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Original article

Impact of self-treated hypoglycaemia in type 2 diabetes: a multinational survey in patients and physicians

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Abstract

Objectives:
The objectives were to estimate the prevalence of self-treated hypoglycaemia in patients using basal insulin analogues; identify demographic, treatment related and behavioural risk factors; and describe patient and physician responses to these events.

Research design and methods:
The GAPP2 (Global Attitude of Patients and Physicians 2) study was an online multinational cross-sectional study of patients with type 2 diabetes currently treated with basal insulin, and healthcare professionals involved in the care of such patients. The primary variable of interest was *s*elf-treated hypoglycaemia within the last 30 days.

Results:
A total of 3042 patients treated with basal insulin analogues and 1222 prescribers completed the full survey. Overall, 36% of patients had experienced self-treated hypoglycaemia during the previous 30 days. In response to self-treated hypoglycaemia, patients reported missing (7%), reducing (11%) or mistiming (4%) basal insulin doses, increasing the level of glucose monitoring (40%) or utilising healthcare resources (7%). Patients reporting irregular basal insulin dosing by missing, mistiming or reducing a dose were also significantly more likely to report an episode of self-treated hypoglycaemia in the same time period: 41% versus 34% ($p=0.004$), 43% versus 33% ($p<0.001$), and 56% versus 32% ($p<0.001$) respectively. Nocturnal events worried significantly more patients than diurnal events (42% versus 23%, $p<0.001$). Patient worry about hypoglycaemia, insulin regimen and reduced basal dosing were identified as the key differentiating variables associated with increased risk of self-treated hypoglycaemic events. Most prescribers (76%) believed that insulin analogues minimised the risk of nocturnal hypoglycaemia when compared to NPH insulin; 46% also reported being contacted at least once a month by insulin analogue patients after self-treated hypoglycaemic events.

Conclusions:
Self-treated hypoglycaemia is common in approximately one third of patients using insulin analogue regimens. Additionally, self-treated hypoglycaemia was found to be associated with clinically significant effects on patient well-being and functioning, patient and physician management and healthcare utilisation despite the potential limitations of an online self-complete survey such as the need to be topic focused, the potential for under-reporting and social bias.

Introduction

Insulin is recognised as the most effective blood glucose lowering treatment in type 2 diabetes mellitus (T2DM)[1] and its initiation, historically the province of specialists, is increasingly being undertaken by primary care physicians[2,3].

Insulin is also widely considered to be the most challenging and time consuming diabetes management approach and self-treated hypoglycaemia, often referred to as minor hypoglycaemia, remains a key consideration[4,5]. The usual symptoms of hypoglycaemia include a pounding heart, trembling, hunger, sweating, difficulty in concentrating and confusion[6] and these minor hypoglycaemic episodes may precede events where patients are unable to treat themselves (severe hypoglycaemic events)[7].

The ongoing interruption to insulin usage related to hypoglycaemic episodes can create a barrier to optimal long-term glycaemic control of patients with T2DM[8–10], and is a substantial, independent cause of excess morbidity resulting in increased costs of T2DM for the patient, employers and society as a whole[8,9]. Additionally, self-treated hypoglycaemia can have a significant impact on diabetes management, patient functioning and productivity[8,9]. Patients who experience hypoglycaemia have been found to be more affected by their diabetes than those who do not experience these events, and often report lower general health indicating that a reduction of the symptoms of hypoglycaemia may be pertinent to improving patient well-being as well as providing potential cost reductions in overall diabetes management[11].

Self-treated hypoglycaemia is inadequately characterised in people with T2DM, most particularly those using insulin analogues. A broad link between hypoglycaemia and insulin adherence may be postulated; however, there is currently little specific data examining this potential association[12]. Moreover, while insulin analogue use is common and has been shown to lower the risk of hypoglycaemia, particularly nocturnal hypoglycaemia, compared to neutral protamine Hagedorn (NPH) insulin[13] as well as provide short-term cost effectiveness on the management of hypoglycaemia in a type 1 patient (T1DM) population[14], there is an absence of real world data specifically on the impact of insulin analogues on self-treated hypoglycaemia in T2DM. Further, there is no data on the relationship between these events and dosing irregularities which may either contribute to or be the result of these events.

The objectives of the current study were to estimate the incidence of self-treated hypoglycaemia in patients using basal insulin analogues; examine attributes of disease history and management including dosing irregularities, patient behaviours, and patient perceptions that may be associated with an increased incidence of hypoglycaemia and thus provide a clinically useful profile of patients at risk; and describe patients' and physicians', including primary care providers', responses to episodes of self-treated hypoglycaemia.

Methods

The GAPP2 (Global Attitudes of Patients and Physicians 2) survey was an online multinational, cross-sectional study of T2DM patients using insulin and physicians (specialists and GPs) managing this condition. The survey was conducted in the US, Canada, Japan, Germany, UK, and Denmark.

Survey development, structure and design

The items for the questionnaires for both patients and physicians were generated from multiple data sources: an international steering committee of diabetes clinical experts; the current literature on dosing irregularities and self-treated hypoglycaemia; and from identifying key concepts and themes from transcripts of nine previously conducted focus groups and interviews with diabetes patients. The content validity was based on prior focus group data.

Prior to the full launch, both surveys were pilot tested in a two-step process. First, both surveys were cognitively debriefed to ensure comprehension and readability by a small sample of pre-recruited respondents who completed the online survey in the presence of a native speaking researcher in each participating country. Minor edits to some items (that did not affect the question asked) were made at this stage, such as the inclusion of don't know/can't remember option or edits to specify the need for an answer in percentages rather than whole numbers. Second, after this refinement 50–100 respondents per country were then invited to each survey. After completing the first 10 surveys, the data and survey mechanism were tested for sense and logic, before invitations were distributed to other research panel members.

