BMJ Open

# FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTRIC STUDY IN BRAZIL



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018094 |
| Article Type: | Research |
| Date Submitted by the Author: | 06-Jun-2017 |
| Complete List of Authors: | ANDRADE, CARINE; Universidade Federal da Bahia, Escola de Nutrição<br>RIBEIRO, GUILHERME; Universidade Federal da Bahia, Institute of Collective Health; Oswaldo Cruz Foundation, Gonçalo Moniz Institute<br>SANTOS, CARLOS ANTONIO; Universidade Estadual de Feira de Santana; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute<br>NEVES, RAIMUNDO CELESTINO; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute<br>MOREIRA JR, EDSON; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute; Obras Sociais Irma Dulce |
| Primary Subject Heading: | Diabetes and endocrinology |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | type 1 diabetes, glycemic control, glycated hemoglobin, Epidemiology < TROPICAL MEDICINE |
| | |

# FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTRIC STUDY IN BRAZIL

Carine Sousa Andrade, PhD[a,b], Guilherme Sousa Ribeiro, PhD[a,c], Carlos Antonio Souza Teles Santos, PhD[a,d], Raimundo Celestino Silva Neves, PhD[a], Edson Duarte Moreira Jr., PhD[a,e]*.

(a) Gonçalo Moniz Institute, Oswaldo Cruz Foundation, Salvador, Brazil;

(b) School of Nutrition, Federal University of Bahia, Salvador, Brazil;

(c) Institute of Collective Health, Federal University of Bahia, Salvador, Brazil;

(d) State University of Feira de Santana, Feira de Santana, Brazil;

(e) Charitable Works Foundation of Sister Dulce, Salvador, Brazil.

*Address for correspondence: Dr. Edson D Moreira Jr.

Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Rua Waldemar Falcão 121, Salvador, Bahia, 40296-710, Brazil.

Tel .: +55 71 3176 2343; Fax: +55 71 3176 2243.

E-mail: edson@bahia.fiocruz.br (E. D. Moreira Jr.).

Word count: 3,093 words

## ABSTRACT

Objective: Long-term complications of type 1 diabetes mellitus (DM1) can be prevented with adequate glycemic control. However, high levels of glycated hemoglobin (HbA1c) occur in 60 to 90% of the DM1 patients. Thus, we aimed to investigate the role of sociodemographic, behavioral and clinical factors on the HbA1c levels of DM1 patients in Brazil.

Design, setting and participants: A cross-sectional study was conducted with ambulatory DM1 patients aged ≥18 years from 10 Brazilian cities. Sociodemographic, behavioral and clinical data were obtained through interviews.

Main outcome measures: HbA1c level was measured by liquid chromatography. Hierarchical multiple variable linear regression models were used to identify factors correlated with high levels of HbA1c.

Results: Of 979 DM1 patients, 63.8% were female and the mean age was 40 (SD: 14.6) years. The mean HbA1c level was 9.4% (SD: 2.2%), and 89.6% of the patients had HbA1c ≥7.0%. Factors independently correlated with increased HbA1c levels included: lower education, non-participation in diabetes classes/lecture during the year before, having a self-perception of poor adherence to diet and insulin, not having private medical care, and not measuring the HbA1c levels in the prior year. Of note, poor adherence to diet and insulin were the independent factors most strongly associated with high levels of HbA1c (mean increment in HbA1c levels of 0.88% and 1.25%, respectively).

Conclusion: Poor glycemic control, which is common among DM1 Brazilian patients, is associated with sociodemographic, behavioral and clinical factors. Specific actions,

particularly those targeting improving adherence to diet and insulin, may contribute to successful management of DM1 patients.

Keywords: type 1 diabetes, glycemic control, glycated hemoglobin, epidemiology.

