Diabetes & its Complications

Reduction of Recurrent Severe Hypoglycemia and Hypoglycemia Unawareness in Type 2 Diabetes by Treatment Modification and Diabetes Education

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ABSTRACT

Introduction: Intensification of diabetes treatment can induce hypoglycemia, representing a barrier to achieve glycemic control increasing the risks of adverse events.

Objectives: To describe changes in the frequency and severity of hypoglycemia following treatment modification in high-complexity type 2 diabetics (T2DM).

Material and Methods: T2DM patients with chronic diabetes complications presenting severe, recurrent and reduced awareness of hypoglycemia (RAH) were analyzed before and three months after treatment modification and diabetes education.

Results: Twelve males aged 68.5 ± 12.6 years-old, BMI: 28.9 ± 4.3 kg/m^2; glycosylated hemoglobin A1c (HbA1c) $8.0 \pm 0.8\%$ and ten females aged: 67.6 ± 8.4 years-old, BMI $31.7 \pm 6.2.0$ kg/m^2, HbA1c $8.4 \pm 2.0\%$, with multiple cardiovascular risk factors, previous cardiovascular disease or renal impairment, requiring insulin treatment alone or with oral agents, were evaluated. All had severe and recurrent hypoglycemia events. Nutritional counselling and diabetes education were provided to all the patients; the pharmacologic treatment was switched from human insulin to insulin analogues and to newer class of oral agents or to GLP-1 receptor agonists. With treatment modification and diabetes education, the frequency and severity of hypoglycemia events diminished. Further, mean insulin doses were reduced from 0.70 ± 0.24 to 0.44 ± 0.9 U/Kg (p=0.01) and from 0.87 ± 0.41 to 0.47 ± 0.21 U/Kg in males and females, respectively (p=0.0001). Concomitantly, HbA1c diminished in females (p=0.02) and for both males and females, the coefficient of variation of fasting glucose declined (p=0.03).

Conclusion: Recurrent severe hypoglycemia and RAH constitute a serious complication which hampers metabolic control and place patients at risk for cognitive dysfunction and cardiovascular complications. Reduction in the frequency, severity of hypoglycemia in high-complexity T2DM was observed after diabetes treatment modification.

Keywords

Recurrent hypoglycemia, Restoration of reduced awareness of hypoglycemia, Diabetes treatment.

Abbreviations

BMI: Body Mass Index kg/m^2, T2DM: Type 2 Diabetes, HbA1c: Glycosylated Hemoglobin A1c, RAH: Reduced Awareness of Hypoglycemia.

Introduction

Diabetes prevalence is rapidly increasing and represents a serious health problem worldwide [1-2]. Diabetes is associated with chronic complications, disabilities, premature death [3] and contribute to the impact on health care costs [4-5]. Long-term glycemic control reduces the risk of chronic complications and death [6-11].

In Latin America, it has been shown poor metabolic control and a high prevalence of microvascular and macrovascular complications in T2DM patients [12-14]. Along with these findings, all-cause mortality among people with diabetes doubles that of those without this condition [15]. Moreover, in Costa Rica, mortality due to diabetes nephropathy is increasing [16] and latest reports demonstrated inadequate metabolic control in our country [17].

Thus, actions have been taken to revert this trend. In consequence, the risks for hypoglycemia in people living with diabetes seem to be increasing. We previously described the occurrence of severe hypoglycemia in T2DM patients attended at the emergency department of a general hospital in San José, Costa Rica [18]. Yet, little is known with respect to hypoglycemia in T2DM patients attended in an out-patient settings in this country.

In this report we describe the clinical presentation, risk factors, potential causes of severe hypoglycemia and the effects of a short-term treatment modification inT2DM patients referred to our out-patient clinic. We aimed to raise glucose levels, avoid hypoglycemia and glucose variability in order to restore the sympathoadrenal response to hypoglycemia in high complexity T2DM.