Questionnaires to patients (90 items) and physicians (58 items) were structured in the same way to ease between-population comparisons, covering demographics and background, diabetes management, self-treated hypoglycaemia and patient functioning and well-being. The patient definition of self-treated hypoglycaemia was: symptoms of low blood sugar such as sweating, weakness, trembling, and difficulty concentrating, which could be self-treated (for example by drinking a glass of juice, eating something, or taking a sugar pill); and the physician definition was: low blood sugar events that the patients can treat themselves, i.e. without medical assistance. When asked about their responses to self-treated hypoglycaemia patients were not asked whether they had or had not been advised to alter their insulin taking behaviour by a healthcare professional as the survey was intended to capture the patient perspective regarding their adherence behaviour. With regard to response after a hypoglycaemic event it was generally assumed that missed/mistimed basal doses would be considered against healthcare professional advice based on common clinical practice whereas reduced basal doses may often be considered in line with clinical recommendations.

The surveys were online self-complete questionnaires which used an adaptive question approach to minimise unnecessary questions and shorten completion times. Questionnaires were translated into the native language of respondents. Additionally, to minimise the impact of recall bias on patient responses, reporting of self-treated hypoglycaemia was focused on events occurring during the last 30 days and respondents were also offered a 'don't know' answer to avoid forcing inaccurate responses.

Recruitment

Participants were recruited from pre-existing general public and healthcare professional online research panels. These panels were identified via an independent research company (Bryter Limited) who contracted commercial research panels such as Research Now, GMI/Lightspeed and WorldOne etc. The panels were comprised of a representative sample of the online population as a whole for each country in order not to bias the sample to any particular demographic group or respondent profile. Members were recruited from a broad array of online and offline approaches that best represent the local online community as a whole within each country. Recruitment techniques include banner placements on websites, email campaigns, online advertising, blogs, social media, referrals through existing panel members, affiliate marketing (including TV/print) and text (SMS) mobile campaigns.

The healthcare professional research panel consists of more than 600,000 members in the countries surveyed. Physicians were contacted by email and provided with a unique uniform resource locator (URL) enabling entry to the online survey. Invitations were initially targeted by pre-registered speciality. Physicians responding to the invitation were then screened to ensure they met the entry criteria in terms of minimum number of years qualified within their current speciality (two years), minimum number of T2DM patients seen in a typical month (20 for primary care physicians (5 in Denmark and Japan) and 40 for diabetes specialists (20 in Denmark and 30 in Japan) to reflect the national situation, of which at least 10 must have been treated with insulin analogues (10 every 3 months in Denmark and Japan). Incentives equivalent of £1 to £3 per minute were offered in line with local rules and regulations, which were often non-monetary.

Patient participants were recruited from established online general population research panels with over 6.5 million members within the countries surveyed. Potential patients were initially contacted on the basis of previous survey evidence of diabetes and age. To be eligible for survey inclusion, patients were required to have been diagnosed with T2DM by a healthcare professional, be aged 40 years or more and to have been diagnosed as having T2DM over the age of 40 (self-report). Patients had to be currently treated using insulin medication, excluding those using premix insulin treatments, those on bolus only insulin or those using insulin pumps. Respondents meeting these entry criteria were also asked whether their insulin(s) were cloudy in appearance to differentiate between basal insulin analogues and NPH. Specific product names were not collected.

Statistical analysis

The primary variables reported in this paper focus on self-treated hypoglycaemia and its impact on T2DM management. Patient reported variables included: self-treated hypoglycaemia (frequency, day-time/night-time), reported behaviour in response to self-treated hypoglycaemia including basal insulin dosing irregularities (missed, mistimed [defined as dosing ±2 hours from the prescribed time in the respondents' judgement] and/or reduced doses), impact on healthcare resource utilisation and patients' attitudes to self-treated hypoglycaemia and their impact on patient functioning and well-being.

Prescriber reported variables included: healthcare utilisation in response to self-treated hypoglycaemia, insulin initiation behaviour due to self-treated hypoglycaemia risk, and clinician response to patient-reported self-treated hypoglycaemia.

Data were stored in compliance with the UK Data Protection Act (1998) on secure servers and each respondent was issued with a unique URL, which could be used once to access the questionnaire. Collected data from the survey was stored by the research company separately from any personal or contact information and electronic data was de-identified with respondents identified by study ID (RESPID) only. Investigators did not have access to any respondents' personal details and data was analysed on an aggregated level.

All data were logic tested to ensure that respondents did not provide contradictory answers and data identified electronically as being incomplete (defined as responses that did not reach the end of the survey) was collected but not processed or included in analysis. Responses to the survey were not checked against patient records or direct observations.

Data was descriptively analysed using mean and range or standard deviation (as stated) for continuous data and frequency (percentage) for categorical variables. Group comparisons were made using the unpaired *t*-test or Pearson's chi square test, where appropriate. Significance was set at alpha = 0.05. Outliers were defined as values lying more than 1.5 interquartile ranges (IQRs) below the first quartile or above the third quartile; and in instances where outlying values exhibited a large degree of influence on the parameter of interest (as assessed by

Cook's distance), these values were removed from the analysis.