**Strengths and limitations of this study**

- This cross-sectional, multicenter study included 979 type 1 diabetes mellitus patients from ten large Brazilian cities, representing four of the five regions of the country.
- We measured the HbA1c levels for all participants in a single laboratory, and used the same reference method of liquid chromatography, thus avoiding problems with lack of standardization reported by other authors.
- In order to identify independent factors associated with increased levels of HbA1c, we applied robust, multiple variable models, using a hierarchical approach according to a previously defined conceptual framework. This method accounts for hierarchical inter-relationships between variables and for the potential underestimation of the effects of distal determinants.
- Data on behavioral and clinical characteristics were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers.

## 1. INTRODUCTION

Type 1 diabetes mellitus (DM1) is characterized by the destruction of the insulin-producing pancreatic β cells, leading to an hyperglycemic state that requires continued reposition of exogenous insulin in order to prevent life-threatening acute and chronic complications[1]. The disease annual incidence varies greatly between countries, ranging from 1.1 to 39.9 per 100,000 persons 15-19 years of age[2], and is globally increasing at a rate of approximately 3% per year[3].

Patients with DM1 are at increased risk for cardiovascular disease, periphery nerve damage, nephropathy, and retinopathy, resulting in reduced life expectancy for those who are not properly treated[1]. This risk can be substantially reduced with intensive glycemic control, aiming glycated hemoglobin (HbA1c) levels <6.0%[4]. However, most patients with DM1 have HbA1c values above the international recommendation of <7.0%[5]. Inadequate glycemic control (HbA1c levels >7.0% in DM1 patients was observed in 77% of the participants of a study in the United States in 2016[6], in 74% of the study patients in the region of Castilla-La Mancha, Spain in 2012[7], and in 84%-90% of the participants of national multicenter studies conducted in Brazil in 2010 and 2015[8,9].

A better understanding of the factors that determine glycemic control is critical to improved management of DM1 patients. However, the majority of studies investigating determinants of glycemic control enrolled patients with type 2 diabetes mellitus (DM2) or studied patients with DM1 and DM2 combined, despite the fact that challenges to achieve glycemic control differ between patients with DM1 and DM2, mainly due to the compulsory need of insulin use in DM1 patients. In the few published reports on

determinants of glycemic control in DM1 patients, high levels of HbA1c have been associated with younger age, low educational level, poor adherence to diet, mode of insulin administration, and infrequent monitoring of blood glucose[10–14]. Here, we describe the results of our study in which we investigated the role of sociodemographic, behavioral and clinical characteristics in the levels of HbA1c in a large sample of patients with DM1 in Brazil, a country where >31,000 persons <15 years of age have DM1[15].

## 2. SUBJECTS, MATERIAL AND METHODS

### 2.1. Study Design and Sample Selection:

This cross-sectional, multicenter study was conducted in ten large Brazilian cities, representing four of the five regions of the country (Southeast region: Belo Horizonte, Campinas, Rio de Janeiro, and São Paulo; South region: Curitiba, and Porto Alegre; Midwest region: Brasilia; and Northeast region: Salvador, Fortaleza and Recife). These cities are the largest in their respective regions, and nine of them were ranked among the most populous municipalities in Brazil. To pursue the selection of the diabetes medical centers, we requested the Brazilian Diabetes Association to identify in each of the study city a list of candidate centers, selected because of previous experience in conducting epidemiological research and where a large number of adult patients are treated for diabetes (minimum of 300 patients per month). In each city, two diabetes centers (20 centers in total) were invited to participate in the study: five university-

affiliated hospitals, eleven general public hospitals, and four not-for-profit private hospitals. All invited centers accepted and were included in the study.

From February 2006 to March 2007, we invited patients fulfilling the eligibility criteria to participate in the study during 30 consecutive days in each of the centers. To be eligible for study enrollment, patients had to be ≥18 years of age and report a prior medical diagnosis of DM1. Patients who had participated in other research in the three months preceding the study were excluded. All patients were informed about the study aims, procedures and risks, and signed an informed consent prior to inclusion. A Research Ethics Committee from each of the selected cities approved the study.

