Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro

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Aim: To identify factors associated with nocturnal hypoglycaemia in patients with type 2 diabetes who were new (< 2 months therapy) to insulin therapy.
Methods: A randomised, multicentre, 12-month parallel open-label study compared the clinical safety and efficacy of insulin lispro with regular human insulin. A cohort of North American patients completed a health-related quality of life (HRQOL) questionnaire which included questions related to the Health Beliefs Model (HBM). Measurements of hypoglycaemia rate and short-and long-term glucose control assessed clinical safety and efficacy. Three hundred and sixty-five type 2 diabetic patients were enrolled in the study, and 195 North American patients completed the HRQOL questionnaire.
Results: After adjustment for demographic and psychological factors, the study population demonstrated lower nocturnal hypoglycaemia risk with insulin lispro. Higher nocturnal hypoglycaemia risk was associated with reduced body mass index (b.m.i.), lower age, and basal ultralente insulin therapy. The associated hypoglycaemia risk was lower with increased alcohol consumption. Patients who completed the HRQOL survey demonstrated higher risk for nocturnal hypoglycaemia if they: (1) had more troublesome hyperglycaemia symptoms in the week before starting insulin; (2) were more confident in their ability to control their diabetes; or (3) thought that diabetes control did not offer a clear health benefit. Nocturnal hypoglycaemia risk was inversely associated with fear of hypoglycaemia.
Conclusions: Type 2 diabetic patients new to insulin therapy demonstrated lower risk of nocturnal hypoglycaemia with insulin lispro. Practitioners should consider patient characteristics and psychological factors that may predispose type 2 diabetes patients to nocturnal hypoglycaemia when initiating insulin therapy.

Keywords: type 2 diabetes mellitus, regular human insulin, insulin lispro, nocturnal hypoglycaemia, quality of life, health beliefs model
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Introduction

Compelling evidence has shown that intensive diabetes mellitus therapy, with near normalisation of haemoglobin A_{1c} may delay the onset and slow the progression of diabetic retinopathy, nephropathy, and neuropathy. Long-term prospective clinical trials to be the only therapy to reduce these complications in patients with type 1 and type 2 diabetes [1,2]. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated

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significant reductions in risk of complications for patients with type 2 diabetes initially randomised to oral hypoglycaemic agents or insulin [3,4]. In the UKPDS study many patients who were originally randomised to oral agents later required insulin to maintain adequate glycaemic control [3]. The most common complication of intensive diabetes therapy, hypoglycaemia, presents a potential barrier to implementation of insulin therapy [1,5]. Avoidance of hypoglycaemia is an important goal in diabetes care for all patients.

Hypoglycaemia during sleep, or nocturnal hypoglycaemia, may lead to neuroglycopenic symptoms such as hemiparesis, organic personality syndrome, and a syndrome masquerading as senile dementia [6]. The patient's ability to recognise nocturnal hypoglycaemia symptoms may be impaired by sleep, thus complicating treatment. The fear of nocturnal hypoglycaemia may be a patient's greatest impediment to implementation of an intensive insulin regimen [7].

Several investigations have targeted severe hypoglycaemia in type 1 diabetes patients. However, the risk factors associated with hypoglycaemia in type 2 diabetes patients have not yet been well identified [5,8]. Patients with type 2 diabetes account for more than 90% of the population with diabetes, and while hypoglycaemia occurs less frequently in this group, mild to moderate hypoglycaemia is not uncommon [9,10]. In this study we: (1) focus on patient demographic characteristics and other factors associated with nocturnal hypoglycaemia; (2) analyse the association between four questions in the health-related quality of life (HRQOL) questionnaire that are similar to the Health Beliefs Model (HBM) and the risk of nocturnal hypoglycaemia in patients from North America who completed a HRQOL questionnaire; and (3) examine the impact of insulin lispro therapy as compared with regular human insulin therapy on the risk of nocturnal hypoglycaemia.

Patients and Methods

Study Design

Three hundred and sixty-five patients with type 2 diabetes and new to insulin therapy were screened and enrolled in this open-label, randomised, parallel, controlled 12-month study to compare the safety and efficacy of insulin lispro (182 patients), a new insulin analogue, with regular human insulin therapy (183 patients) [11]. Forty-eight principal investigators from Europe, North America and South Africa conducted the multicentre, multinational study. The ethical committee of each participating centre approved the study protocol. All patients provided written informed consent according to Good Clinical Practice guidelines and the Declaration of Helsinki.