Chi-squared Automatic Interaction Detection (CHAID) analysis[15] was employed to identify combinations of patient characteristics most highly associated with the incidence of self-treated hypoglycaemia. CHAID evaluates all of the values of potentially associated variables using a decision tree format. Values that are judged to be statistically similar with respect to the target variable are merged and dissimilar variables are maintained. The most strongly associated variable, differentiating patients at higher risk from those at lower risk, is then selected to form the highest branch in the decision tree and this process continues recursively until completion of a decision tree. The CHAID tree branches show the proportion of total events (top section of the boxes) and proportion of patients (bottom section of the boxes).

In order to construct the decision tree, factors from the survey were grouped according to four conceptual domains to provide a structure and informed analysis framework: (1) disease history and management (duration of diabetes, diabetes specific co-morbidity, non-insulin antidiabetes treatments, duration of insulin therapy, insulin regimen, current method of basal insulin administration, number of insulin injections per day, and number of visits to a healthcare professional in the last 12 months); (2) patient behaviours (missed, mistimed or reduced basal insulin doses in the last 30 days; (3) patient perceptions (perceived diabetes control, basal insulin inconvenience, and the extent to which basal insulin interferes with lifestyle and activity, patient satisfaction with current basal insulin treatment, patient comfort with taking insulin, patient guilt or worry about missed doses, patient downplaying or hiding missed doses from healthcare professionals, worry about hypoglycaemia; and (4) patient attributes (age at diagnosis, current age, gender, BMI, current working situation, educational level, lifestyle activity and eating meals at regular times). Hypoglycaemia was defined as an ordinal outcome with three possible outcomes: no events (0), one to three events in the previous 30 days (1), and four or more events in the previous 30 days (2). Bonferroni adjustment was used to correct for the number of different ways that the categories in a single predictor variable can be merged.

Results

Participants and demographics

A total of 1,034,363 individuals (from general population research panels) were invited to participate in the patient survey, of which 101,449 responded and were screened (response rate 9.8%). These general population respondents produced 13,057 eligible patients who met the prespecified entry criteria, of whom 3587 eligible respondents went on to complete the full survey (Figure 1). A total of 36,240 healthcare professionals were invited to participate in the survey, of whom 5115 responded and 1653 completed the study (Figure 1). In this paper, data are presented on 3042 T2DM patients taking insulin analogues and 1222 physicians. No outlier values were identified in reported variables.

Patient and prescriber demographics are summarised in Table 1.

Incidence of self-treated hypoglycaemia

Overall, 36% of respondents had experienced self-treated hypoglycaemia during the previous 30 days, 30% experiencing a daytime event and 13% a nocturnal event (Table 2). Patients using more complex regimens (basal and bolus insulin regimens) were more likely to have reported self-treated hypoglycaemia, with a greater proportion of these patients also reporting having five or more self-treated episodes (Table 3).

Patient reported impact of self-treated hypoglycaemia on diabetes management

Patients reported responding to self-treated hypoglycaemic events. Seven percent of patients said that they had missed, 11% said they had reduced and 4% said they had mistimed their basal insulin dose. Additionally, 40% said that they had increased their level of glucose monitoring. A small proportion of patients (7%) reported utilising healthcare resources available to them (Table 4).

Patients who reported dosing their basal insulin irregularly by missing, mistiming or reducing a dose were also significantly more likely to report an episode of self-treated hypoglycaemia in the same time period (41% versus 34% ($p = 0.004$), 43% versus 33% ($p < 0.001$), and 56% versus 32% ($p < 0.001$) respectively.

Furthermore, to reduce their risk of nocturnal hypoglycaemia, patients reported that they had intentionally let their blood glucose go high (14%) or had not taken their insulin as prescribed (16%).

Patient reported impact of self-treated hypoglycaemia on functioning and well-being

Self-treated hypoglycaemia also had a substantial effect on patient functioning and well-being. In particular, it impacted negatively on patients' ability to focus and concentrate, or carry out spontaneous activities, such as playing sport/exercising or changing plans (Figure 2). Patients were especially concerned about experiencing a hypoglycaemic event where they had no easy access to food or drink, or while sleeping or driving. Nocturnal events also worried significantly more patients than