### 2.2. Data Collection:

Trained interviewers who were not part of the medical centers staff interviewed the participants using a structured and pre-tested questionnaire to obtain data on demographic and socioeconomic indicators, self-perception of diet and insulin treatment adherence, attendance to diabetes education lectures, participation in associations of patients with diabetes, and clinical characteristics. Data on education attainment (primary school or less, complete or incomplete secondary/high school, or at least some college level education) and on race/skin color were self-reported. Data on self-perception of diet adherence and of insulin adherence were collected using the following ordinal scale: poor/fair, good, or excellent. Clinical data included time since first diagnosis of diabetes, number of insulin doses per day, frequency of self-monitoring of blood glucose, as well as frequencies, in the previous 12 months, of consultation in public and private medical service facilities, consultation with an endocrinologist, prior

hypoglycemic episodes, prior hospitalizations due to ketoacidosis and HbA1c measurements. Interviews were conducted in a private room and lasted 20-25 minutes. The response rate was 84% (ranging from 78% to 95%).

### 2.3. Measurement of Glycated Hemoglobin (HbA1c):

A blood sample was collected from participants at enrollment and tested by automated high performance liquid chromatography to determine HbA1c levels. All exams were performed in the same laboratory, according to standard procedures. The HbA1c levels data were reported as mean and standard deviation (SD) and, categorically, as a frequency of <7.0%, 7.0-8.9%, 9.0-10.9%, or ≥11.0%. We considered glycemic control to be inadequate when the HbA1c concentration was ≥7.0%[5].

### 2.4. Statistical Analysis:

Data were double entered into a computerized database using the EPI INFO version 3.04 software system (Centers for Disease Control and Prevention, Atlanta, USA). Subsequently, the two databases were electronic compared to validate the accuracy and internal consistency of the data. Statistical analyses were performed using version 12 of STATA (StataCorp., College Station, USA).

Participants' characteristics were presented using means and standard deviation for continuous variables, and frequencies for categorical variables. We applied bivariate and multiple variables linear regression models to estimate the effect of the independent variables on the level of HbA1c. Variables with a significant association at p value of ≤0.20 in the bivariate analyses were included in robust, multiple variable models using a

hierarchical approach according to a previously defined conceptual framework that accounted for hierarchical inter-relationships between variables and for the potential underestimation of the effects of distal determinants.

The hierarchical model grouped variables in three blocks (Figure 1). Block 1 contained socioeconomic variables, such as education level and race/skin color. Block 2 contained behavioral variables, such as attendance to diabetes class/lectures, participation in associations of patients with diabetes, and self-perception of adherence to diet and insulin treatment. Block 3 comprised of clinical characteristics, including time since first diagnosis of diabetes, number of insulin doses per day, and frequency of self-monitoring of blood glucose, consultation with an endocrinologist, and HbA1c measurement in the previous 12 months (Figure 1).

A backward elimination strategy was then performed for each block. Block 1 variables that were significantly correlated with HbA1c serum levels at a *p* value ≤0.05 were maintained in the subsequent backward elimination model with block 2 variables. Using the same approach, block 2 variables that were significantly correlated with HbA1c serum levels at a *p* value ≤0.05 were maintained in the subsequent backward elimination model with block 3 variables. Finally, block 3 variables with a *p* value ≤0.05 were defined as factors independently correlated with the HbA1c levels. Variables from block 1 and block 2 that were selected to be included in following models were considered to be significantly correlated with HbA1c levels, regardless of their *p* value in the subsequent models. Sex and age were included in all models to ensure adjustments to these factors at all stages of the multiple variable analyses. We used the Akaike

Information Criterion (AIC) to estimate the goodness of fit of the successive adjusted models.

## 3. RESULTS

Of the 979 DM1 patients enrolled in the study, 625 (63.8%) were female, and 296 (30.2%) were 18-29 years of age, 412 (42.1%) 30-49 years of age, and 271 (27.7%) ≥50 years of age (Table 1). About half (488, 49.8%) of the patients self-referred to be white, and 398 (40.8%) had not studied beyond the primary school level. The Southeast region of Brazil accounted for 611 (62.4%) participants. Although all the diabetes centers were affiliated with the Brazilian public health care system, 95 (9.7%) of the patients reported they had also received private assistance during the past 12 months.