Material and Methods

Twenty-two T2DM patients with long-term insulin usage and cardiovascular, neurologic or renal complications were referred to the Diabetic Clinic of Hospital CIMA due to severe, recurrent and RAH [19-21]. Hypoglycemia events occurred during the previous six months when insulin doses were changed aiming to improve glucose control. We used previously tested questionnaires to record the severity of the hypoglycemia events and to classify them according to a validated score system [22]. All the patients were accompanied with close relatives whom helped record hypoglycemia events. Age, sex, co-morbidities, clinical characteristics of the hypoglycemia events, it´s causes and risk factors were recorded. These events were register as an adverse event according to the regulation of the National System of Surveillance [23].

Nutritional counselling and diabetes education were provided to all the patients and family members as recommended [24-25] and consisted of: 1) understanding of the problem, 2) identification of hypoglycemia manifestations, 3) frequent capillary glucose monitoring, 4) personalized meal plan, 5) modification of pharmacologic treatment, 6) daily report of glucose monitoring and 7) treatment adjustment as necessary. The pharmacologic treatment was switched from human insulin to insulin analogues, to newer class of oral agents or to GLP-1 receptor agonists as necessary

[24-25]. The patients were asked to make weekly telephone or email contacts with the health providers for insulin adjustments or dietary modifications. Lifestyle modifications, timing of insulin administration and meal patterns were closely supervised. The patients were seen monthly for three months. At each subsequent visit weight, hypoglycemia questionnaires, glucose monitoring and HbA1c were obtained. Results are expressed as mean ± SD. Differences between groups were analyzed using Student T test. All analyses were performed using Microsoft Excel and Epidat 4.2.

Results

Twelve males (age: 68.5 ± 12.6 years old, BMI: 28.9±4.3 kg/m2; fasting glucose:136.3 ± 40.6 mg/dL; HbA1c: 8.0±0.8%) and ten females (age: 67.6 ± 8.4 years old, BMI: 31.7 ± 6.2 kg/m2, fasting glucose: 136.3 ± 32.6 mg/dL; HbA1c: 8.4 ± 2.0%) were evaluated. Baseline clinical characteristics are shown in table 1. The hypoglycemia events were documented by finger stick glucose levels measured at home, by paramedics or at the emergency department. There were five patients who had non-severe hypoglycemia and perceived hypoglycemia events within the past 6 months; however, they reported progression to reduced perception of hypoglycemia. Nineteen required third party assistance and twelve had cognitive dysfunction. Ten males and eight females presented RAH; three presented nocturnal jerks and jumps and other three had seizures. In eleven occasions emergency department/paramedic visits were required. The symptoms of the hypoglycemia events are illustrated in figure 1. As compared to females, more males had hypoglycemia symptoms. Based on those symptoms, T2DM patients were grouped as having awareness of hypoglycemia (n=5), RAH (n=9) or having both (n=7) according to the predominant symptom category. Patients with awareness hypoglycemia had lower hypoglycemia score and higher glucose concentrations at which the patients became symptomatic as shown in figure 2A and 2B, respectively.

Gender		Males	Females	p value
n		12	10	
Age (years)		68.5 ± 12.6	67.6 ± 8.4	0.89
Duration of diabetes (years)		21.5 ± 7.9	18.3 ± 7.9	0.36
Body mass index (kg/m²)		28.9 ± 4.3	31.7 ± 6.2	0.35
Duration of insulin treatment (years)		13.4 ± 6.5	7.5 ± 3.1	0.01
Fasting plasma glucose (mg /dL)		136.3 ± 40.6	136.3 ± 32.6	0.99
Mean fasting glucose (mg /dL)*		124.3 ± 37.0	142.4 ± 45.6	0.35
Coefficient of variation of glucose (%)		36.8 ± 14.3	26.0 ± 8.3	0.06
HbA1c (%).		8.0 ± 0.8	8.4 ± 2.0	0.58
Hypertension (%)		75	90	0.05
Dyslipidemia (%)		91	60	0.05
Retinopathy (%)		8	10	ns
CKD stage (%)	I-II	75	70	ns
	III a / III b	16	20	
	IV	8	10	

