

Age, the Number of Medicines Taken and Comorbidities are Associated with Changes of Fasting Blood Glucose Levels in Elderly Diabetics Taking Propranolol and Hydrochlorothiazide

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Abstract

To achieve glycemic control in patients with Diabetes, various medicines are prescribed; however, some may affect blood glucose concentration, requiring dose adjustment. Studies with small sample size, reported that propranolol and hydrochlorothiazide may change glycemic levels but this data are conflicting. The aim of this study is evaluating if propranolol and hydrochlorothiazide change glycemic control in elderly hypertensive diabetics compared to diabetics without hypertension. We conducted a cross-section study and included hypertensive diabetics of both genders from 18 yrs to 90 yrs of age, using propranolol and hydrochlorothiazide (DHPH) taken orally either together or separate. The group of diabetics without hypertension was composed of patients of both genders from 18 yrs to 90 yrs of age. Clinical parameters being fasting blood glucose, postprandial glycaemia and glycated hemoglobin from the last six months was collected from medical records. The differences between groups were compared by the Student's t-test (continuous variables) and the X²-test (categorical variables). Logistic regression analyses were used to compare the influence of variables in glycemic control in both groups. The per capita income (<0.01), age (<0.01), complexity of pharmacotherapy (<0.01), number of medicines taken (<0.01) and comorbidities (<0.01) in the DHPH group was significant. Logistic regression analyses demonstrated that the comorbidities (<0.01), number of drugs taken (<0.01) and age (<0.01), influence fasting blood glucose in the DHPH group. Fasting blood glucose levels of elderly hypertensive diabetics taking propranolol and hydrochlorothiazide are influenced by age, number of medicines taken and number comorbidities.

Keywords: Propranolol; Hydrochlorothiazide; Diabetes; Glycemic control; Fasting blood glucose

Introduction

Currently 382 million people are affected by diabetes worldwide and 85% of patients have comorbidities that require them to take various medications [1-3]. Medications used in disease control are essential but they may affect blood glucose concentration, requiring insulin dose adjustment. An extensive list of medications that may adversely affect glycemic control in diabetics was evaluated by the European Medicines Agency and Internet-based information resources (e.g. Diabetes in Control and dLife) [4-6]. Propranolol and hydrochlorothiazide presented in the list are frequently used by hypertensive diabetics, but your effects in change of glucose levels are still conflicting [7-9].

Propranolol is antihypertensive drug used by elderly hypertensive diabetics with adverse effects in carbohydrate metabolism, producing distinct effects in blood glucose control [10]. It may reduce blood glucose concentration by blocking catecholamine stimulating glycogenolysis and gluconeogenesis [11] or increase glucose concentration by inhibition of the release of insulin from pancreatic β -cells mediated by β_2 adrenoreceptors [12]. Clinical trials suggest that hypertensive diabetics can take beta-blockers safely but the results are conflicting due to small sample size [13,14].

Diuretics are used in low doses by elderly hypertensive diabetics in the prevention of major cardiovascular events [15,16]. However, the use of diuretics in elderly diabetics is dangerous because of the affect of release of insulin and when combined with propranolol may increase blood glucose concentration [17]. Besides producing hypoglycemia [18], thiazide diuretics are associated with adverse metabolic effects, glucose intolerance and hyperglycaemia as well as the incidence of diabetes [19,20].

This evidence suggests that propranolol and hydrochlorothiazide may affect glycemic control in elderly hypertensive diabetics although studies found in the literature report a small sample size. To our knowledge, no study has been performed to analyze the influence of propranolol and hydrochlorothiazide in elderly hypertensive diabetics compared to diabetics without hypertension, with a large sample size. The hypothesis to be tested is that elderly hypertensive diabetics have changed in glucose levels due to use of propranolol and hydrochlorothiazide. In this context, this study aimed to evaluate if propranolol and hydrochlorothiazide modify glycemic control in elderly hypertensive diabetics.

