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Risk factors associated with symptomatic hypoglycemia in type 2 diabetes mellitus patients

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ABSTRACT

Objective. To identify risk factors associated with symptomatic hypoglycemia (SH) (≤ 72 mg/dL) in patients with type 2 diabetes mellitus (t2DM) treated at a general hospital during July 2003 to December 2004. **Material and methods.** Ninety four t2DM patients (incident cases) with a primary diagnosis of SH matched with 188 t2DM patients (incident controls) with a diagnosis other than hypoglycemia were included in a case-control study. Demographic and clinical variables entered into an automated binary logistic regression model from which odds ratio (OR) and 95% confidence intervals (95% CI) for variables with a p value < 0.05 were obtained. **Results.** The binary logistic model determined that age had a "protective" effect, while duration of t2DM, educational level (Illiteracy-primary education, OR 3.7, [95% CI 1.4 to 10]; p = 0.009), attending physicians' specialty (family physician, OR 2.8, [1.02 to 7.9]; p = 0.04), chronic renal failure presence (OR 3.0, [1.2 to 7.7]; p = 0.01), antihyperglycemic treatment (combined therapy, OR 5.2, [2.3 to 11.8]; p < 0.01), fasting (OR 19.8, [9.1 to 43.1]; p < 0.001) and history of hypoglycemia (OR 2.9, [1.3 to 6.5]; p = 0.01) were all risk factors associated with SH. The variable "exposure to polypharmacy" was excluded from the logistic model (OR 4.86; [0.7 to 35.1]; p = 0.11). **Conclusions.** According to our results, physicians should be cognizant of the possibility that the odds of SH might be increased when treating patients with t2DM fulfilling factors, such as those identified in this investigation.

Key words. Type 2 diabetes mellitus. Symptomatic hypoglycemia. Risk factor. Family physician. Schooling.

Factores de riesgo asociados a hipoglucemia sintomática en pacientes con diabetes mellitus tipo 2

RESUMEN

Objetivo. *Identificar factores de riesgo asociados a hipoglucemia sintomática (HS) (≤ 72 mg) en pacientes con diabetes mellitus tipo 2 (DM2), atendidos en un hospital de la ciudad de Mérida, durante 2003-2004.* ***Material y métodos.*** *Se incluyeron 94 pacientes con HS (casos incidentes) y 188 con diagnóstico diferente del de hipoglucemia (controles incidentes). Factores de tipo demográfico y clínico fueron incluidos en un modelo binario de regresión logística (MRL) del que se obtuvieron las razones de momios (RM) y los intervalos de confianza de 95% (IC 95%) para las variables con p < 0.05.* ***Resultados.*** *La edad tuvo un efecto protector. La duración de la DM2, la escolaridad (analfabeta-educación primaria, RM 3.7, [IC 95% 1.4 a 10]; p = 0.009), el tipo de especialista que usualmente daba atención médica (Médico de la familia, RM 2.8, [1.02 a 7.9]; p = 0.04), tener insuficiencia renal crónica (RM 3.0, [1.2 a 7.7]; p = 0.01), el esquema hipoglucemiante utilizado (terapia combinada, RM 5.2, [2.3 a 11.8]; p < 0.01), la ingesta reducida de alimentos la semana previa a la hospitalización (RM 19.8, [9.1 a 43.1]; p < 0.001) y el antecedente de episodios previos de hipoglucemia (RM 2.9; [1.3 a 6.5]; p = 0.01) estuvieron asociados con HS. El MRL excluyó la exposición a polifarmacia como factor de riesgo asociado a hipoglucemia (RM 4.86; [0.7 a 35.1]; p = 0.11).* ***Conclusiones.*** *El médico debe tener en consideración la probabilidad de hipoglucemia sintomática cuando trate pacientes con DM2 que reúnan características demográficas y clínicas como las de la presente muestra.*

Palabras clave. *Diabetes mellitus tipo 2. Hipoglucemia sintomática. Factores de riesgo. Médico de la familia. Escolaridad.*