The major eligibility criteria included a diagnosis of type 2 diabetes, as defined by the World Health Organisation (WHO), insulin treatment < 2 months before study entry; and an age of 35–85 years [12]. table 1 summarises the baseline characteristics of the study population.

The primary outcomes of the trial were to measure overall metabolic control and the frequency of hypoglycaemic episodes in patients with type 2 diabetes mellitus new to insulin therapy. A secondary objective was to investigate health-related quality of life outcomes in the North American patient group of the clinical trial population.

Baseline Psychological Measures

The HRQOL questionnaire was administered to the study population from the USA and Canada [13]. Several domains and questions related to the HBM were included: impact of diabetes on quality of life, hypoglycaemic fear, frequency and bothersomeness of symptoms, perceived harm of diabetes, perceived benefit of diabetes control, and confidence in controlling diabetes. One hundred and ninety-five (99 on insulin lispro therapy and 96 on regular human insulin therapy) North American patients who answered the aforementioned questions at baseline were analysed to assess the relationship between the occurrence of nocturnal hypoglycaemia and the psychological measures in addition to baseline characteristics.

Treatment and Follow-up

Patients were randomised to receive either insulin lispro or regular human insulin therapy. They were instructed to inject either the rapid-acting insulin (insulin lispro) or short-acting insulin (regular human insulin) into the subcutaneous (s.c.) tissue of the abdomen before each meal. The difference in time-action profiles of the two insulins necessitated that patients be instructed to inject insulin lispro within 15 min of the meal and regular human insulin 30–45 min before the meal. Patients were not asked to perform 'two injections per each insulin dose' as would be necessary for a blinded study design. Hence, our selection of an open-label study design. In both treatment groups, NPH human insulin and ultralente human insulin were administered once or twice daily as basal insulin. Glycaemic control goals were fasting blood glucose values < 7.8 mmol/l (< 140 mg/dl)

Table 1 Baseline characteristics of patients with type 2 diabetes*

Characteristics	Clinical trial patients (n = 365)	Subset of clinical trial patients who completed HRQOL (n = 195)
Age (years)	56.4 ± 10.1	55.6 ± 10.2
Male sex (%)	55.6	56.9
Caucasian race (%)	75.6	79.0
North Americans (%)	73.4	100
Duration of type 2 diabetes (years)	7.9±6.5	7.1±5.6
B.m.i. (kg/m2)	28.0±4.3	28.5±4.1
Hypertension (%)	43.6	40.0
Alcohol-drinker (%)	23.6	29.2
Basal insulin type		
Humulin® N(%)	80.1	78.7
Humulin® U(%)	19.9	21.3
Basal insulin inj. freq.		
0 or 1 (%)	52.2	39.4
⩾2 (%)	47.8	60.6
Baseline HbA (%)	9.5±1.9	9.7±1.7
Living alone(%)†	–	14.9

HRQOL = Health-Related Quality of Life Questionnaire.
* Plus/minus values are means ± s.d.
†This question is included only in the HRQOL questionnaire, and thus not available in the entire Clinical Trial Population.

without hypoglycaemia and maintenance of 2-h postprandial glucose values < 10 mmol/l (< 180 mg/dl). The investigators adjusted insulin dosages according to their clinical judgement to achieve these target goals.

Definition of Nocturnal Hypoglycaemia

For the purpose of this study, a hypoglycaemic episode was defined as: (1) any time a patient felt he/she was experiencing signs or symptoms that he/she associated with hypoglycaemia; or (2) had a blood glucose measurement < 3.5 mmol/l (63 mg/dl) even if it was not associated with signs, symptoms or treatment. These episodes were reported spontaneously and were recorded by the patients in their study diaries. Nocturnal hypoglycaemia was defined as hypoglycaemia that occurred between midnight and 6.00 a.m. Previous experience with these criteria demonstrate high sensitivity and specificity for determining hypoglycaemia [14,15]. This is neither new nor unfamiliar in diabetes research.

Statistical Methods and Procedures

The Kaplan–Meier estimators were used to describe the percentage of patients free of nocturnal hypoglycaemia in the insulin lispro and regular human insulin groups, respectively, and the difference between the curves was tested for statistical significance using the log-rank test.

To explore the relationship between the occurrence of nocturnal hypoglycaemia and baseline characteristics, the Andersen–Gill model under the proportional hazards framework was used to analyse the multiple recurrent events. A reduced model was obtained by successively deleting covariates that were not significant at 0.1 nominal level [16,17].