Materials and Methods

Study design

This is cross-sectional study that was conducted in a care home for diabetics in the Franca city (344.706) inhabitants located in the interior of São Paulo-Brazil. Currently, the city Franca have fourteen public

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health system units, five family health programs, as well as outpatient and specialty care units (Assistance Management Center, Adult and Infantile Mental Health Outpatient Clinic, Diabetic Care Home, Ophthalmology Center), DILC – Diagnostic Image and Laboratory Center and ready-to-care (Adult and Child Emergency, X-ray). The public health unit in the study had a mean monthly attendance of 350 people. The patients were recruited in this unit between August 2016 and December 2016 and the STROBE Statement was followed in this study.

Selection of patients

We included all patients that were attendance in the health unit in the period of study, thus we did not calculate the sample size. The study sample included elderly hypertensive diabetics of both genders with between 18 yrs and 90 yrs of age in use of insulin NPH and oral hypoglycemic agents, using propranolol and hydrochlorothiazide (DHPH) taken orally together or separated. As control group, we recruit elderly diabetics without hypertension (DWH) was composed of both genders between 18 yrs and 90 yrs of age. Clinical parameters such as fasting blood glucose, postprandial glycaemia and glycated hemoglobin from the last six months were collected from medical records. An average of the last six months this parameters. We excluded patients of both groups without medical records of glycemic control levels because this variable is crucial for this study and patients in use of medicines that may change glycemic control as glucocorticoids.

Data collection

Participant recruitment occurred as follows: Patients were selected before medical consultation, interviews were made in a room separate from the doctor's office and the average time of each interview was 20 min. A questionnaire consisting of open questions was applied to all patients by one of the authors of this study. A pilot study was made for validation and standardization of the questionnaire in twenty patients to correct difficulties in interpretation and these volunteers were excluded from the analysis. The variables collected through the questionnaire were age, gender, marital status, per capita income, schooling, comorbidities, diabetes diagnosis time, number of drugs taken, fasting blood glucose levels, postprandial glycaemia and glycated hemoglobin.

The complexity of pharmacotherapy and complications of diabetes can modify quality of life by altering blood glucose control. Thus, the instruments: Complexity of Pharmacotherapy Index (CPI) and Diabetes Complications Index (DCI) were applied to both groups. CPI is an instrument divided into three sections: A, B and C. CPI is obtained by the sum of scores of the three sections. High section scores are defined as greater complexity [21].

DCI is an instrument composed of 17 questions to analyze the complications related to diabetes. Five questions evaluate coronary heart disease, three questions for stroke, two questions for peripheral vascular disease, two questions for neuropathy, three questions for diabetic foot complications and two questions for diabetic retinopathy [22]. Each complication is determined for two or more questions, for example, coronary heart disease is present if the patient reported having myocardial infarction, symptoms of angina pectoris, or having been diagnosed by a doctor. The sums of any complications that are present are calculated, resulting in scores from 0 to 6. High section scores are defined as greater complications of Diabetes.

Ethics

All individuals who fulfilled the inclusion criteria were invited to sign the Free and Informed Consent Terms and this study was approved by Ethics Committee, protocol number No.7724/2015.

Statistical analysis

Statistical analysis was performed using SAS version 9.3. Continuous variables were reported as means and standard deviations (sd) and the categorical variables were reported as frequencies and percentages. Approximate normality of distributions was assessed by normal probability plots.

Considering the relatively small number of independent variables and the absence of effect of collinearity, it was used a multiple logistic regression model simultaneously including all the variables and this procedure allows us to identify the variables that have any association with the outcome. It was therefore not necessary to use any type of method for selection of variables, such as the forward or backward. In addition, we observed that these methods of variable selection do not provide any gain in the results (the conclusions are the same as before). Significance was set as $p < 0.05$.