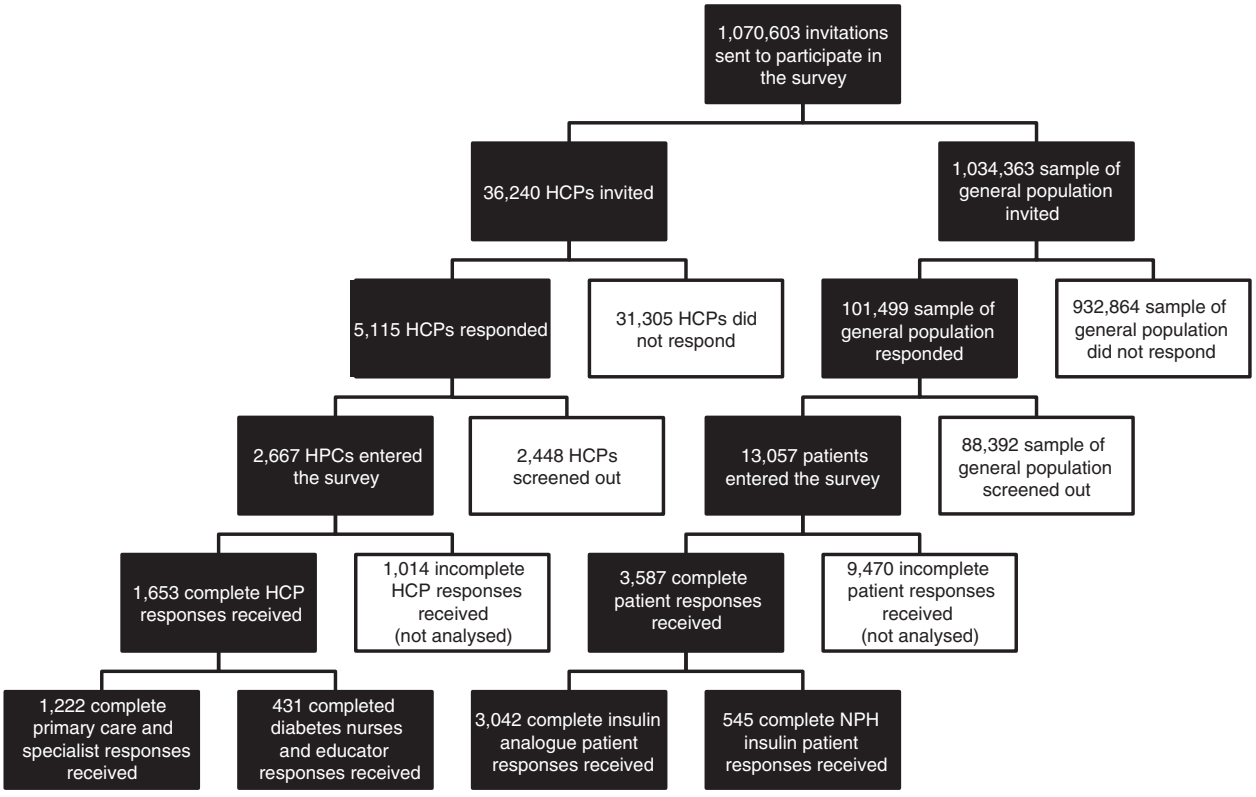

Figure 1. Patient and healthcare professional survey recruitment flow diagram.

diurnal events (42% versus 23%, $p<0.001$) with 69% saying they worried to some degree and over half (57%) being concerned about the potential negative impact of nocturnal events on their long-term health.

Physician reported impact of self-treated hypoglycaemia on diabetes management

When questioned about their beliefs about currently available insulin therapies, the prescriber cohort believed that insulin analogues minimised the risk of hypoglycaemia when compared to NPH insulin: 76% agreed insulin analogues were better at minimising the risk of nocturnal hypoglycaemia and 71% agreed insulin analogues were better at minimising diurnal hypoglycaemic events.

Physicians reported an impact of self-treated hypoglycaemia on resource utilisation and disease management: 46% of physicians reported being contacted at least once a month by insulin analogue patients after these events. Additionally, 83% of physicians reported that they considered hypoglycaemic risk when choosing the type of insulin on which to initiate patients and 56% started patients on a lower insulin dose than recommended due to risk of hypoglycaemic events. Physicians reported that on most occasions they advised patients who had a number of hypoglycaemic episodes to increase their blood glucose monitoring (29%), temporarily reduce their basal insulin dose (19%), reduce basal insulin long-term (15%) or split their basal insulin dose (3%) (Figure 3).

CHAID analysis: patient characteristics associated with a greater likelihood of experiencing self-treated hypoglycaemia

As shown in Figure 4, the amount of worry about hypoglycaemia (as defined by the number of situations that patients reported worrying about these episodes) was identified as the variable most individually associated with the number of hypoglycaemic events, and was therefore the primary differentiator in the top branch in the CHAID tree. In contrast, those who did not worry (worried about 0 situations) were shown to be at the least risk of hypoglycaemia.

For patients with only minor worry (worry in 1–3 situations) their hypoglycaemia risk profile was greatest if they reduced their basal insulin dose regardless of insulin regimen or if they were on a basal only regime and had not reduced a basal dose. Those with moderate worry (worry in 4–5 situations) were more likely to have self-treated hypoglycaemia if they had reduced a dose of basal insulin or if they were female and had not reduced a basal dose in the last 30 days. In those patients with the most worry (6–9

Table 1. Patient and prescriber demographics.