To assess the impact of the selected HRQOL domains on the occurrence of nocturnal hypoglycaemia, baseline psychological measures related to HBM were added to the previous regression model. This analysis was performed only for the patient group from North America since they provided the largest homogeneous patient group. The HRQOL instrument was not administered outside North America because the affiliate sample populations were too small for separate statistical comparison. All data are expressed as the mean ± s.d. and the statistical significance (p-value) is provided, as well as relative risks (RR) and 95% confidence intervals (CI).

Results

One hundred and fifty-seven patients in the insulin lispro group (86.3%) and 164 (89.6%) in the regular

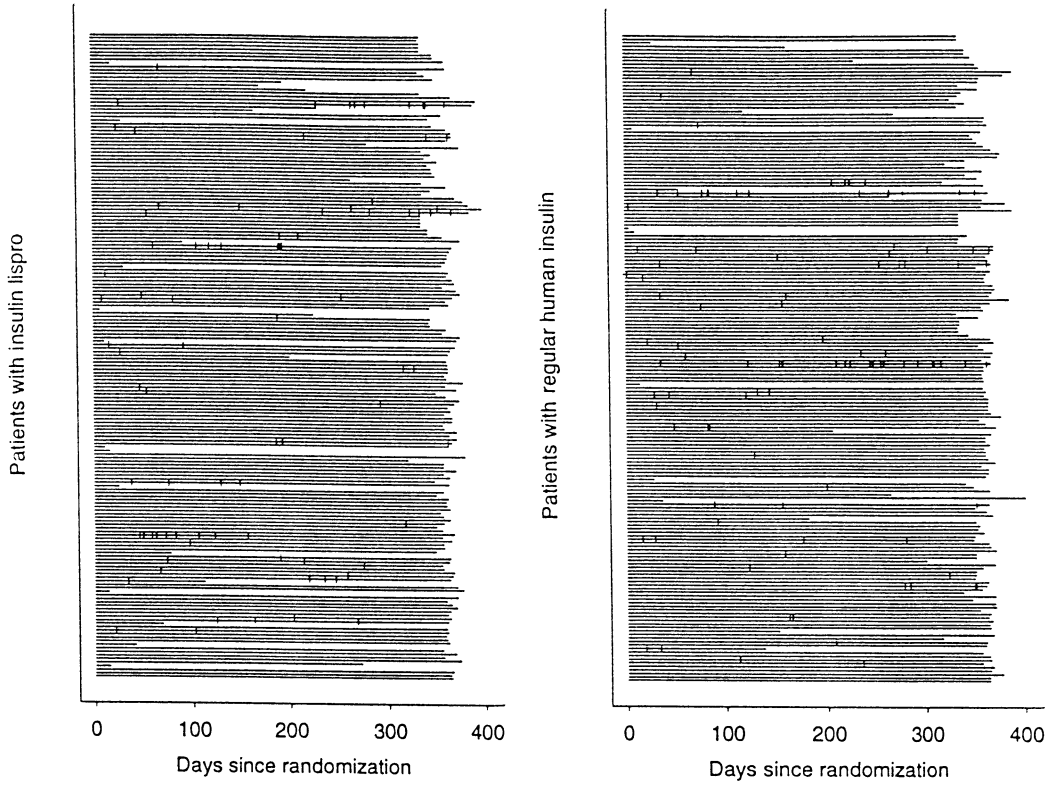

Fig. 1 Follow-up of the study patients: nocturnal hypoglycaemic episodes are represented as vertical bars.

human insulin treatment group completed the 1-year study. Among the patients receiving insulin lispro, 10.4% experienced only one episode and 9.3% had more than one episode of nocturnal hypoglycaemia during the 1-year trial period. In the regular human insulin treatment group, 13.7% had only one episode and 8.2% had more than one episode of nocturnal hypoglycaemia. Episodes of nocturnal hypoglycaemia in all patients are shown in figure 1.

Figure 2 shows the Kaplan–Meier estimates of the percentage of patients free of nocturnal hypoglycaemia in the two treatment cohorts, respectively. The treatments were not significantly different with respect to time to the first episode of nocturnal hypoglycaemia ($p = 0.69$).