TABLE 1. Sociodemographic and clinical characteristics of 979 Brazilian patients with type 1 diabetes, Brazil.

| Characteristics | n (%) |
|---|---|
| SOCIODEMOGRAPHICS | |
| Age (years) | |
| 18 – 29 | 296 (30.2) |
| 30 – 49 | 412 (42.1) |
| ≥ 50 | 271 (27.7) |
| Sex Female | 625 (63.8) |
| Racial/Ethnic | |
| White | 488 (49.8) |
| Mixed | 286 (29.2) |
| Black | 122 (12.5) |
| Other | 83 (8.5) |
| Education[1] | |
| At least some College | 154 (15.8) |
| Secondary/High school | 424 (43.4) |
| Primary school or less | 398 (40.8) |
| Brazilian Region | |
| Southeast | 611 (62.4) |
| Northeast | 174 (17.8) |
| South | 104 (10.6) |
| Center-west | 90 (9.2) |
| Type of service for medical care in the last year | |
| Public | 884 (90.3) |
| Private | 95 (9.7) |
| CLINICAL COMPLICATIONS | |
| Hypoglycemic episodes in the last year | 497 (50.8) |
| Ketoacidosis hospitalization in the last year | 248 (25.3) |
| Reported complications | |
| Retinopathy | 427 (43.6) |
| Neuropathy[2] | 381 (39.2) |
| Nephropathy | 207 (21.1) |
| Angina[3] | 129 (13.2) |
| Vasculopathy[3] | 125 (12.8) |
| LABORATORY | |
| Glycated Hemoglobin (HbA1c) (%) | |
| <7.0 | 102 (10.4) |
| 7.0 – 8.9 | 366 (37.4) |
| 9.0 – 10.9 | 287 (29.3) |
| >11.0 | 224 (22.9) |

[1] Data available for 976 patients

[2] Data available for 973 patients

[3] Data available for 977 patients

The diabetes complications most frequently reported by the study participants were retinopathy (427, 43.6%), followed by neuropathy (381, 39.2%) and nephropathy (207, 21.1%). Episodes of ketoacidosis and hypoglycemia in the previous year were common, affecting 248 (25.3%) and 497 (50.8%) patients, respectively. The majority (887, 89.6%) of patients had inadequate glycemic control (HbA1c ≥7.0%), and the mean HbA1c level was 9.4% (SD: 2.2%).

Bivariate analysis pointed to a correlation of higher levels of HbA1c with black race, lower education attainment, self-perception of fair/poor adherence to diet and to insulin treatment, not participating in diabetes class/lectures during the previous year, and never having participated in associations of patients with diabetes (Table 2). In addition, patients who reported that in the previous year had neither regular medical appointments, nor consultations with an endocrinologist, private consultations or health care delivered in the same diabetes center had significantly higher HbA1c. Finally, patients not performing regular self-monitoring of blood glucose, those with no measure of HbA1c during the previous year, and patients receiving less than four doses of insulin per day also had higher levels of HbA1c.

TABLE 2. Factors associated with glycated hemoglobin (HbA1c) levels in Brazilian patients with type 1 diabetes.