	Global	USA	Canada	Japan	UK	Denmark	Germany
PATIENTS							
Base (*n*)	3042	1850	156	355	322	57	302
Age (years)	61 (8.12)	62 (7.63)	60 (8.26)	57 (8.12)	60 (8.63)	62 (8.27)	57 (7.75)
Male (%)	59%	50%	54%	85%	67%	65%	70%
Duration of diabetes (years)	11 (6.70)	12 (6.56)	12 (8.05)	10 (6.87)	11 (6.45)	11.7 (6.47)	9 (5.94)
BMI (kg/m^2)	34 (19.22)	36 (19.37)	38 (30.75)	26 (13.71)	32 (17.84)	35 (33.89)	32 (7.42)
Number of diabetes complications (13 listed) – median (range)	2 (0–13)	2 (0–10)	2 (0–11)	1 (0–13)	3 (0–10)	3 (0–8)	3 (0–9)
Duration of insulin treatment (years)	5 (4.44)	5 (4.46)	5 (4.92)	5 (4.28)	5 (4.28)	7 (5.80)	5 (4.03)
Insulin regimen							
Basal only	48%	51%	50%	43%	52%	51%	33%
Basal–bolus	52%	49%	50%	57%	48%	49%	67%
Number of basal injections per day	1.3 (1.21)	1.3 (1.04)	(1.3 (0.57)	1.3 (0.75)	1.3 (0.69)	1.4 (0.77)	1.7 (2.60)
Injection device basal insulin (%)							
Prefilled pens	61%	54%	47%	90%	77%	77%	53%
A vial and syringe	33%	49%	8%	6%	5%	12%	14%
Refillable pens	11%	2%	49%	7%	20%	12%	41%
Education							
Some high school	3%	1%	1%	2%	14%	5%	5%
High school graduate	23%	21%	14%	32%	22%	14%	32%
Some college (no degree)	23%	29%	17%	17%	12%	5%	8%
College (degree)	37%	35%	34%	49%	43%	63%	36%
Masters/PhD/post doctorate	13%	14%	34%	-	7%	6%	17%
Working (%)	36%	28%	40%	65%	33%	32%	44%
Living alone (%)	22%	23%	29%	11%	21%	21%	26%
Perceived diabetes control (%)							
Poor	10%	10%	7%	21%	6%	4%	5%
Moderate	56%	58%	54%	64%	53%	39%	39%
Good	34%	32%	38%	15%	41%	58%	56%
PHYSICIANS							
Base (*n*)	1222	311	202	222	208	70	209
Time since qualified (years)	17 (8.17)	17 (7.66)	21 (8.46)	16 (8.54)	14 (7.27)	18 (9.39)	14 (6.32)
Specialty							
Primary care	55%	51%	79%	40%	50%	73%	51%
Specialist	45%	49%	21%	60%	50%	27%	49%
Average number of insulin treated patients with T2DM aged 40+							
Primary care	67 (63.42)	89 (67.44)	80 (73.29)	27 (21.30)	70 (60.30)	26 (15.93)	73 (59.91)
Specialist	147 (112.02)	165 (101.48)	130 (81.01)	113 (125.68)	130 (89.05)	69 (28.87)	197 (126.41)
Percentage of insulin treated patients with T2DM using analogue insulin (%)	73%	79%	65%	82%	70%	67%	65%
Type of insulin analogues used (%)							
Basal–bolus taken separately	31%	34%	32%	27%	28%	19%	34%
Premix	22%	15%	20%	33%	27%	30%	17%
Bolus only	11%	8%	10%	13%	10%	5%	15%
Basal only	36%	42%	38%	27%	35%	47%	33%
Other	0%	0%	0%	1%	0%	0%	1%

Table 2. Self-treated hypoglycaemia frequency in the last 30 days.

	Global	US	Canada	Japan	UK	Denmark	Germany
Effective base (*n*)	2918	1777	153	347	308	52	281
Self-treated hypoglycaemia (%)							
Incidence (events/last 30 days)	3.1 (1–30)	3.2 (1–30)	3.7 (1–10)	2.7 (1–8)	2.7 (1–20)	2.1 (1–4)	3.4 (1–14)
Patients with at least one event (*n*)	36% (1042)	38% (676)	33% (51)	27% (95)	37% (114)	38% (20)	31% (86)
5+ times in past 30 days (*n*)	6.8% (197)	7.3% (129)	9.2% (14)	5.5% (19)	4.5% (14)	0% (–)	7.5% (21)
Daytime self-treated hypoglycaemia (%)							
Incidence (events/last 30 days)	2.3 (0–25)	2.3 (0–25)	2.6 (0–10)	2.5 (0–8)	1.9 (0–18)	1.8 (0–4)	2.5 (0–12)
Patients with at least one event (*n*)	30% (888)	32% (563)	29% (45)	27% (92)	31% (94)	35% (18)	27% (76)
5+ times in past 30 days (*n*)*	4.1% (119)	4.3% (77)	5.2% (8)	3.5% (12)	2.9% (9)	0% (–)	4.6% (13)
Nocturnal self-treated hypoglycaemia (%)							
Incidence (events/last 30 days)	0.8 (0–15)	0.9 (0–15)	1.1 (0–6)	0.2 (0–2)	0.7 (0–15)	0.3 (0–2)	0.9 (0–5)
Patients with at least one event	13% (390)	15% (267)	16% (24)	5%(16)	14% (43)	10% (5)	12% (35)
5+ times in past 30 days (*n*)*	1.1% (34)	1.5% (26)	1.3% (2)	0% (-)	0.3% (1)	0% (-)	1.8% (5)

Incidence is provided as mean (range).
*Proportions for 5+ events may not add to the total as patients may have reported a mixture of daytime and night-time events in a 30 day period which would therefore not be included in these sub-sets.

Table 3. Self-treated hypoglycaemia in the previous 30 days, by insulin regimen.

	Basal insulin only	Basal and bolus insulin	*p* value
Effective base (*n*)	**1400**	**1518**	
Self-treated hypoglycaemia (%)			
Incidence (events/last 30 days)	2.9 (1–20)	3.2 (1–30)	
Patients with at least one event	25% (355)	45% (687)	<0.0001
Patients with ≥5 events (*n*)	4% (56)	9% (141)	<0.0001
Daytime self-treated hypoglycaemia (%)			
Incidence (events/last 30 days)	1.9 (0–12)	2.5 (0–25)	
Patients with at least one event	20% (277)	40% (611)	<0.0001
Nocturnal self-treated hypoglycaemia (%)			
Incidence (events/last 30 days)	1.1 (0–15)	0.7 (0–12)	
Patients with at least one event	10% (140)	16% (250)	<0.0001

Incidence is provided as mean (range).

Table 4. Behaviours in response to self-treated hypoglycaemia, and utilisation of healthcare resources in past 30 days.

	Reporting of self-treated hypoglycaemia
Behavioural Response	
Base (*n*)	1042
Missed Doses	
Proportion of patients	7%
Number of missed doses	2 (1–10)
Mistimed Doses	
Proportion of patients	4%
Number of mistimed doses	1.8 (1–4)
Reduced Doses	
Proportion of patients	11%
Number of reduced doses	2.4 (1–16)
Increased level of blood glucose monitoring	40%
Healthcare Utilisation	
Unplanned trip to see a GP/PCP	2%
Unplanned trip to see a diabetes specialist	1%
Unplanned trip to a hospital emergency department	<1%
Emailed a healthcare professional e.g. your doctor	1%
Searched for information/advice online	3%
Contacted another patient with diabetes for information/advice	1%

Continuous variables are provided as mean (range).
GP: general practitioner; PCP: primary care practitioner.