The effect of patient baseline characteristics on the occurrence of nocturnal hypoglycaemia was explored using the Andersen–Gill model. The occurrence of multiple episodes of nocturnal hypoglycaemia was modelled as a non-homogeneous Poisson process modulated by multiplicative effects of covariates. The candidate factors considered were insulin treatment (insulin lispro vs. regular human insulin), basal insulin (NPH vs. ultralente human insulin), basal insulin injection frequency (0 or 1 vs. 2 or more), age, geographical area (North America, North Europe, South Europe, or South Africa), body mass index (b.m.i.), duration of type 2 diabetes, presence of hypertension, alcohol-consumption status, and baseline haemoglobin A_{1c}. A reduced model is presented in table 2 in which covariates that were not significant at $p < 0.10$ nominal level were successively deleted. After successive deletion of nonsignificant covariates, any covariate with a p-value < 0.05 was considered statistically significant. In this model, geographical association with the risk of nocturnal hypoglycaemia is statistically significant. Higher risk of nocturnal hypoglycaemia was associated with the use of regular human insulin (as compared with insulin lispro), ultralente human insulin (as compared with NPH human insulin), smaller b.m.i., and younger age. Also, alcohol consumption was found to be associated with a lower risk of nocturnal hypoglycaemic events.

A second regression model was constructed in a similar manner to explore the relationship between nocturnal hypoglycaemia and the baseline psychological measures, in addition to baseline characteristics in the previous model. The data set for this model was restricted to North

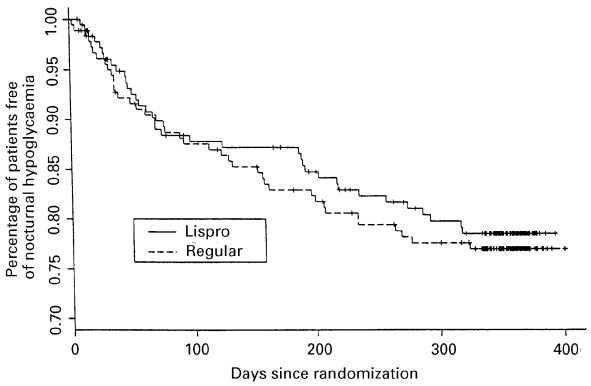

Fig. 2 Kaplan–Meier estimates of the percentage of patients free of nocturnal hypoglycaemia.

Table 2 Model one: risk factors for nocturnal hypoglycaemia identified with an patients and only baseline characteristics considered

Variable	Estimated RR (p-value)	95% CI
Age (⩽1 year)	1.051 (0.000)	1.035–1.066
Basal insulin (Humulin® U vs. Humulin® N)	1.531 (0.021)	1.066–2.197
Body mass index (⩽1 unit)	1.109 (0.000)	1.073–1.147
Geographical area		
N. America	3.461 (0.000)	1.944–6.160
N. Europe	4.120 (0.000)	2.216–7.660
S. Europe	3.061 (0.000)	1.649–5.684
S. Africa	1 (reference)	
Non-alcohol-drinking	2.189 (0.000)	1.475–3.247
Treatment (Humulin® vs. Lispro)	1.312 (0.072)	0.977–1.764

RR = relative risk, CI = confidence interval.

Americans who completed these baseline HRQOL questions, since they represented the largest homogeneous patient population. In this model, higher risk of nocturnal hypoglycaemia was associated with the use of regular human insulin, smaller b.m.i., younger age, less hypoglycaemia fear, more troublesome symptoms, less perceived health benefit of diabetes control, and stronger confidence in controlling diabetes. Alcohol-consumers had a smaller number of recorded nocturnal hypoglycaemic events. This model is shown in table 3.

Discussion

Hypoglycaemia is a major risk factor in the care of patients with type 2 diabetes mellitus who are new to insulin. The present analysis extends these findings by identifying demographic factors and patient characteristics as well as HRQOL measures which significantly impact upon the risk of nocturnal hypoglycaemia.

The higher risk of nocturnal hypoglycaemia in this patient group is associated with the demographic factors including smaller b.m.i., younger age, and the use of ultralente insulin; while a lower risk of hypoglycaemia is associated with alcohol consumption. The mechanism by which each of these factors impacts nocturnal hypoglycaemia risk remains speculative.

Patients with smaller b.m.i. may have less insulin resistance and greater insulin sensitivity resulting in a higher risk of nocturnal hypoglycaemia as we observed. The lower risk of nocturnal hypoglycaemia in older patients may be due to better self-care or less aggressive treatment. Both have been described in the geriatric population [18,19]. The slower onset of action and longer duration of action of ultralente insulin as compared with NPH human insulin may explain the higher risk of nocturnal hypoglycaemia in patients using ultralente insulin in our population.

