 1.04	0.441
Diabetes duration (years)	1.02	0.94, 1.11	0.594
Type of insulin therapy			
Short-acting (reference)	-	-	-
Long-acting	0.54	0.10, 3.07	0.489
Long and short-acting	0.70	0.21, 2.28	0.550
Mixed	NC	NC	NC
Other	0.36	0.08, 1.57	0.175
Blood glucose testing (per day)	1.08	0.84, 1.38	0.555
Hypoglycaemia unawareness	1.00	0.44, 2.24	0.996
Fear of hypoglycaemia	1.20	1.05, 1.37	0.009
Diabetes type 2	0.72	0.20, 2.67	0.627

NC-not calculable. Model adjusted for: age, gender, HbA1c at baseline, duration of diabetes, duration of insulin therapy, type of Insulin therapy, frequency of blood glucose monitoring, knowledge of hypoglycaemia, hypoglycaemia unawareness, fear of hypoglycaemia, period, diabetes type.

After experiencing hypoglycaemia in the prospective 4 weeks of the study, patient actions differed substantially between Type 1 and Type 2 diabetes, as represented in Figure 3.

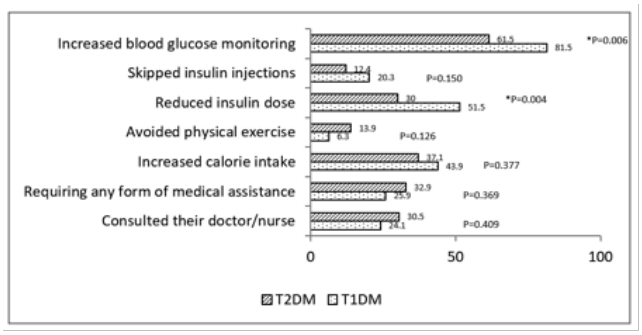

Figure 3. Actions resulting from hypoglycaemia in patients with Type 1 and Type 2 diabetes. (Statistically significant differences are marked with *).

4 DISCUSSION

This is the first study that reports hypoglycaemia incidence in a large cohort of insulin-treated patients with type 1 and type 2 diabetes mellitus in Slovenia. The self-reported rates of hypoglycaemia in this study are substantially higher than previously observed in other studies, especially in randomised controlled trials.

Hypoglycaemia is considered a major obstacle for optimal glycaemic control achievement in insulin-treated patients with diabetes. Moreover, a severe hypoglycaemia is strongly associated with a series of negative outcomes, including the increased risk of a major macrovascular event, as well as the increased risk of a cardiovascular or non-cardiovascular death (3,10). Therefore, prevention of severe hypoglycaemia is of central importance in delivering care to insulin-treated patients with diabetes. Interestingly, severe hypoglycaemia could not be predicted in our patients by any measured factor, including gender, diabetes duration, HbA1c, age, frequency of blood glucose measurement, or type of insulin therapy. The only factor that was significantly and independently associated with severe hypoglycaemia incidence in the fully adjusted multivariate model was greater fear of hypoglycaemia. Although from our model we cannot conclude that greater fear of hypoglycaemia was the direct consequence of severe hypoglycaemia experience in the past, it is the possible explanation, and in line with other studies (11, 12). Even more importantly, recognising fear of hypoglycaemia as a predictor of future severe hypoglycaemia gives us an important message – that addressing that fear by a tailored education we could potentially avoid severe hypoglycaemia.

The incidence of non-severe hypoglycaemia is not easily assessed in everyday life of insulin-treated patients, which is at least partly due to different levels of hypoglycaemia awareness. However, data on severe hypoglycaemia incidence is much more reliable (13). Nonetheless, in our study, severe hypoglycaemia incidence in type 2 diabetes was more than 20-times greater than, for example, in the ACCORD study (8), and more than 10-times greater than in the observational UK Hypoglycaemia study (6). In type 1 diabetes, on the other hand, difference in severe hypoglycaemia rate was smaller, but still 10-times higher in our study compared to the intensive arm of the DCCT trial (14), and almost 2-times higher compared to the UK Hypoglycaemia study (6). Not surprisingly, our data are very near to other real-world patient cohort studies (12, 15). Such a pronounced difference in hypoglycaemia incidence is likely due to the nature of the studies and study methodology. In other words,, results of our study reflect data on patients from the everyday practice, whereas patients with concomitant diseases, recurrent hypoglycaemia, or hypoglycaemia unawareness are usually excluded from randomised controlled trials. In addition, the incidence of severe hypoglycaemia was self-reported in our study, as experienced by the patients, and was not confirmed by means of patient medical files. Moreover, our patient population, especially with type 2 diabetes, was rather older and had, on average, diabetes for a substantially longer time period, compared to similar studies. The other important fact is also that the definitions of hypoglycaemia changed over the last years, even in the last few years (13, 16); however, the findings of our study go beyond the definitions and reveal what patients consider relevant for their everyday life with insulin.