Variables	DWH (n=93)	DHPH (n=61)	OR (CI)	P
Sex				
Male	42 (45%)	21 (74%)	1.56 (0.80-3.5)	0.18
Female	51 (55%)	40 (26%)		
Race				
White	41 (45%)	26 (44%)	0.70 (0.22-2.2)	0.57
Black	11 (11%)	5 (8%)		
Brown	41 (44%)	30 (48%)	1.15 (0.58-2.2)	0.68
Marital status				
Married	45 (48%)	38 (63%)	0.56 (0.29-1.0)	0.09
Single/divorced	48 (52%)	23 (27%)		
Levels schooling (years)				
0-8	64 (69%)	53 (86%)	0.33 (0.14-0.78)	<0.01*
09-12	29 (31%)	8 (14%)		
Comorbidities				
Dyslipidemia	20 (22%)	28 (46%)		
Obesity	44 (47%)	36 (59%)		
Retinopathy	17 (18%)	21 (34%)		
Depression	8 (9%)	14 (23%)		
Thyroid disorders	11 (18%)	11 (12%)		
Time of diagnosis (months)	195 ± 99	204 ± 91	174-215 ^a 180-226 ^b	0.59
Age (years)	58 ± 15,7	63,9 ± 10,3	54-61 ^a 61-66 ^b	<0.01*
Per capita income	523,6 ± 240	629,8 ± 242	473-573 ^a 568-691 ^b	<0.01*
Fasting blood glucose (mg/dl)	150,8 ± 73	167 ± 69	135-165 ^a 149-184 ^b	0.15
Postprandial glucose (mg/dl)	219 ± 93	212 ± 99	200-239 ^a 186-237 ^b	0.62
HbA _{1c} (%)	9 ± 2	8,8 ± 1,5	8.5-9.4 ^a 8.4-9.1 ^b	0.54
Number of comorbidities	3,5 ± 2,2	4,5 ± 1,9	3-3.9 ^a 4.2-5 ^b	<0.01*
Complications diabetes index	2,2 ± 1,4	2,4 ± 1,3	1.9-2.5 ^a 2-2,7 ^b	0.4
Number drugs taking	4,2 ± 2,2	7,3 ± 1,9	3.7-4.6 ^a 6.8-7.7 ^b	<0.01*
Complexity of pharmacotherapy	15,3 ± 5	21,8 ± 5,6	14-16 ^a 20-23 ^b	<0.01*

Table 1: Demographic and basic characteristics of patients.

Results

In baseline, the final sample consisted of 154 patients. The DWH group consisted of 93 patients (45% male and 55% female) and the DHPH group consisted of 61 patients (26% male and 74% female). The DWH group had 41 (45%) white, 11 (11%) black and 41 mixed race people and the DHPH group had 26 (44%) white, 5 (8%) black and 30 (48%) mixed race people. Marital status in DWH had more people married (45 vs. 38) and single/divorced (48 vs. 23) compared to DHPH. The schooling level was significant in the DWH group 0.33 (95% CI: 0.14-0.78, <0.01) compared with the DHPH group (Table 1).

The time of diagnosis in diabetes in the DHPH group was higher (204 ± 91 vs. 195 ± 99) compared to DWH. Fasting blood glucose levels in the DHPH group was higher (167 ± 69.1 vs. 150.8 ± 73) compared to DWH however, postprandial glycaemia levels (219 ± 93 vs. 212 ± 99) and glycated hemoglobin (9 ± 2 vs. 8.8 ± 1.5) of the DWH group were slightly higher compared to the DHPH group.

There were significant differences in age (63.9 ± 1.3 vs. 59.5 ± 1, <0.01), per capita income (629.8 ± 242.4 vs. 523.6 ± 240, <0.01), comorbidities (4.5 ± 1.9 vs. 3.5 ± 2.2, <0.01), number drugs taken (7.3 ± 1.9 vs. 4.2 ± 2.2, <0.01), CPI (21.8 ± 5.6 vs. 15.4 ± 5, <0.01) of DHPH compared to DWH.