INTRODUCTION

Stricter glycemic control (< 126 mg/dL and/or glycated hemoglobin [A1C] < 7%) in patients with type 2 diabetes mellitus (t2DM) has been considered useful in delaying the onset and/or reducing the rate and progression of related microvascular complications. Using any antihyperglycemic drug, either a secretagogue, an insulin-sensitizing medication alone or combined with insulin, are some of the proposed strategies to achieve those goals, although the latter is not exempt from producing symptomatic hypoglycemia. In the clinical context, symptoma-tic hypoglycemia (SH), defined as that requiring medical intervention, is a cause of frequent hospitalizations and psychosocial morbidity, becoming in not a few occasions a barrier to glycemic control in t2DM patients.[1,2]

Hypoglycemia prevalence, defined as glucose concentration less than or equal to 4 mmol/L (72 mg/dL),[3,4] ranges from 11% to 36%[1] according to the glucose-lowering drug used. Shorr, *et al*.[5] documented a crude rate of 17 cases per 1,000 patients/year in users of glyburide, whereas Miller, *et al*.[6] have reported that the prevalence ranges from 16% in users of any oral antihyperglycemic drug to 30% in insulin users. Such a life-threatening complication will develop more frequently and could even be persistent when a particular patient carries risk factors for developing that complication,[7-12] especially when certain of these risk factors are surrogates related to autonomic failure.[4] Researchers have identified as such the stricter glycemic control itself (A1C < 7%),[1] the antihyperglycemic drug used, use of combinations[1,2] and the pharmacologic half-life (long-acting *vs.* short- acting) of each drug.[7]

Moreover, age, race,[5,8] presence of comorbidities restricting endogenous or exogenous supply of glucose, ingestion of pharmacological agents that may interfere with the antihyperglycemic drugs' metabolism,[9,10] presence of chronic renal failure (CRF),[11] history of hypoglycemic episodes[6,12] and history of hospitalization due to hypoglycemia,[8] have all been associated with SH.

In outpatients with t2DM treated at medical units staffed by family physicians, and less frequently by internal medicine-endocrinology specialists of the Instituto Mexicano del Seguro Social (IMSS) in the city of Merida, Yucatan, Mexico, prescription of an oral antihyperglycemic drug and less frequently insulin is the general rule independent of the medical and educational level of the patient.

Among those individuals there is still not a defined proportion of patients hospitalized because of SH. Additionally, to our knowledge potential associated risk factors, including educational level and the attending physicians' specialty, have still not been analyzed. Taking into consideration the latter, we conducted a case-control study in which we proposed as a primary objective to identify potential risk factors that could be associated with the development of SH in t2DM patients hospitalized for that very reason.

MATERIAL AND METHODS

The project was previously analyzed and approved by the Committee of Investigation and Ethics of the Hospital General where these patients were attended, affiliated with the IMSS, in the city of Merida, Yucatan, Mexico. Participants were drawn from the patient population attended in the Emergency Room (ER), and were chosen through a convenience, non-random selection process. They were patients 30 years of age and older consecutively hospitalized between July 2003 to December 2004 in the Internal Medicine ward. By consensus with the medical staff, nine variables were selected for inclusion, certain of those have been inconsistently identified as potential risk factors in diabetic populations different from ours, and two other factors (educational level and physicians' specialty) have not previously been identified as such, to our knowledge. Gender and glycemia upon arrival at the ER were two complementary variables not taken into account by us as potential risk factors.

By employing a binary multivariable logistic regression model (LRM), we entered both age and duration time of t2DM into the model as continuous variables, while the others were entered as dichotomous, coding the reference variable as (0) and the independent variable as ("1"). In that way educational level entered as illiterate-primary level ("1") *vs.* secondary level and/or higher education (0). The presence of CRF ("1" = Yes, 0 = No), implied as having a serum creatinine level ≥ 1.8 mg/dL in at least two routine laboratory results in the previous six months prior to actual hospitalization. That cutoff value is 20% higher than Ellis and Cairns[13] took into account to define renal impairment in a group of patients with hypertension and diabetes.

The attending physician, whether family practitioner ("1"), general internist or endocrinologist (coded as 0), who usually attended the patient on an

outpatient bases, comprised another variable. The number of antihyperglycemic drugs used for controlling the glycemia took into account whether the patient was either on monotherapy (0), independent of the prescribed drug or in combined therapy ("1"), having taken two or more antihyperglycemic drugs at least in the two months prior to current hospitalization. Regarding the notorious variability of type, dose and combinations, antihyperglycemic drugs including insulin were only described as a bivariate analysis among cases and controls.