However, comparing results from the Slovenian cohort to the recently published results of the study analysing hypoglycaemia incidence in more than 27,000 patients globally (9), the incidence of severe hypoglycemia in Slovenian type 1 diabetes was higher (5.9 vs. 4.9 events-patient-year) and in type 2 diabetes was lower (1.5 vs. 2.5 events-patient-year). The incidence of nocturnal hypoglycaemia in type 1 diabetes was similar in Slovenia and globally, whereas in type 2 diabetes, it was almost twice as common as elsewhere (6.4 vs. 3.67 events-patient-year) (9). Data on nocturnal hypoglycaemia is quite of a concern. Firstly, nocturnal hypoglycaemias can lead to sleep deprivation, lower quality of life, lower work performance, worse driving skills, etc. (17). Secondly, nocturnal hypoglycaemias are characterised by the lower intensity and recognizability of counterregulatory responses, thereby depriving individuals of the adequate stimulus to counteract hypoglycaemia. Therefore, nocturnal hypoglycaemias can pass by unrecognized and lead to lower hypoglycaemia awareness (18). Lastly, awakening response after nocturnal hypoglycaemia is lower and may affect the patient's ability to intake adequate amount of carbohydrates, especially in elderly people with possibly pre-existing cognitive impairment (17).

In type 1 diabetes, comparing prospective hypoglycaemia count with a retrospective recall, we detect a large discrepancy, especially in mild hypoglycaemia. Because it is a frequent event, patients probably consider it normal and devote less attention to it. However, the way the mild hypoglycaemia is perceived might be crucial to prevent hypoglycaemia desensitisation and even hypoglycaemia unawareness, often stemming from repetitive hypoglycaemia (19). A similar trend in mild hypoglycaemia was seen in our type 2 diabetes patients. However, in this group, reported past incidence of nocturnal hypoglycaemia was higher than in the prospective part of the study, possibly indicating that experience of nocturnal hypoglycaemia is more stressful than day hypoglycaemia, and leads to oversizing its appearance. Nocturnal hypoglycaemia, in particular, impacts one's sense of well-being because of its impact on sleep quality and quantity (20). Fear of hypoglycaemia, especially nocturnal one, may be one of the important reasons patients rather choose higher glycaemic targets (21).

From the DCCT trial, the association between lower HbA1c and higher hypoglycaemia incidence is well established (22). Yet, the results of our study underline that higher HbA1c values are not protective from experiencing hypoglycaemia, since hypoglycaemia was reported with similar frequency with low as well as with high levels of glycated haemoglobin. The association is easily understood with low levels of glycated haemoglobin, since frequent hypoglycaemias lower average glucose levels. On the other hand, it may be quite surprising to see that hypoglycaemias are no less frequent in patients with high glycated haemoglobin values. A possible explanation could be that patients experiencing hypoglycaemia deliberately lower insulin dose, as also reported in Figure 3 in our cohort of patients, or maybe even skip insulin application (23).

In our study, a very high average glycated haemoglobin value was reported, even substantially higher from the global report of the same study (9). If this value holds true, it is very alarming for the diabetes patient care in Slovenia, and definitely deserves further assessments. However, due to the study design, where data were not captured by patient medical files, but rather by a patient recall, there is a possibility that patients reported values of average plasma glucose concentration rather than glycated haemoglobin percentages. Similarly, we explain a very high reported percentage of continuous glucose monitoring usage in type 2 diabetes with misunderstanding of the meaning of the question. Furthermore, in this

study, we did not collect data on education level, which is, together with low socioeconomic status, a very well recognised factor associated with higher hypoglycaemia risk in patients with diabetes (13, 24, 25). This patient population could also comprise a large part of the group of non-responders. Unfortunately, we do not have exact data on them, since they did not complete any questionnaire. We observed that the non-respondent population is of two categories. One is a working population, which did not decide to participate in the study due to lack of time. For this group, we expect it to be of younger age and not to have increased the number of overall hypoglycaemia incidence. The second group is a group of patients who could not be included because of illiteracy or other issues resulting in the inability to complete the written questionnaire, like vision impairment and the lack of language understanding. We expect this group of patients to be even more vulnerable to hypoglycaemia and, if included, would be expected to further increase hypoglycaemia incidence reported in the study.

Despite some limitations of the design of the present study, this study design gives unique insights into the issue of hypoglycaemia through patient experience. In this way, new strategies can be employed that address this iatrogenic diabetes treatment complication more efficiently. Firstly, at the patient and the patient organisations level, the awareness of hypoglycaemia incidence should be raised, and instructions on the ways to decrease their occurrence should be given in a number of different formats, including visual and auditory message modes. In addition, fear of hypoglycaemia as a predictor of severe hypoglycaemia should be further addressed in the future studies as well as in routine clinical practice. Diabetes educators and medical doctors should become even more sensitised to the issue of high hypoglycaemia incidence, accurately assess it at every patient visit, and learn about the ways patients engage with them. Moreover, development of new treatment modules that include cognitive restructuring for addressing fear of hypoglycaemia should be welcomed. Furthermore, research with innovative methodological approach (26) and deep understanding of possibly preventable socioeconomic inequalities (27) could lead to a creation of patient-tailored, most probably region-specific approaches to deliver the maximally efficient education on hypoglycaemia for its prevention.

5 CONCLUSIONS

In conclusion, our study is the first comprehensive report on patient-reported hypoglycaemia incidence in Slovenian insulin-treated type 1 and type 2 diabetes patients that highlights several important aspects. Firstly, the incidence of hypoglycaemia, especially severe ones, is substantially higher than the ones reported from randomised controlled trials. Secondly, higher glycated haemoglobin values do not exclude high hypoglycaemia event rate. Thirdly, nocturnal hypoglycaemia needs special consideration in everyday management of insulin-treated patients, especially type 2. Fourthly, since factors associated with hypoglycaemia remained largely unidentified, especially in the context of the socioeconomic status, such as education level, addressing hypoglycaemia efficiently in the future calls for a much broader mixed research method approach, including qualitative research.

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CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

The study was approved by the Slovenian Ethics Committee, reference number 116/02/13.

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