Peripheral neuropathy (%)	58	50	ns
Atherosclerosis cardiovascular disease (%)	58	40	ns
Cerebrovascular disease (%)	25	10	ns
Drepression (%)	25	2	ns
Malignancy (%)	16	2	ns
Hypothyroidism (%)	16	4	ns
Non-alcoholic liver disease (%)	0	1	
Parkinson's disease (%)	8	0	ns
Panhipopitiuarism (%)	0	10	
History of alcohol abuse (%)	18	0	

Table 1: Clinical characteristics of T2DM patients with severe and recurrent hypoglycemia events.

Results: expressed as means ± SD or percentage when indicated. * Finger stick glucose levels measured daily for 7-10 days at baseline. ns: not significant.
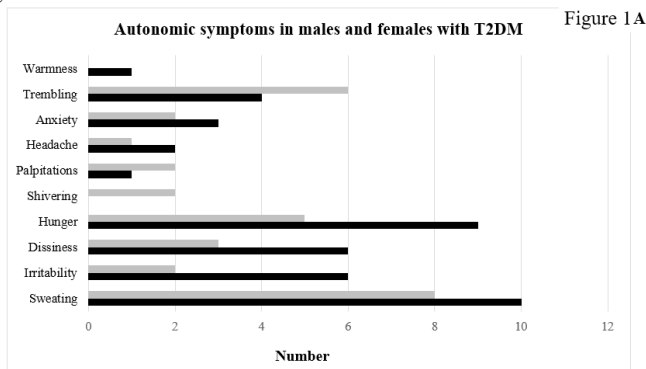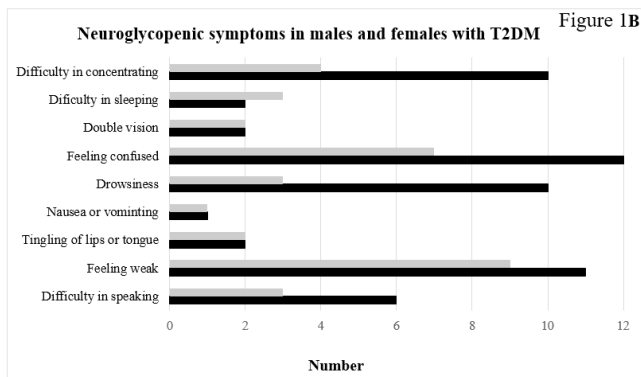

Figure 1A

Figure 1: Number of T2DM patients with autonomic (A) and neuroglycopenic hypoglycemia symptoms (B) in ■males and ▨females.
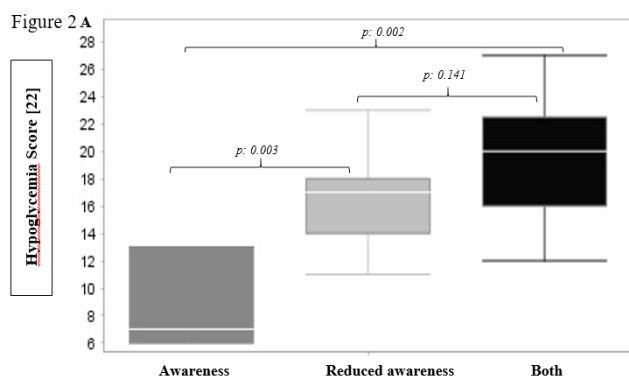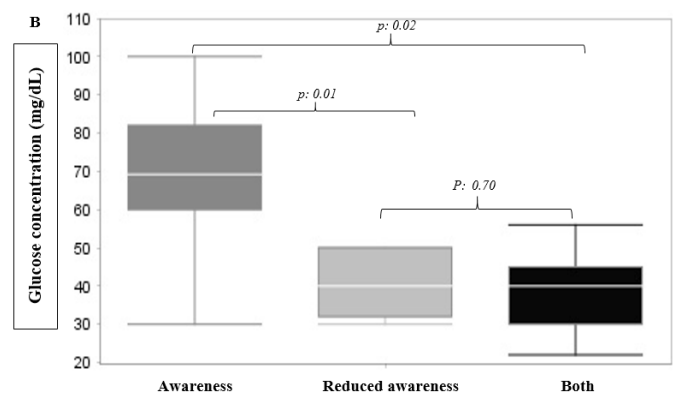