Using medications other than antihyperglycemic drugs, that is exposure to polypharmacy ("1" = Yes, 0 = No), referred to whether the patient was routinely taking antihypertensive medications such as angiotensin-converting-enzyme inhibitors (ACE inhibitors), coronary vasodilators, statins, fibrates, β-blockers, nonsteroideal antiinflamatory drugs, or even certain antimicrobial agents two weeks prior to hospitalization. History of hypoglycemia considered whether the patient had had at least one episode ("1") or none (0) in the twelve months prior to current hospitalization, while history of fasting or missed meals referred to whether the patient either restricted ("1") or not (0) carbohydrate intake some days before his/her hospitalization.

To define a "case" of SH which entered into the LRM coded as ("1"), the Whipple's triad was taken into consideration.[3,4] Glycemia upon admission to the ER was considered to be in hypoglycemic range when the venous glucose concentration (Dimension AR, Dade Behring) or when the fingerstick glucose measurement using an electronic sensor (Accu-Check Sensor, Roche Group, Mannheim, Germany) was ≤ 72 mg/dL in the presence of a patient with a neurological clinical picture consistent with a severely confused mental state or worse, non arousable, should respond clinically to the administration of intravenous hypertonic glucose.[2-4]

Patients with at least one year of t2DM, treated with any antihyperglycemic medication, with or without comorbid disorders other than alcoholism, epilepsy, sepsis or acute stroke; taking or not medications other than antihyperglycemic drugs, with severe and protracted hypoglycemia diagnosed upon admission to the ER, were the inclusion criteria for incident cases, while t2DM patients treated with diet alone, type 1 diabetes mellitus (t1DM) patients and those with hypoglycemia different from t2DM, were excluded. Type 2DM patients with the same demographic and clinical characteristics of cases, admitted for diverse manifestations were the inclusion criteria for incident controls, which entered into the LRM coded as (0). Exclusion criteria were the same as previously applied to included cases.

With the aim of balancing exposures among cases and controls and to guarantee that the latter adequately represented the target population from which cases were selected, every case was matched with two controls hospitalized the same week that the case was. Once the case or the control was identified, one of the researchers proceeded to interview him/her when feasible; if not, the next of kin was interviewed. Certain data such as the glycemia tests results as well as the ER registrations of the capillary glycemia were taken from the patient's clinical records at the time he/she arrived at the Internal Medicine ward.

Considering a 0.05 α error, a 0.1 β error, an expected frequency of hypoglycemia as low as 2% as that seen among t2DM patients treated with diet alone[1] and an expected frequency as high as 14%, a proportion nearest 16% prevalence of hypoglycemia documented by Miller, *et al*.[6] between patients treated with antihyperglycemic drugs, a sample size was calculated resulting in 258 patients from which 86 were included cases and 172 were included controls. Nonetheless, because we considered nine variables to analyze and to fulfill criterion of "sufficient events per variable" of 10:1 to avoid overfitting referred by Peduzzi, *et al*.[14] we decided to include at least 90 cases and their corresponding controls.

Two-tailed bivariate analysis, as Chi Square (χ^2) for categorical data and/or Student t test for independent samples for continuous data, was performed as an initial analytic procedure to identify variables statistically and clinically significant ($p \leq 0.05$). In a second step we entered these variables into an automated binary LRM (Enter method), declaring to remove from the model those classified with $p \geq 0.10$. According to the Wald χ^2 test, p values < 0.05 for significance, the odds ratio (OR) and their corresponding 95% confidence intervals (95%CI) were also obtained for the independent variables from the automated LRM. In building 2 x 2 contingency tables for subject classification, a 0.5 cutoff point was set, a default value the automated statistical program includes. Both correlation among variables (multicollinearity) and goodness-of-fit for the full logistic model were also automatically obtained.

The Epi-Info 2002 (Center for Disease Control and Prevention, Atlanta Ga) and the SPSS 8.0 (SPSS Inc., Illinois) statistical packages were used for calculating the sample size and for analyzing data, respectively.