Alcohol consumption was associated with fewer recorded nocturnal hypoglycaemia events in our study, a finding which is at variance with previous reports [20]. The difference in findings may be attributed to data collection technique, since our data was collected by self-reporting. Therefore, it is unclear whether alcohol consumption has a beneficial effect or whether alcohol simply blunts the symptoms of hypoglycaemia and, hence, the hypoglycaemia goes unreported.

Analysis of hypoglycaemia events with fasting blood glucose was not available to determine if alcohol may have suppressed nocturnal hepatic gluconeogenesis. It was not determined if patients who consumed alcohol may have also ingested significant quantities of carbohydrate as well as their alcohol containing beverage.

In patients with type 2 diabetes who are new to insulin therapy, insulin lispro therapy is associated with lower risk of nocturnal hypoglycaemia as compared with regular human insulin therapy after adjustment for demographic and psychological factors. The present analysis is consistent with and supports previous reports in patients with either type 1 or type 2 diabetes [21,22]. Anderson and colleagues described the reduction in risk of hypoglycaemia in patients with type 1 diabetes when treated with insulin lispro as compared with regular human insulin regardless of basal insulin used [21,23]. Although there was a reduction in hypoglycaemia risk throughout the day, the greatest reduction in hypoglycaemia rate occurred between the hours of midnight and 6.00 am. Bastyr *et al.* [22] identified persons with type 2 diabetes at greatest risk of developing hypoglycaemia as those with: (1)

Table 3 Model two: risk factors for nocturnal hypoglycaemia identified with patients from North America having health benefits measures at baseline

Variable	Estimated RR (p-value)	95% CI
Age (≤1 years)	1.058 (0.000)	1.037–1.077
Body mass index (≤1 unit)	1.075 (0.000)	1.030–1.122
Troublesomeness of symptom (≤10 units less)*	1.114 (0.031)	1.010–1.229
Confidence in controlling diabetes (10 units more)*	1.124 (0.059)	0.995–1.270
Hypoglycaemic fear (≤10 units)*	1.177 (0.013)	1.036–1.337
Non-alcohol-drinking	2.458 (0.000)	1.490–4.049
Perceived benefit of diabetes control (≤10 units)*	1.189 (0.000)	1.078–1.312
Treatment (Humulin R® vs. Lispro)	1.623 (0.015)	1.098–2.404

RR = relative risk, Cl = confidence interval.
*These domains were scored on a 100 point scale. Thus, a ⩾10 unit decrease represented a 10% or more change in domain score.

lower haemoglobin A_{1c} values; and (2) reduced fear of hypoglycaemia. Their analysis concluded that, when compared with regular insulin therapy, insulin lispro might reduce the risk of hypoglycaemia in patients with type 2 diabetes at the highest risk for hypoglycaemia. The patient population in the present analysis is representative of those previously studied testing the impact of insulin lispro therapy compared with regular human insulin therapy.

The mechanism by which insulin lispro therapy reduces the risk of nocturnal hypoglycaemia is not clear. For all patients, the mean haemoglobin A_{1c} on therapy in the current study was not statistically different when the insulin lispro-treated group was compared with the regular human insulin-treated patients (8.48% ± 1.23% vs. 8.31% ± 1.31%, $p = 0.185$). There was also no difference between insulin lispro and regular human insulin groups for total daily rapid-acting insulin dose (0.25 + 0.18 vs. 0.25 + 0.13 units/kg, $p = 0.997$) nor total daily basal insulin dose (0.31 + 0.20 vs. 0.29 + 0.18 units/kg, $p = 0.606$).

A recent study of the pharmacokinetic profile of insulin lispro following s.c. injection may provide insight into the mechanism for the reduction in hypoglycaemia [24]. When injected into s.c. fat, insulin lispro achieves maximum serum concentrations much faster than regular human insulin (46.3 vs. 78.8 min, $p < 0.001$) [23]. Since insulin lispro and regular human insulin are cleared with equal rapidity, the duration of action of insulin lispro can be from 2 to 4 h shorter [24]. The shorter duration of action may result in less overlap with basal acting insulin at night resulting in the observed reduction of risk of nocturnal hypoglycaemia.

To evaluate a nocturnal blood glucose profile, we relied on a patient self-reporting mechanism. While an absolute hypoglycaemia rate may not have been captured, the percentage of patients experiencing symptomatic episodes of nocturnal hypoglycaemia in each group was accurately discovered and protected through randomisation.