Figure 2 A

B

Figure 2: Association of awareness and reduced awareness of hypoglycemia according to hypoglycemia score (A) and of glucose concentrations at which hypoglycemia symptoms occurred, according to awareness of hypoglycemia, reduced awareness of hypoglycemia and both conditions in T2DM patients (B).

Moreover, the causes of hypoglycemia were: prolonged fasting, physical activity, concomitant illness, inadequate insulin dosing, mistakes in insulin administration, insufficient steroid replacement therapy during stress conditions and alcohol abuse.

In one male and two females the diagnosis of RAH was done retrospectively during the present evaluation as they nor the medical provider neither family members identified their symptoms as RAH.

As a result of treatment modification patients treated with human insulins were switched to insulin analogues and oral agents including dipeptidyl peptidase-4 inhibitors (DPP-4i) (n=11), sodium-glucose transporters inhibitors (SGLT2i) (n=7) or GLP-1 receptor agonists (n=1) were added as recommended [24-25].

With this intervention hypoglycemia events ceased in three males and in seven females. In those in whom hypoglycemia remained, the frequency and severity of events diminished. Nonetheless, RAH persisted in six males and two females. In such patients the hypoglycemia symptoms were detected at glucose levels between 50 and 60 mg/dL which were higher as compared to baseline and none required third party assistance neither emergency/paramedics visits.

The sum of autonomic and neuroglucopenic symptoms according to the score system [22], at baseline and three months after treatment is illustrated in figures 3A and B. Similarly, table 2 illustrates the changes in body weight, insulin doses, mean fasting glucose levels, the coefficient of variation of glucose and the mean of hypoglycemia score [22] measured at baseline and after treatment modification. In two females the HbA1c levels were not obtained after treatment modification, thus the results of baseline HbA1c presented in table 2 differ from that of table 1.

We found that in females but not in males a reduction in HbA1c levels occurred (p=0.01) However, in all the patients the coefficient of variation of fasting glucose declined significantly (p=0.01).

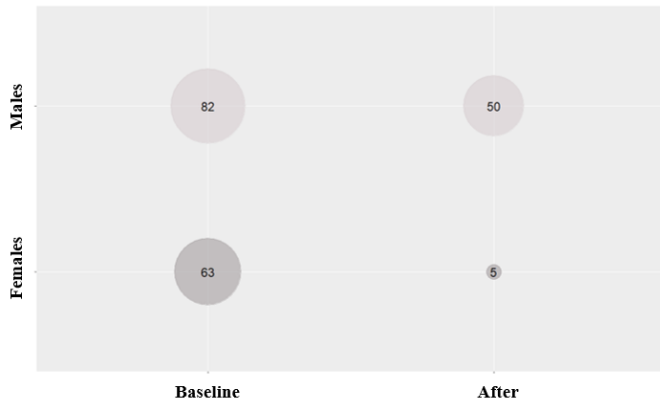| Variables	Males		Females	
	Baseline	After	Baselinet	After
Weight (Kg)	83.0 ± 28.2	81.6 ± 27.3	78.1 ± 17.3	74.3 ± 15.6‡
Insulin doses (U/Kg)	0.70 ± 0.24	0.44 ± 0.9‡	0.87 ± 0.4	0.47 ± 0.2‡
Mean fasting glucose (mg/dL) ¶	124.3 ± 37.0	127.6 ± 56.1	142.2 ± 45.6	121.1 ± 27.1
CV of fasting glucose (%) ¶¶	36.8 ± 19.3	24.7 ± 14.3†	26.1 ± 8.3	16.3 ± 6.0‡
HbA1c (%)	8.0 ± 0.9	7.7 ± 1.0	9.1 ± 3.7	7.6 ± 2.9‡
Mean hypoglucemia score	16.6 ± 5.6	5.5 ± 3.8§	14.1 ± 6.2	3.6 ± 0.51§

Table 2: Body weight, insulin doses, glucose parameters and mean hypoglycemia score at baseline and three months after treatment modification and diabetes education.