RESULTS

Data collected during the inclusion period was complete. No outliers were documented among continuous data since skewness was < 1 for both age and duration of t2DM, so both variables were statistically approached as symmetrically distributed. Two hundred eighty-two patients were included as the entire sample from which 176 (62.4%) were female. Age ranged from 32 to 83 years (mean 59.2 ± 11.3), while t2DM duration ranged from 1 to 35 years (mean time 13.7 ± 8.3). Ninety-four were cases (only one hypoglycemic event per patient was considered) and 188 were controls, which meant 10.4 events (cases) per variable analyzed as potential risk factors.

Thirty-one cases (29.2%) were male and 63 (35.8%) were female (OR 1.3 for female, 95% CI 0.8 to 2.3; χ^2, p = 0.25). Upon admission to the ER average glycemia among cases was 33.2 ± 14.5 mg/dL (range 10 to 72), while among controls was 236.9 ± 126.4 mg/dL (range 89 to 800) (p < 0.01 for mean difference). Due to diverse antihyperglycemic drugs both cases and controls received (Table 1), we decided the "antihyperglycemic treatment" variable categorized as "monotherapy *vs.* combined therapy" should enter into the LRM.

Regarding glibenclamide, this antihyperglycemic drug was prescribed to 235 patients of which 159 (67.7%) were treated with glibenclamide only and 76 (32.3%) with glibenclamide plus another antihyperglycemic drug. Among these groups, cases (51.4%) prevailed over controls (23.6%) in the glibenclamide-combination treated group (OR 3.4, 95% CI 1.9 to 6.1). Analyzing glibenclamide dose, among the 159 glibenclamide-only treated patients cases (69.4%) prevailed over controls (47.2%) in those treated with > 10 mg/day (OR 2.54, 95% CI 1.15 to 5.62). Data distribution is shown in table 2.

In performing the bivariate analysis age and t2DM duration mean time were both statistically significant, since mean age of cases was 63.1 ± 8.3 years (40 to 75) and that of controls 57.3 ± 12.1 years (32 to 83) (p < 0.01 for mean difference), while t2DM duration mean time of cases was 17.4 ± 8.8 years (3 to 35) and that of controls 11.8 ± 7.4 years (1 to 34) (p < 0.01 for mean difference). Educational level (illiteracy-primary level, OR 3.98, 95% CI 1.98 to 8.0), attending physicians' specialty (family physician, OR 2.56, 95% CI 1.2 to 5.36), presence of CRF (OR 3.37, 95% CI 1.8 to 6.3), antihyperglycemic treatment (combined therapy, OR 2.95, 95% CI 1.7 to 5.0), use of polypharmacy (OR 7.2, 95% CI 2.1 to 24), history of fasting before hospitalization (OR 20.1, 95% CI 10.7 to 37.8) and history of hypoglycemia (OR 3.7, 95% CI 2.15 to 6.4), were also statistically and clinically significant (p < 0.05 for each). Complementary data is shown in table 3.

Table 1. Distribution of antihyperglycemic drugs among 94 type 2 diabetes mellitus patients with hypoglycemia (cases) and 188 without it (controls). Oral drugs in mg/day; insulin in IU/day.

Drugs	Cases n (%)	Control n (%)	p*
Glibenclamide only	36 (38.3)	123 (65.4)	
Glibenclamide + metformin	34 (36.2)	33 (17.6)	
Insulin only (IU/d)	15 (16.0)	15 (8.0)	
Glibenclamide + insulin	3 (3.2)	5 (2.7)	
Metformin only	0	7 (3.7)	
Tolbutamide	1 (1.1)	4 (2.1)	
Metformin + insulin	3 (3.2)	1 (0.5)	
Others†	2 (2.2)	0	

* Distribution was statistically significant according to two-tailed χ^2 test (p < 0.01). †: One patient with glibenclamide plus pioglitazone, and one patient with only chloropropamide treatment are included.

Table 2. Type of treatment prescribed to 235 patients in which glibenclamide was included. One hundred fifty nine (67.7%) (†) were treated with glibenclamide only and 76 (32.3%) (‡) with glibenclamide plus another antihyperglycemic drug.