| Independent variable | Nº participants | HbA1c means in % (SD) | β Coefficient (CI 95%) | *p* value |
|---|---|---|---|---|
| BLOCK 1 – SOCIODEMOGRAPHIC | | | | |
| Age (years) | | | | |
| 18 – 29 | 296 | 9.35 (2.36) | Ref | |
| 30 – 49 | 412 | 9.54 (2.28) | 0.186 (-0.146; 0.517) | 0.273 |
| ≥ 50 | 271 | 9.24 (1.95) | -0.118 (-0.484; 0.248) | 0.527 |
| Sex | | | | |
| Male | 354 | 9.25 (2.08) | Ref | |
| Female | 625 | 9.48 (2.29) | 0.229 (-0.061; 0.518) | 0.122 |
| Racial/Ethnic | | | | |
| White | 488 | 9.26 (2.10) | Ref | |
| Mixed | 286 | 9.32 (2.33) | 0.133 (-0.191; 0.456) | 0.421 |
| Black | 122 | 9.84 (2.34) | 0.576 (0.136; 1.017) | 0.010 |
| Other | 83 | 9.62 (2.31) | 0.361 (-0.155; 0.877) | 0.170 |
| Education | | | | |
| At least some College | 154 | 9.13 (1.82) | Ref | |
| Secondary/High school | 424 | 9.21 (2.15) | 0.084 (-0.325; 0.492) | 0.688 |
| Primary school or less | 398 | 9.70 (2.40) | 0.565 (0.154; 0.977) | 0.007 |
| BLOCK 2 – BEHAVIORAL | | | | |
| Self-perception of adherence to diet | | | | |
| Excellent | 129 | 8.79 (2.22) | Ref | |
| Good | 327 | 9.13 (2.09) | 0.344 (-0.103; 0.792) | 0.131 |
| Fair / Poor | 523 | 9.72 (2.25) | 0.931 (0.508; 1.354) | <0.001 |
| Self-perception of adherence to insulin | | | | |
| Excellent | 750 | 9.28 (2.12) | Ref | |
| Good | 144 | 9.59 (2.30) | 0.315 (-0.074; 0.703) | 0.112 |
| Fair / Poor | 62 | 10.82 (2.49) | 1.543 (0.978; 2.107) | <0.001 |
| Participation in lecture for diabetes in the last year | | | | |
| Yes | 345 | 9.11 (2.09) | Ref | |
| No | 540 | 9.67 (2.31) | 0.549 (0.247; 0.850) | <0.001 |
| Participation in association of diabetics patients | | | | |
| Yes, still participate | 116 | 9.09 (1.88) | Ref | |
| Yes, but no more participate | 124 | 9.02 (1.80) | -0.067 (-0.627; 0.492) | 0.814 |
| No, I never participated | 713 | 9.51 (2.32) | 0.418 (-0.016; 0.851) | 0.059 |
| BLOCK 3 – CLINICAL | | | | |
| Regular medical visit in the last year | | | | |
| Yes | 878 | 9.34 (2.19) | Ref | |
| No | 101 | 9.89 (2.42) | 0.541 (0.084; 0.998) | 0.020 |
| Endocrinologist visit in the last year | | | | |
| Yes | 800 | 9.32 (2.15) | Ref | |
| No | 177 | 9.77 (2.50) | 0.453 (0.091; 0.814) | 0.014 |

| | | | | |
|---|---|---|---|---|
| Diabetes care in specialized service in the last year | | | | |
| Yes | 661 | 9.32 (2.18) | Ref | |
| No | 318 | 9.56 (2.29) | 0.236 (-0.061; 0.533) | 0.120 |
| Diabetes care in private clinic in the last year | | | | |
| Yes | 95 | 8.87 (1.61) | Ref | |
| No | 884 | 9.46 (2.27) | 0.586 (0.117; 1.055) | 0.014 |
| Diabetes care in the same service | | | | |
| Yes | 921 | 9.36 (2.18) | Ref | |
| No | 57 | 10.10 (2.64) | 0.735 (0.142; 1.328) | 0.015 |
| Time since diabetes onset (years) | | | | |
| < 10 | 261 | 9.43 (2.66) | Ref | |
| 10 – 19 | 307 | 9.52 (2.11) | 0.094 (-0.273; 0.460) | 0.616 |
| ≥ 20 | 408 | 9.27 (1.97) | -0.115 (-0.497; 0.192) | 0.386 |
| Self-monitoring glucose | | | | |
| Yes, regularly | 663 | 9.25 (2.14) | Ref | |
| Yes, when decompensated | 160 | 9.72 (2.28) | 0.463 (0.080; 0.845) | 0.018 |
| No | 151 | 9.74 (2.46) | 0.489 (0.097; 0.881) | 0.015 |
| Number insulin doses per day | | | | |
| 4 times | 168 | 8.91 (1.97) | Ref | |
| 3 times | 290 | 9.38 (2.10) | 0.451 (0.002; 0.899) | 0.049 |
| 2 times or less | 505 | 9.61 (2.29) | 0.712 (0.302; 1.121) | 0.001 |
| Measurement HbA1c in the last year | | | | |
| Yes | 533 | 9.10 (1.93) | Ref | |
| No | 184 | 10.00 (2.48) | 0.901 (0.576; 1.226) | <0.001 |
| Do not know | 261 | 9.40 (2.43) | 0.298 (-0.070; 0.665) | 0.112 |

Bivariate linear regression analyses.