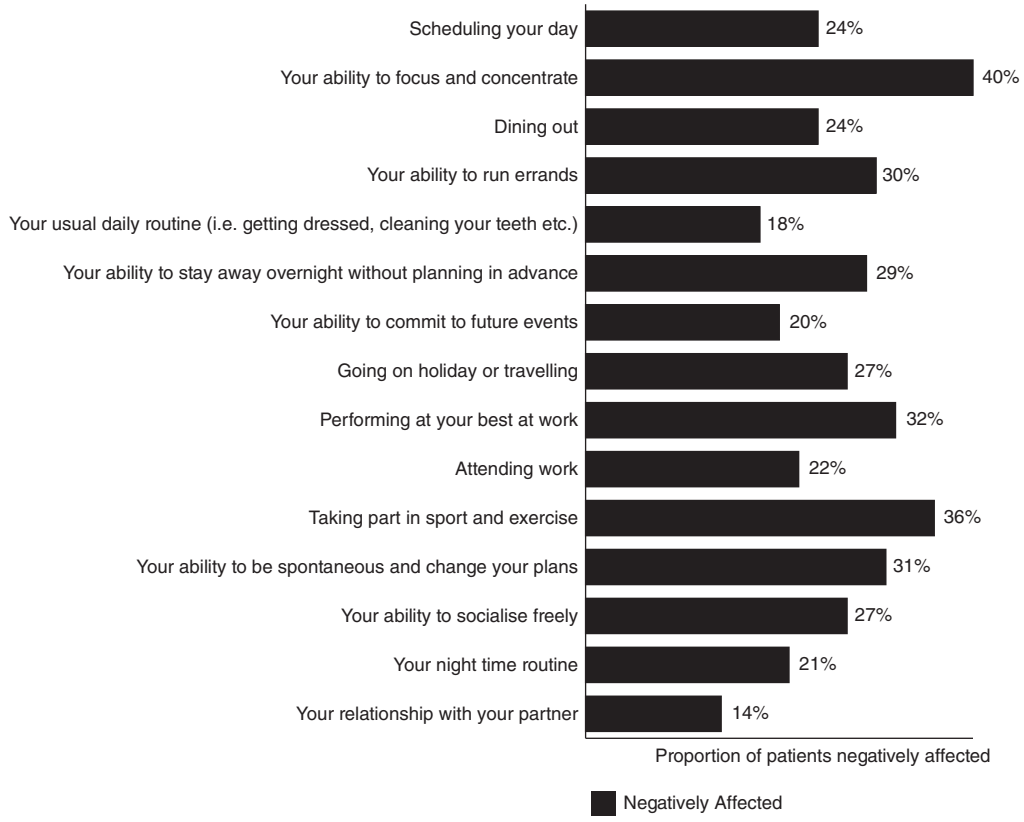

Figure 2. The effect of self-treated hypoglycaemia on patient well-being and function.

situations) the characteristics that defined those at risk of increased risk were the use of a basal–bolus regimen regardless of gender or the use of a basal only regimen with insulin injection dissatisfaction. The group at most risk (defined by the ratio of the proportion of reported hypoglycaemic events to the population proportion) were those who reported moderate worry and a reduced basal insulin dose in the last 30 days. This group of patients represented 1.9% (57 patients) of the patient sample but accounted for 5.4% of all reported episodes of self-treated hypoglycaemia.

When considering all of the characteristics entered in to the CHAID analysis, the profile of patients who are at increased risk of self-treated hypoglycaemia are those patients who expressed worry about hypoglycaemia, are on more complex regimens, admit to reducing their basal insulin dose (regardless of regimen), or are dissatisfied with their insulin treatment. While these at risk patients comprise 38.2% of the surveyed population they accounted for 65.8% of all events.

Discussion

Patient reported self-treated hypoglycaemia remained common despite treatment with basal insulin analogues, and was associated with reduced patient functioning, well-being and treatment interference.

The level of self-treated hypoglycaemia reported in this paper is similar to that seen in other studies[13,16]. T2DM patients have been shown to experience an average of 16 hypoglycaemic events per year[17], and a recent survey reported that over a third of patients had at least one daytime, non-severe hypoglycaemic event in the last month[6]. In addition, because as few as ten symptomatic non-severe hypoglycaemic episodes per year may be considered clinically relevant (increasing with the frequency of episodes)[18], the incidence of self-treated hypoglycaemia reported in the study is believed to be at a clinically significant level. This serves to reinforce the importance of hypoglycaemia in the management of T2DM patients, even in those using basal insulin analogues.

Moreover, the study found that patients using basal–bolus insulin regimens were more likely to experience self-treated hypoglycaemia, which is in line with the fact that T2DM patients are likely to have to intensify their insulin regimen as β-cell function declines. This leads to a closer resemblance to the pathophysiology, and hence hypoglycaemia rate, of insulin replacement in T1DM as opposed to insulin supplementation in early T2DM[17,19].