	Cases n (%)	Control n (%)	Total n (%)	p*
• Type of treatment (n = 235)				< 0.001
• Glibenclamide only†	36 (48.6)	123 (76.4)	159 (67.7)	
• Glibenclamide + another‡	38 (51.4)	38 (23.6)	76 (32.3)	
• Glibenclamide dose (n = 159)†				
≤ 10 mg/day	11 (30.6)	65 (52.8)	76 (47.8)	0.019
> 10 mg/day	25 (69.4)	58 (47.2)	83 (52.2)	

†: Among those 159 patients treated with glibenclamide only, 76 received ≤ 10 mg/day and 83 > 10 mg/day.

Overall, accuracy of the LRM for predicting was 85.1%, while the resulting automated Hosmer-Lemeshow goodness-of-fit for the full model prediction did not differ from our observed data (χ^2 value of 11.97, 8 df, p = 0.15), which indicated that our data fitted the model well. According to the standard errors of β coefficients and the correlation matrix values, we inferred there were no correlations between variables, which meant that the logistic model was statistically stable.

The LRM identified age as a reducing risk variable; since a decrease in one year in age had a 7% (95% CI 2% to 12%) decreased odds of developing hypoglycaemia. On the contrary, duration of t2DM was a positive risk variable, since an increase in one year of diabetes duration had an 11.9% (95% CI 5% to 20%) increased odds of developing SH. Likewise, educational level (illiteracy-primary level), attending physicians' specialty (family physician), presence of CRF, antihyperglycemic treatment

Table 3. Bivariate analysis and distribution of clinical and demographic variables among 94 type 2 diabetes mellitus patients with symptomatic hypoglycemia (cases) and 188 without it (controls).

Variable	Cases n (%)	Controls n (%)	p*
Educational level:			< 0.01
Illiteracy-elementary school	83 (88.3)	123 (65.4)	
Secondary school- higher degree	11 (11.7)	65 (34.6)	
Attending physician:			0.01
Family physician	84 (89.4)	144 (76.6)	
Specialist physician	10 (10.6)	44 (23.4)	
Chronic renal failure:			< 0.01
Yes	28 (29.8)	21 (11.2)	< 0.01
Antihyperglycemic therapy:			
One drug	53 (56.4)	149 (79.3)	
Two drugs	41 (43.6)	39 (20.7)	
Polypharmacy:†			< 0.01
Yes	91 (96.8)	152 (80.9)	
No	3 (3.2)	152 (80.9)	
Fasting or missed meals:			< 0.01
Yes	71 (75.5)	25 (13.3)	
History of hypoglycemia:			< 0.01
Yes	44 (46.8)	36 (19.1)	

* Two-tailed χ^2 test. †: Antihypertensives, vasodilators, antimicrobials and/or non-steroidal antiinflamatory drugs were included.

Table 4. Variables clinically and statistically significant among 94 type 2 diabetes mellitus patients with hypoglycemia (cases) and 188 without it (controls), according to the logistic regression model.

Variable	β	SE *	Wald†	OR‡	(95% CI)§	p‖	CM¶
Age (years)	-0.07	0.02	6.84	0.93	(0.88-0.98)	0.008	-0.636
Diabetes duration (years)	0.11	0.03	10.26	1.119	(1.05-1.2)	0.001	0.400
Illiteracy-primary	1.31	0.50	6.72	3.7	(1.4-10.0)	0.009	-0.172
Attending physician (FP)	1.04	0.52	4.0	2.8	(1.02-7.9)	0.04	-0.198
Chronic renal failure (Yes)	1.11	0.47	5.62	3.0	(1.2-7.7)	0.01	-0.056
Missed meals (Yes)	2.98	0.39	56.24	19.8	(9.1-43.1)	< 0.001	-0.035
Previous hypoglycemia (Yes)	1.06	0.41	6.52	2.9	(1.3-6.5)	0.01	0.197
Combined therapy (Yes)	1.64	0.41	15.56	5.2	(2.3-11.8)	< 0.01	-0.238
Polypharmacy use (Yes)	1.58	1.0	2.45	4.9	(0.7-35.1)	0.11	-0.601
Intercept	-3.69	1.65	4.99			0.02	1.000

* Standard error for the β coefficients. †: Wald χ^2 test. ‡: Odds ratio (Exponent β values). §: 95% confidence intervals. ‖: p values from the Wald χ^2 test. ¶: Correlation matrix.