Results: expressed as means ± SD or percentage when indicated. ‡p = 0.01; †p = 0.03; §p = 0.001

¶ Finger stick glucose levels were measured daily for 7-10 days. ¶¶ CV: Coefficient of variation glucose levels measured daily for 7-10 days at baseline and at 3 months.
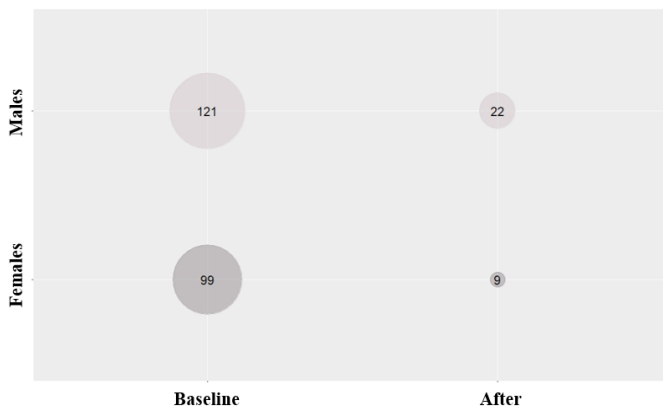

Figure 3: The sum of the scores of autonomic (A) and neuroglycopenic (B) symptoms measured according to a validated score system [22], in males and in females with T2DM at baseline and three months after treatment modification.

Discussion

Most clinical practice guidelines recommend aimed to HbA1c levels less than 6.5% to 7.0% [23-24]. In the UKPDS newly diagnosed T2DM patients changes of 0.9% in HbA1c over median 10.0 years resulted in a significant reduction of microvascular complications [7] and in the post-trial evaluation, cardiovascular benefits were observed in participants who had strict glucose control [9]. In contrast, in the ACCORD trial, T2DM patients with high cardiovascular risk, the intensive therapy increased mortality and did not significantly reduce major cardiovascular events after 3.5 years of follow-up [26]. Thus, T2DM patients with reduced life expectancy are less likely to derive long-term benefit from intensive glycemic control [26]. Moreover, the accumulated evidence suggests that with treatment intensification, hypoglycemia events are 2-3 times more frequent and it is associated with significant morbidity and even mortality in patients with ischemic heart disease, in aging population and hospitalized patients [27-35]. Currently, the importance of individualized glycemic goals and hypoglycemia avoidance are an essential component of diabetes management [24-25]. In particular, people living with diabetes who had suffered hypoglycemia or fragile patients with long diabetes duration and short life expectancy, a higher HbA1c level can be recommended [36].

The broad spectrum of clinical hypoglycemia in the elderly and high-complexity T2DM patients represent a challenge to the health care personnel. In patients with defective awareness of hypoglycemia the incidence of severe hypoglycemia was several fold higher than those with normal hypoglycemia awareness [37]. Further, T2DM patients with recurrent hypoglycemia events can develop RAH due to reduced hormonal and autonomic responses to subsequent hypoglycemia [27-32]. Nocturnal hypoglycemia and reduced perception of hypoglycemia may contribute to cardiovascular mortality in elderly patients [33-39].

Due to the recent deterioration in glycemic control in Costa Rica [12-14] intensification of diabetes treatment has been implemented. However, the risks of adverse events including hypoglycemia increased [18].