Although the statistically significant difference in hypoglycaemic episodes (10.4% in the insulin lispro group, 13.7% in the regular human insulin group) may appear to be small, it does translate into a clinically significant difference for those affected. Whether patients, new to insulin therapy, are more susceptible to long-term psychological effects of hypoglycaemia, was not determined in this study. As stated above, however, excessive hypoglycaemia in other patient groups may motivate those patients to compromise glycaemic control and increase their risk of microvascular and neuroglycaemic complications [1,5].

Measures used in this study that are related to HBM also had a significant impact upon the occurrence of nocturnal hypoglycaemia. Hypoglycaemia fear, hypoglycaemia symptoms, lack of perceived benefit of diabetes control and confidence in ability to control diabetes impact the risk of nocturnal hypoglycaemia and further identify a high and low risk population.

The HBM is a conceptual framework for behavioural research on patient compliance [25]. It consists of four domains: perceived susceptibility, perceived severity, perceived benefits and perceived barriers. Under this framework, patient behaviours depend mainly upon two variables: (1) the desire to avoid illness; and (2) the belief that a specific health action will prevent or ameliorate illness. The HBM provides a theory to explain patient compliance in diabetes treatment [26].

The HRQOL questionnaire identified a high risk group for nocturnal hypoglycaemia in these insulin naive patients with type 2 diabetes. Those patients with constant symptoms of hyperglycaemia (blurred vision, nocturia, polyuria, polydipsia) reported as being very troublesome within the week before starting insulin, were associated with a higher risk of hypoglycaemia. Patients less experienced with insulin use and who are anxious to rid themselves of symptoms of hyperglycaemia may be more aggressive in their demand for treatment. They may not heed the prudent advice of the diabetes educator or clinician with regard to diet and timing of insulin injections resulting in unnecessary exposure to hypoglycaemia risk. This may explain the

Table 4 Patient characteristics associated with risk of hypoglycaemia

Lower hypoglycaemia risk	Greater hypoglycaemia risk
Alcohol consumption	Less fear of hypoglycaemia
Use of insulin lispro	Less perceived benefit of diabetes control
Use of NPH insulin as basal insulin	More troublesome symptoms of hyperglycaemia before initiating therapy
	Stronger confidence in controlling diabetes
	Use of regular human insulin
	Use of ultralente insulin as basal insulin
	Younger age

reason for the higher preponderance for hypoglycaemia. Patients with more confidence in controlling diabetes had a higher risk of nocturnal hypoglycaemia. Patients who are more confident in their knowledge of diabetes may also invest more effort in controlling blood glucose resulting in attempts at possibly tighter control and the observed higher risk of nocturnal hypoglycaemia. Patients who had less perceived health benefit for good control of blood glucose exhibited a higher risk of nocturnal hypoglycaemia. Although this observation is unexpected, it might be explained by greater variability in blood glucose values with larger swings in glucose. Variability of blood glucose values and the frequency of hyperglycaemia were not measured during the study. Alternatively, less monitoring of blood glucose or less compliance with diet or adjustment of insulin in this patient group might account for this finding.

Only one psychological measure was linked to a lower risk of nocturnal hypoglycaemia. Those patients with greater hypoglycaemia fear may be expected to exhibit behaviours leading to the maintenance of elevated blood glucose levels and, thus, a lower risk of nocturnal hypoglycaemia [27]. In our patient population, those with the greatest hypoglycaemia fear demonstrated the lowest risk of nocturnal hypoglycaemia.

Although the analysis was exploratory in nature, these findings may identify a high risk group for nocturnal hypoglycaemia in patients with type 2 diabetes, who are new to insulin therapy. These results should be interpreted with caution because trial participants may differ from the general population of type 2 diabetes patients. These findings may, however, provide clinicians with a list of characteristics to identify newly diagnosed patients with type 2 diabetes at greatest risk for nocturnal hypoglycaemia.

In conclusion, patients with type 2 diabetes mellitus who were new to insulin therapy demonstrated that insulin lispro is associated with a lower risk of nocturnal hypoglycaemia than regular human insulin. We identified patient demographic characteristics and factors as well as psychological measures that may impact the risk of nocturnal hypoglycaemia in this patient cohort (see table 4). These findings may help practitioners to identify insulin-requiring type 2 diabetes patients at greatest risk for hypoglycaemia and provide them with a therapeutic means to reduce that risk.

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