There were no significant differences between groups in Table 2, but the levels of fasting blood glucose and Hb1Ac of elderly hypertensive diabetics taking propranolol, propranolol+hydrochlorothiazide and hydrochlorothiazide alone, were high comparing in the DWH.

Logistic regression analysis demonstrated that the number of comorbidities (<0.01), number of drugs taken, (<0.01) and age (<0.01) can influence the levels of fasting blood glucose in the DHPH group (Table 3).

Discussion

In this study, we demonstrated that of propranolol and hydrochlorothiazide taken orally alone or concomitantly may alter fasting blood glucose concentration in elderly hypertensive diabetics

compared with DWH. This is an original study and to our knowledge, no previous report has compared elderly hypertensive diabetics taking propranolol and hydrochlorothiazide orally alone or concomitantly with elderly diabetic patients without hypertension especially in the basic unit health.

As the main result, logistic regression analyses (Table 3) demonstrated that age, number of comorbidities and number of drugs taken, influence fasting blood glucose in the DHPH group. The study confirms the hypothesis that the use of propranolol and hydrochlorothiazide in elderly hypertensive diabetics added to the number of drugs taken and CPI, influence fasting blood glucose. In 2015, a systematic review showed that propranolol and hydrochlorothiazide increased fasting blood glucose and HbA1c in hypertensive diabetics [23]. Poor glycemic control can cause long-term macrovascular and microvascular diabetes complications, thus the patients require use of various medications for the control of diabetes complications. Interestingly, our study demonstrated that there were significant differences (Table 1) in the CPI of the DHPH group compared with the DWH group. It is noteworthy that the biggest number of comorbidities, number of drugs taken and age contributed to higher CPI scores of the DHPH group compared with the DWH group. The comorbidities can progress to development of macrovascular and microvascular complications in diabetes, increasing the number of drugs taken; producing adverse effects that compromise the quality of life of diabetic patients.

There were no significant differences of glycemic control in comparing the groups (Table 2). Although when separate levels of fasting blood glucose were analyzed, postprandial glucose and glycated hemoglobin according to the drugs taken (propranolol 80 mg/day, hydrochlorothiazide 50 mg/day or taken together), verified a small difference. Fasting blood levels of six patients taking only propranolol were increased when compared to DWH. When only the six elderly hypertensive diabetics taking propranolol and hydrochlorothiazide were analyzed, it is noteworthy that there were differences of glycemic levels compared to DWH, though they are not significant. Only a small clinical trial with 14 male hypertensive diabetics followed for 3 weeks, taking drugs in the dosages described above, showed that both drugs change fasting blood glucose concentration and glycated hemoglobin [17]. Comparing the fasting blood glucose levels of hypertensive diabetics taking only propranolol 80 mg/day with those taking only hydrochlorothiazide, a small difference was verified.

The clinical trials with non-selective beta-blockers found that propranolol increased levels of fasting blood glucose more than selective beta-blockers; however these data are conflicting [7-9]. The opposing mechanism of action of non-selective beta-blockers that can alter insulin secretion and glucose utilization and increase glucose concentration in elderly hypertensive diabetics taking propranolol, predominate over those that could cause a reduction due to the effects of mediated *via* B2-adrenoceptors.

Hydrochlorothiazide has been associated with hyperglycemia in hypertensive diabetics [24,25]. In our study, fasting blood glucose levels of 49 patients taking only hydrochlorothiazide were increased when compared to DWH were demonstrated, but not significant. Interestingly, elderly hypertensive diabetics taking both medications had all clinical parameters increased when compared to the other groups (Table 2). This fact may be due to diuretics probably only affecting insulin secretion and when combined with beta-blockers can increase blood glucose concentration [17,24,25].