Our T2DM patients received an absolute or relative excess of insulin and had several risk factors for hypoglycemia events. As shown in Table 1, risk factors for hypoglycemia were: advance age, diabetes duration, the presence of cardiovascular, cerebrovascular disease, diabetes neuropathy, renal complications and a long-term insulin requirement. Of note, some of our patients who had non-severe hypoglycemia during the previous six months worseness the severity of hypoglycemia as reported before [38]. On the other hand, the potential causes of hypoglycemia were prolonged fasting, lower fasting glucose, high glucose variability, physical activity, concomitant illness, ill-timed or excessive insulin dosing and alcohol abuse [39].

In the present report we investigated the characteristics of severe hypoglycemia events in high-complexity T2DM attended in an outpatient setting. Patients had recurrent hypoglycemia events which often occurred at night. In some cases, even seizures occurred and alterations in patient´s mental state, freakish behavior, with scanty or none autonomous responses consistent with RAH were

observed as depicted in figure 1. Of note, in comparison to females, severe hypoglycemia events and RAH were more commonly found in males, who were older and had longer duration of insulin treatment. They also had a higher prevalence of atherosclerosis cardiovascular disease.

Previous studies have shown that hypoglycemia associated autonomic failure represents the underlying mechanisms which occur in patients with severe and recurrent hypoglycemia [28-30]. In such events of non-symptomatic hypoglycemia, the defective contra regulatory mechanisms result in an inability to respond and recover to subsequent hypoglycemia [28-30]. As compared to type 1 diabetics, insulin treated T2DM patients have less hypoglycemia events but in long-lasting T2DM with prolonged insulin therapy the frequency and severity of hypoglycemia increases and RAH can occur [28-30], as seen in our patients.

Our intervention consisted of dietary counseling, behavioral intervention, changes in pharmacologic approach with close supervision of insulin administration. In the setting of diabetic ageing patients with cardiovascular complications and renal impairment, adjustments in insulin doses were made. This approach impacted the frequency and severity of hypoglycemia and RAH after three months treatment modification. There was an initial rise in glucose concentrations (data not shown), and at the end of the three-month period fasting glucose and HbA1c concentrations decreased in females. On the other hand, the coefficient of variation of fasting glucose declined significantly in both sexes indicating a reduction in glucose variability.

In our patients with RAH, a partial restoration of awareness of hypoglycemia took place. Interestingly, hypoglycemia symptoms occurred at higher glucose concentrations, suggesting that treatment modification helped recover the physiologic mechanisms which operate in response to declining glucose levels.

In the Hypo Compass [40-41], type 1 diabetes restored hypoglycemia awareness and prevented severe hypoglycemia events without a deterioration of glucose control. A systematic review and meta-analysis of clinical trials showed that a stepped-care approach including multiple intervention restore awareness hypoglycemia in T1DM [41]. This included structured diabetes education, individualized insulin regimens, adding behavioral therapies and diabetes technology, namely, sensors and insulin pumps. The latter is a well-known tool, which allows for better monitor complex diabetic patients [42]. Although, in our study continuous glucose monitoring system was not employed, which we recognized as an important limitation, our patients performed multiple fingerstick glucose measurements allowing us to modify diabetes treatment when necessary. Another limitation, which needs to be addressed, is the fact that we documented hypoglycemia events retrospectively. However, in previous reports the association between retrospective and prospective records of hypoglycemia symptoms was positive [22]. In addition to that, we also revised the hypoglycemia symptoms in each visit, thus we believe that our results are well founded.

In conclusion, this study reflects the seriousness of hypoglycemia in patients with a high hypoglycemia risk. Besides, highlights that hypoglycemia has deleterious consequences and hamper metabolic control. With treatment modification we were able to mitigate recurrent severe hypoglycemia and RAH through minimizing glycemic variability and improved HbA1c concentrations.

Finally, it is important to acknowledge that current pharmacologic approaches and diabetes education programs for people living with diabetes require revision in Costa Rica. Improvements in diabetes education and adherence to international guidelines are mandatory actions strongly recommended [43-44].

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