(combined therapy), history of fasting or missed meals prior to hospitalization and having had a history of hypoglycemia served as high risk variables. The only variable excluded from the LRM was "use of polypharmacy". Complementary data is shown in table 4.

DISCUSSION

The present study brought together cases of SH, all of which had a diagnosis based on established criteria,[3,4] coincident to those recently established by the American Diabetes Association,[15] and to those cases found by Miller, *et al*.[6] who described patients with a hypoglycemic clinical picture when plasma glucose level was 75 mg/dL (4.2 mmol/L).

Diverse demographic and clinical risk factors associated with SH have been identified in time in t2DM patients, so searching which ones are most relevant for a particular diabetic group is the most appropriate. Among those analyzed in this case-control study, the LRM identified the educational level as an factor independently associated with SH, since the illiteracy-primary level exposed patients to almost four-fold odds of developing that complication, a finding relevant to us because to our knowledge that variable had not been identified as such, although indirect data do exist in that respect.

Several authors[16,17] have documented how illiteracy, one of two mediators of the socioeconomic status, associates t2DM[17] with high morbidity and how it acts as a barrier to high-quality care.[16] In the same context Leese, *et al*.[18] have found an association between increasing socioeconomic deprivation and severe hypoglycemia, a finding that could be explained by the difficulty that patients with such demographic characteristics would have in understanding verbal or written medical instructions about diabetes care and surrounding circumstances regarding appropriate use of antihyperglycemic drugs. Ko, *et al*. in a Chinese population-based study[19] documented how low educational level increased more than twice the odds for developing diabetes, glucose intolerance and obesity in both men and women respectively.

Patients' age ≥ 60 years old[8,18,20] and t2DM duration time[4,11,18] are two factors previously associated with SH, although other researchers[6,11,12] found no such associations, findings partly coincident with ours since even when both variables were clinically and statistically relevant, t2DM duration time had a positive effect (increased risk) but not age. Concerning this variable, we documented a "protective" relationship between age and hypoglycemia, since the younger the patient the lesser the odds of developing hypoglycemia, although the opposite was also seen regarding t2DM duration time, since the longer the diabetes duration the greater the odds of developing hypoglycemia. Explanations for those results do exist and could even diverge. On one hand, our findings would make sense if both age and duration of t2DM, are taken together in a pathophysiological context in which counterregulatory mechanisms opposing hypoglycemia would be sufficiently deteriorated, as is expected to occurs in older patients with advanced t2DM duration time.[21] On the other hand, to assert that protracted t2DM instead of age acts as the relevant factor associated with SH would also make sense because diabetes in the long-term will damage the autonomic counterregulatory mechanism-opposing hypoglycemia, as can be seen in younger (< 40 year old) t1DM patients.[22] This argument can be supported by Burge, *et al*.[23] who in a clinical trial found no hypoglycemic episodes among otherwise healthy elderly t2DM patients receiving maximal doses of a sulfonylurea during a short-term fast period. The authors documented at the same time a rise in serum epinephrine concentration, which indicates counterregulatory mechanisms-opposing hypoglycemia are not necessarily deteriorated in older patients, but they are in long-standing t2DM.[21,22]

In the present study, prescription of antihyperglycemic medications varied among cases and controls, monotherapy prevailing over combined therapy; in fact, combined therapy increased at least five-fold the odds of developing a hypoglycemic episode. This could occur because higher doses, alone or in combined schema, are usually prescribed by physicians whose rationale is to achieve strict glycemia control when confronted with long-standing hyperglycemia.[12,18]

There is little doubt about the role glibenclamide played in SH genesis due to its inherent pharmacological action or due to its reinforced effect when administered with another antihyperglycemic drug, findings consistent with that of other investigators;[1,6,7] nonetheless, contrary to these statements in the randomized trial of Burge, *et al*.[23] no hypoglycemic episodes were documented among patients who received up to 20 mg a day of glyburide or glipizide, although in this trial only comorbidity-free patients and polypharmacy-free patients were included.