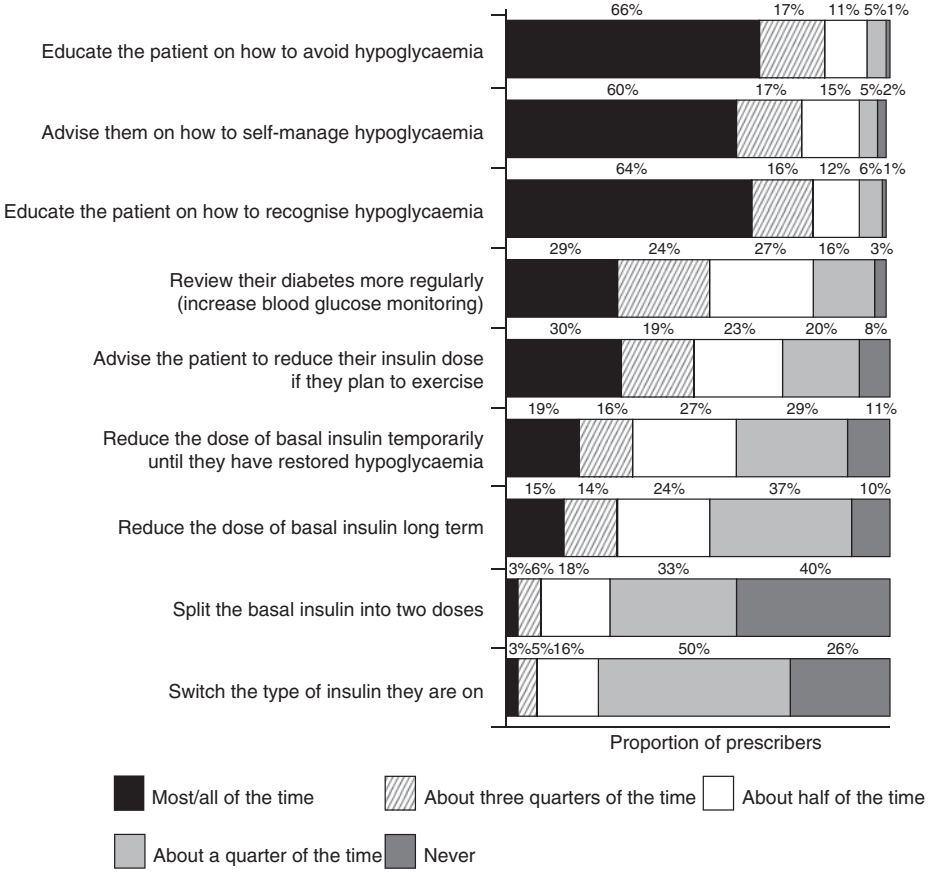

Figure 3. Physician reports of recommended management approach for patients who experience self-treated hypoglycaemia.

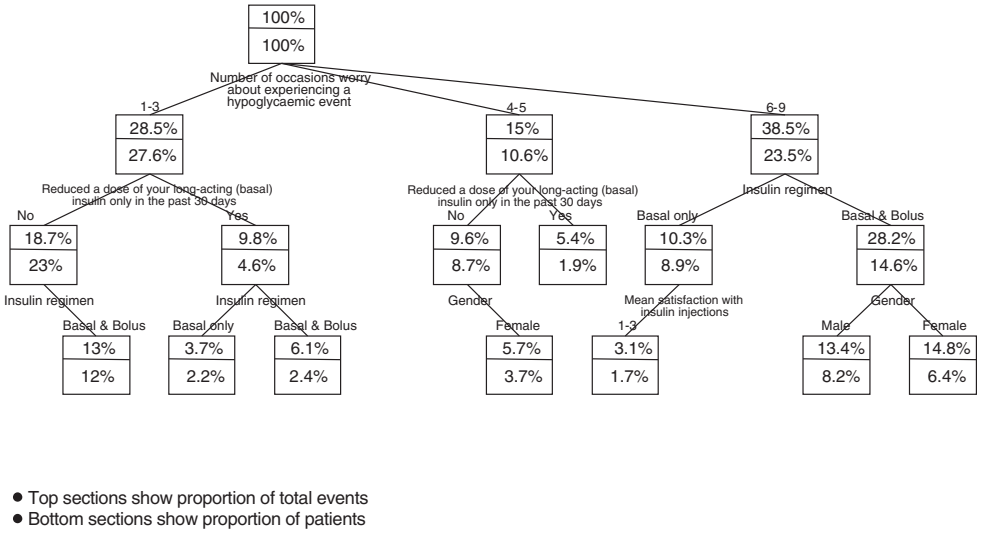

Figure 4. The CHAID tree showing combinations of patient characteristics that are associated with increased risk of self-treated hypoglycaemia in the last 30 days.

Findings from this study also indicate that self-treated hypoglycaemic events affect diabetes management behaviours for both patients and physicians. Patients reported both adjusting their basal dosing and increasing their blood glucose monitoring in response to a self-treated hypoglycaemic event. In addition, patients reported that on some occasions they did not dose their basal insulin as prescribed, as a preventative measure to avoid

nocturnal hypoglycaemia. The statistically significant association between patients who missed, mistimed and reduced basal insulin doses and those who experienced self-treated hypoglycaemia, and the results of the CHAID analysis, reinforce the directly reported impact of self-treated hypoglycaemia on diabetes management.

Furthermore, despite the growing consensus amongst clinician respondents to the study on the benefits of insulin analogues compared to NPH in T2DM in terms of the minimisation of hypoglycaemia risk, physicians reported that they considered the risk of hypoglycaemia when choosing which insulin to initiate in their patients, and over half started patients at a lower than recommended dose. These data support previous findings that physicians would treat patients more aggressively if they were not concerned about hypoglycaemia, as they believe that their patients do not have adequate glucose control[20].