	DWH ^a n=93	Hydro ^b . 50 mg n=49	Prop ^c .80 mg n=6	Prop ^d .80+Hydro.50 n=6	p
Fasting blood glucose	150.7 ± 72.8	162.9 ± 72.9	169 ± 33.2	201 ± 58.4	0.32
Postprandial glucose	219 ± 93.2	209.4 ± 100	197 ± 80	246 ± 116	0.75
HbA1 _c	8.9 ± 2,1	8.7 ± 1.5	8.5 ± 1,2	9.8 ± 1,5	0.53

Table 2: Influence of hydrochlorothiazide and propranolol in glycemic control. a) DWH: Diabetics without hypertension; b) Hydrochlorothiazide 50 mg/day; c) Prop.80: Propranolol 80 mg/day; d) Prop.80/day+Hydro.50/day; mean and sd, t-student test.

Predictors variables	Estimate	Standard error	Chi-square	P
Comorbidities	0.36	0.1	11.41	<0.01
Gender	-0.17	0.19	0.76	0.38
Age	0.03	0.01	4.66	<0.03
Number medications	0.71	0.12	33.9	<0.01
Fasting blood glucose	0	0.01	4.39	<0.03
Postprandial glucose	0	0	0.94	0.32
HbA1 _c	0	0.13	0	0.94
Diabetes complications	-0.26	0.16	2.54	0.11
p-value < 0.05				

Table 3: Results of logistic regression analysis of predictor's variables control glycemic.

Beta-blockers and thiazide diuretics are widely used for people with diabetes for blood pressure control, nevertheless there are few studies showing adverse effects of propranolol and hydrochlorothiazide and the follow-up of these patients using these drugs is relatively short [17]. Several studies reported that some drugs can affect blood glucose control, but there is little information about which drugs should be avoided in people with diabetes. There is strong evidence targeting the use of other classes of antihypertensive when possible and closer monitoring of glycemic control for a short time after initiating one of these medications [23]. A list of the drugs that affect glycemic control placed on the table of doctor would help both physicians and patients.

This study had some limitations. First, the group of hypertensive diabetic had only six patients taking propranolol orally and six patients taking both medications orally. Even with small sample size, we can demonstrate that propranolol and hydrochlorothiazide taken orally alone or concomitantly may alter the fasting blood glucose concentration in hypertensive diabetics compared with diabetics without hypertension. A larger sample in the DHPH group would argue significant differences. Moreover, all trials were small when compared with this study and none analyzed the influence of these drugs between hypertensive diabetics compared with diabetics without hypertension. The largest level of schooling was in the DWH group which influenced glycemic control compared with DHPH. Second, the associations are cross-sectional, limiting causal inference and cross sectional and longitudinal studies are both observational studies; cross sectional studies provide only a single "snapshot". Third, we no recruit patients without diabetes or others diseases (negative control) for comparing with the others groups. Finally, our study was conducted in a single service, so the generalization of data should be performed with caution.

Conclusions

The results obtained in this work showed that propranolol and hydrochlorothiazide taken orally alone or concomitantly may alter the fasting blood glucose concentration in elderly hypertensive diabetics compared with diabetics without hypertension. Fasting blood glucose levels of the DHPH group were influenced by age, number of comorbidities and number of drugs taken, according to logistic regression analysis. Poor glycemic control contributes to macrovascular and microvascular complications in diabetes, thus it is recommended to replace propranolol and hydrochlorothiazide in the elderly by other drugs that do not modify fasting blood glucose. Furthermore, closer monitoring of glycemic control time after initiating one of these medications is advisable. However, it is not possible to attribute all weightings of glycemic change levels in propranolol and hydrochlorothiazide because diabetes complications and poor adherence to medication may influence glycemic control. Controlled clinical trials with a larger sample, evaluating the adherence to medication, longer follow-up, must be performed in the future to evaluate the change in glycemic control caused for both medicines.

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