In the present study the attending physicians' specialty was one of the searched variables identified in LRM as associated with SH. We decided to include this variable in the analysis because to our knowledge nothing has been mentioned about it and

because we know a high proportion of patients, cases and controls had been and are still being treated by family practitioners. In that respect there exist data ascribing primary care practices of poor quality of diabetes care in various medical aspects.[24-26] Possible reasons for that are related to the perspective primary care providers have regarding t2DM management, such as characteristics of the disease that make it harder to treat,[24] how these specialist physicians structure time during patient visits for diabetes control,[25] or even related to the professional profile as was documented among a sample of Mexican family physicians.[26]

One of the comorbid processes frequently found in t2DM is CRF whose association with SH was documented by us and other investigators.[11,20] Holstein, *et al*.[20] analyzing risk factors associated with SH stressed irrespective of the prescribed treatment that such a comorbidity is one of the most frequent contributing factors for developing SH in t2DM, as evidenced in 54% of their cases. The mechanisms by which CRF participates in hypoglycemia genesis resides as much in the way certain antihyperglycemic drugs and/or their metabolites are excreted through the kidneys, as in the organ's ability for producing glucose from noncarbohydrate precursors[27,28] –both mechanisms are usually compromised in subjects with either long-standing t1DM or t2DM–.[21,22]

History of fasting or missed meal before hospitalization and history of hypoglycemia were both strongly related to SH, since the former increased almost 20-fold odds and the latter almost three-fold odds of developing hypoglycemia, findings in agreement with that of other investigators who documented such associations.[4,6] Nonetheless, in relation to missed meals as a cause of hypoglycemia Burge, *et al*.[23] did not uncover hypoglycemic episodes among older, fasting diabetic patients, even when treated with high dose long-acting sulfonilureas. On the other hand, relevance of history of hypoglycemia must be seen in the context of the new episode as in that of avoiding subsequent events, because every episode could be manifesting the presence of hypoglycemia-associated autonomic failure, an inducible but reversible pathophysiological state in which the homeostatic glucose compensatory mechanisms are no longer efficient, being therefore the cause of neurogenic responses seen as part of the hypoglycemic clinical picture, including the so called hypoglycemia unawareness state.[4,21]

Employing concomitant polypharmacy was not statistically associated with SH, a finding on one hand in agreement with investigators who did not detect any association when β-blockers, ACE drugs, and/or calcium antagonists were concomitantly taken with glucose-lowering drugs,[8,11] contrasting on the other hand with findings[3,20] in which exposure to such drugs or even to certain classes of ACE inhibitors[10] are actually associated with hypoglycemia. By the same token, using antimicrobial agents such as quinolones[29] could be associated with hypoglycemia, although only sporadic cases have been described, especially in subjects with chronic comorbidities. Patients from this investigation were frequently treated with either ciprofloxacin and contrary to other researchers,[29] we were not able to find such an association in the context of polypharmacy usage.

The reasons why polypharmacy was rejected as statistically and clinically significant from the LRM could have at least two explanations. One reason, although unlikely, is related to sample size included in the logistic regression model, since even though the variable had a high β coefficient its standard deviation was also higher, and consequently its Wald statistic a lower value. In that respect it has been said[30] that for large logit coefficients, standard error is inflated, lowering the Wald statistic as occurred in our analysis, which should lead to type II error; that is, thinking the effect is not significant when in fact it is. A second explanation might have to do with the fact that polypharmacy really have no influence on hypoglycemia development, since the type of drugs our patients were usually exposed to were of the same class Shorr, *et al*.[8] did not find associated with hypoglycemia. To our knowledge certain findings relating polypharmacy to hypoglycemia[10] are still questionable.

CONCLUSION

In conclusion, duration of t2DM, educational level (illiteracy-primary level), attending physicians' specialty, presence of CRF, combined antihyperglycemic therapy, history of fasting or missed meals and history of hypoglycemia were all risk factors associated with SH, while age had a "protective" effect. In this context physicians should be cognizant that the odds of symptomatic hypoglycemia might very well be increased when treating patients with t2DM fulfilling factors, such as those identified in this investigation.