These results are in agreement with the prior findings that 43% of T2DM patients modify their insulin dose after a mild or moderate hypoglycaemic episode[21], and that some patients modify their blood glucose levels by manipulating their insulin dose due to fear of hypoglycaemia[10]. However, it is unclear from our results whether the significant association between reported dosing irregularities and self-treated hypoglycaemia was driven by dosing adjustments as a precipitator (inappropriate dose reduction due to fear of subsequent event) or as a consequence of a self-treated hypoglycaemic event. Post-event adjustments may, in some instances, be appropriate given that a substantial number of clinicians in our study reported that they would recommend a reduction of basal insulin dose (short or long term) or a splitting of basal insulin administration in response to self-treated hypoglycaemia. This management approach by clinicians also reflects guideline recommended trade-offs between glycaemic control and hypoglycaemia[22].

This study confirmed previous findings that a proportion of patients utilise healthcare services as a consequence of self-treatable hypoglycaemia[8]. These patient reports of healthcare utilisation were substantiated by prescriber feedback on contacts to them triggered by self-treated episodes. This resource utilisation has the potential to lead to an increased cost in diabetes management, which is already a large burden on international healthcare systems[6,8,11].

Further, the present study also confirmed findings that self-treated hypoglycaemia impacts patient functioning, lifestyle and well-being. The results of our CHAID analysis point to a primary association between higher levels of self-treated hypoglycaemia and patient worry about these events. This is likely to relate to the increased worry experienced by patients who are having more hypoglycaemic events and aligns with previous findings that over 29.9% of patients who have experienced a mild or moderate hypoglycaemic event are more fearful about future episodes[10]. In particular, nocturnal events caused more people to worry than diurnal events and over half of patients were concerned about their potential impact on long-term health. The nocturnal hypoglycaemia and the concern caused by these events affected patients' usual daily functioning. This aligns with previous research which has shown that during the time spent recovering from a single non-severe (self-treated) hypoglycaemic event (which can be up to several days), patient functioning and diabetes management are both negatively affected[8].

Implications for clinical practice

There is a strong need to raise awareness about hypoglycaemia so that all patients are able to recognise and deal appropriately with this common complication of insulin treatment, as well as a need to help identify subsets of patients particularly at risk. The higher level of patient worry and deliberately reported dosing modification behaviour associated with nocturnal hypoglycaemia also warrant particular clinical focus. While some of the associated risk factors may be modifiable through appropriate increases in education and social support, some may involve consideration of the prescribed insulin regimen. Given their higher risk of self-treated hypoglycaemia, patients who have expressed worry about hypoglycaemia, those on more complex regimens, those who admit to reducing their basal dose (regardless of insulin regimen), and those who have expressed dissatisfaction with their insulin treatment (regardless of regimen) should be proactively approached around the topic of hypoglycaemia to establish the frequency and impact of these events with a view to mitigating their potential impact on diabetes management.

Limitations

This study was not designed to examine country specific differences; however, self-treated hypoglycaemic events were reported by patients regardless of country of origin, gender or insulin regimen (basal only or basal and bolus). Further study is needed to better understand these influences such as the potential role of cultural influences and differing healthcare systems.

Additionally, the survey was designed to focus on self-treated hypoglycaemia and basal insulin dosing irregularities in T2DM and as such did not provide an exhaustive list of patient behaviours and characteristics for consideration as part of the CHAID analysis. This means that some key influences on the risk of self-treated hypoglycaemia may have been missed such as typical diet and frequency of blood glucose monitoring[23].

It is also likely that dosing irregularities relating to self-treated hypoglycaemia are underestimated in our

dataset for several reasons. The surveys were self-completed and reported basal dosing irregularities that were based on patient judgement which may have led to incorrect classifications. Additionally, recall bias may have led to an underestimation of dosing irregularities particularly when considered with the social bias against admitting potentially inappropriate medication taking behaviour. However, attempts were made to mitigate these factors, definitions were always provided in the survey whenever dosing irregularities were reported, data is presented focusing on a 30 day period only and patients were informed that results were confidential and were aware that the data would not be shared with their physician.

Finally, the study was conducted via the internet which may introduce certain biases particularly given that online surveys select for respondents with internet access. While the response rate may seem low, the respondents were targeted via general population research panels which recruit participants in order to be representative of the online community and not through patient specific channels. Therefore, the response rates seen in the survey were in line with initial estimations used as part of the sample size calculations. However, we acknowledge that this methodology may lead to over-representation of some key groups, for example a slightly younger overall age group (although the average in this cohort was 61 years), those still in employment and those living in non-isolated situations. It is also the case that the impact of the online nature of the survey may vary by country. However, this bias was considered minor as computer access and familiarity are now very widely available within the participating countries.

Conclusions

Self-treated hypoglycaemia is common in approximately one third of patients using insulin analogue regimens and is associated with clinically meaningful effects on patient well-being and functioning, patient and physician management and healthcare utilisation. In response to self-treated hypoglycaemia many patients increase their blood glucose monitoring and some adjust their basal insulin dosing. Additionally, nocturnal episodes of hypoglycaemia, which worry more patients than diurnal events, also lead some people to keep their blood glucose at a higher than appropriate level or adjust their basal insulin dosing to proactively avoid events.

Research to further characterise patient attributes that increase the risk of hypoglycaemia, including the association between self-treated hypoglycaemia and dosing irregularities established by these results, is required. Despite clinical awareness of hypoglycaemia, T2DM patients using insulin analogues still need further support to reduce rates of hypoglycaemia and improve their self-management of hypoglycaemia risk.

Transparency

Declaration of funding

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Declaration of financial/other relationships

M.B. and A.H.B. have received consulting fees and support for travel to meetings from Novo Nordisk in association with the GAPP2 study. A.R. is an employee of Novo Nordisk A/S.

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