The first multiple variable model, built with the socioeconomic variables (Model A, Table 3), showed that for each one year rise in age, HbA1c level were reduced by 0.01% (β=-0.013, 95% CI: -0.025, -0.002) and that education level only up to primary school was correlated with higher HbA1c levels (β=0.565, 95% CI: 0.154, 0.977). The second multiple variable model, which combined the behavioral variables with the selected variables from model A (Model B, Table 3), found that not participating in diabetes class/lecture during the previous year (β=0.503, 95% CI: 0.208, 0.799) and a self-perception of fair/poor adherence to diet (β=0.889, 95% CI: 0.446, 1.332) and to insulin therapy (β=1.385, 95% CI: 0.764, 2.007) were also positively correlated with HbA1c levels. The third multiple variable model, which incorporated the clinical variables with those selected in model B (Model C, Table 3), found that not consulting at a private clinic during the previous year (β=0.545, 95% CI: 0.021, 1.069) and having no HbA1c measurement performed in the previous year (β=0.770, 95% CI: 0.418; 1.122) were positively correlated with the HbA1c levels.

TABLE 3. Hierarchical model of multiple linear regression analyses for determinants of inadequate glycemic control in 846 Brazilian patients with type 1 diabetes.

| Independent variable | Unadjusted | Model A | Model B | Model C |
|---|---|---|---|---|
| | β coefficient (95% IC) | β coefficient (95% IC) | β coefficient (95% IC) | β coefficient (95% IC) |
| BLOCK 1: SOCIODEMOGRAPHIC | | | | |
| Age (years) | -0.003 (-0.012; 0.007) | -0.013 (-0.025; -0.002) | -0.008 (-0.019; 0.002) | -0.009 (-0.020; 0.001) |
| Sex | | | | |
| Male | Ref | Ref | Ref | Ref |
| Female | 0.229 (-0.061; 0.518) | 0.243 (-0.065; 0.551) | 0.311 (0.012; 0.610) | 0.286 (-0.009; 0.582) |
| Education | | | | |
| At least some College | Ref | Ref | Ref | Ref |
| Secondary/High school | 0.084 (-0.325; 0.492) | 0.141 (-0.288; 0.572) | 0.081 (-0.336; 0.499) | -0.254 (-0.709; 0.199) |
| Primary school or less | 0.565 (0.154; 0.977) | 0.765 (0.313; 1.217) | 0.551 (0.106; 0.996) | 0.090 (-0.409; 0.590) |
| BLOCK 2: BEHAVIORAL | | | | |
| Self-perception of adherence to diet | | | | |
| Excellent | Ref | | Ref | Ref |
| Good | 0.344 (-0.103; 0.792) | | 0.401 (-0.062; 0.866) | 0.377 (-0.081; 0.836) |
| Fair / Poor | 0.931 (0.508; 1.354) | | 0.889 (0.446; 1.332) | 0.876 (0.439; 1.313) |
| Self-perception of adherence to insulin | | | | |
| Excellent | Ref | | Ref | Ref |
| Good | 0.315 (-0.074; 0.703) | | 0.295 (-0.112; 0.702) | 0.239 (-0.164; 0.642) |
| Fair / Poor | 1.543 (0.978; 2.107) | | 1.385 (0.764; 2.007) | 1.242 (0.625; 1.858) |
| Participation in lecture for diabetes in the last year | | | | |
| Yes | Ref | | Ref | Ref |
| No | 0.549 (0.247;0.850) | | 0.503 (0.208; 0.799) | 0.482 (0.184; 0.779) |
| BLOCK 3: CLINICAL | | | | |
| Diabetes care in private clinic in the last year | | | | |
| Yes | Ref | | | Ref |
| No | 0.586 (0.117; 1.055) | | | 0.545 (0.021; 1.069) |
| Measurement HbA1c in the last year | | | | |
| Yes | Ref | | | Ref |
| No | 0.901 (0.576; 1.226) | | | 0.770 (0.418; 1.122) |
| Do not know | 0.298 (-0.070; 0.665) | | | 0.243 (-0.170; 0.657) |
| AIC*: | Not Applicable | 3,735.893 | 3,685.672 | 3,666.879 |