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REFERENCES

1. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-53.
2. Cryer PE, Childs BP. Negotiating the barrier of hypoglycemia in diabetes. *Diabetes Spectr* 2002; 15: 20-7.
3. Yale JF, Begg I, Gerstein H, Houlden R, Jones H, Maheux P, Pacaud D. 2001 Canadian Diabetes Association clinical practice guidelines for prevention and management of hypoglycemia in diabetes. *Can J Diabetes* 2001; 26: 22-35.
4. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003; 26: 1902-12.
5. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 1996; 44: 751-5.
6. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 2001; 161: 1653-9.
7. Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. *Diabet Med* 1999; 16: 586-90.
8. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 1997; 157: 1681-6.
9. Sone H, Takahashi A, Yamada N. Ibuprofen-related hypoglycemia in a patient receiving sulfonylurea. *Ann Intern Med* 2001; 134: 344.
10. Morris AD, Boyle DI, McMahom AD, Pearce H, Evans JM, Newton RW, et al. ACE inhibitor use is associated with hospitalization for sever hypoglycemia in patients with diabetes. *Diabetes Care* 1997; 20: 1363-7.
11. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea –induced hypoglycemia in diabetic patients with end-stage renal disease. *Am J Kidney Dis* 2000; 35: 500-05.
12. Klein BE, Klein R, Moss SE. Risk of hypoglycemia in users of human insulin. *Diabetes Care* 1997; 20: 336-9.
13. Ellis PA, Cairns HS. Renal impairment in elderly patients with hypertension and diabetes. *Q J Med* 2001; 94: 261-5.
14. Peduzzi P, Concato J, Kemper E, Holford TR Feinstein AR. A simulation study of the number of events per variable in a logistic regression analysis. *J Clin Epidemiol* 1996; 49: 1373-9.
15. American Diabetes Association. Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 2005; 28: 1245-9.
16. Williams MV. Recognizing and overcoming inadequate health care literacy, a barrier to care. *Cleve Clin J Med* 2002; 69: 415-8.
17. Zgibor JC, Songer TJ. External barriers to diabetes care: addressing personal and health systems issues. *Diabetes Spectr* 2001; 14: 23-8.
18. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes. *Diabetes Care* 2003; 26: 1176-80.
19. Ko G, Chan J, Yeung V, Chow CC, Tsang L, Cockram CS. A low socioeconomic status is an additional risk factor for glucose intolerance in high risk Hong Kong Chinese. *Eur J Epidemiol* 2001; 17: 289-95.
20. Holstein A, Plaschke A, Egberts EH. Clinical characterisation of severe hypoglycemia: a prospective population-based study. *Exp Clin Endocrinol Diabetes* 2003; 111: 364-9.
21. Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 2002; 51: 724-33.
22. Cersosimo E, Garlick P, Ferreti J. Abnormal glucose handling by the kidney in response to hypoglycaemia in type 1 diabetes. *Diabetes* 2001; 50: 2087-93.
23. Burge MR, Schimitz-Fiorentino K, Fischette C, Qualls CR, Schade DS. A prospective trial of risk factors for sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus. *JAMA* 1998; 279: 137-43.
24. Larme AC, Pugh JA. Attitudes of primary care providers toward diabetes. *Diabetes Care* 1998; 21: 1391-6.
25. Yawn B, Zyzanski SJ, Goodwin MA, Gotler RS, Stange KC. Is diabetes treated as an acute o chronic illness in a community family practice? *Diabetes Care* 2001; 24: 1390-6.
26. Rodríguez-Moctezuma R, Magaleno-Tobías ME, Murguía-Miranda C, Hernández-Santiago JL, De la Torre EC. Factores de los médicos familiares asociados al control glucémico de sus pacientes con diabetes mellitus. *Gac Med Mex* 2003; 139: 112-7.
27. Cersosimo E, Garlick P, Ferreti J. Renal glucose production during insulin-induced hypoglycemia in humans. *Diabetes* 1999; 48: 261-6.
28. Cersosimo E, Garlick P, Ferreti J. Renal substrate metabolism and gluconeogenesis during hypoglycemia in humans. *Diabetes* 2000; 49: 1186-93.
29. Roberge RJ, Kaplan R, Frank R, Fore C. Glyburide-ciprofloxacin interaction with resistant hypoglycemia. *Ann Emerg Med* 2000; 36: 160-3.
30. Garson D. Logistic regression. Disponible en: http://www2.chass.ncsu.edu/garson/pa765/logistic.htm. Accessed august 10, 2008.

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