Note: The Model shows associations between sociodemographic factors (block 1) and the levels of glycated hemoglobin (HbA1c). Model B shows associations between sociodemographic factors and behavioral (blocks 1 and 2) and HbA1c levels. Model C shows associations between sociodemographic factors, behavioral and clinical (blocks 1, 2 and 3), and HbA1c levels. *Akaike Information Criteria.

## 4. DISCUSSION

Our results indicate that sociodemographic, behavioral and clinical factors in DM1 patients are independently associated with high levels of HbA1c. Of note, self-reported poor adherence to diet was strongly associated with elevated HbA1c levels. This finding is of special relevance because adherence to diet is a modifiable factor, possibly accomplished by specific actions targeting those noncompliant to dietary recommendations. In addition, we found that some of the socioeconomic factors influencing the inadequacy of glycemic control, such as low educational attainment, are mediated by behavioral and clinical aspects. These findings add valuable information for a better understanding of the barriers to achieve adequate glycemic control in adult patients with DM1.

The American Diabetes Association (ADA) recommends that patients with a recent diagnosis of diabetes and without major complications or prior history of severe hypoglycemic episodes should target HbA1c levels of <6.5%, while patients with advanced micro and macrovascular complications or comorbidities aim towards HbA1c levels of <8.0%[5]. This recommendation is supported by studies conducted over two decades ago, showing that poor glycemic control is associated with microvascular and macrovascular complications in patients with diabetes[4,5]. Despite that, the majority of DM1 patients worldwide have inadequate glycemic control[7,16,17]. In our study, we found that the mean HbA1c level was 9.4%, the same result observed in another multicenter, DM1 study, conducted in 20 Brazilian cities between 2008 and 2010[9]. This study also found that the quality of life of DM1 patients was inversely related to the levels of HbA1c.

In our multiple variable model including only the sociodemographic variables, we found that patients with primary school or less had a mean level of HbA1c nearly 1% greater than patients with at least some college level education. The relation between lower educational attainment of DM1 patients and higher levels of HbA1c has been previously reported[7,11]. However, a noteworthy finding of our study is that the correlation coefficient between educational levels and HbA1c levels decreased after we incorporated the behavioral variables (Model B) and almost disappeared when the clinical factors were included (Model C). The differences observed in the education level correlation coefficients among these models indicate that the effect of lower education on the level of HbA1c is possibly mediated by behavioral and, especially, by clinical factors.

Regarding the behavioral factors, we found that participation in diabetes education programs was associated with better glycemic control, consistent with previous studies. In a case-control study conducted in Saudi Arabia, patients with DM1 or DM2 who had received monthly counseling about the disease, had significantly reduced HbA1c levels compared to those who had received counseling only at the beginning of the study[18]. In another single-arm, pre-post cohort study, aiming to estimate the impact of improving the knowledge, skills and confidence in self-management of DM1, the average HbA1c levels was significantly reduced from baseline to follow-up measurements[19]. The mechanisms by which diabetes education programs help achieve a better glycemic control are likely diverse, and may include provision of knowledge about the disease, aid in developing skills and techniques for disease self-management, and support for adoption of healthy eating and lifestyle habits.

A lower degree of self-perceived adherence to diet and insulin therapy were also strongly associated with higher levels of HbA1c among our study patients. These findings are in accordance with other studies of DM1 patients, in which the average HbA1c was significantly lower among patients who followed dietary recommendations, compared to those who did not[13,20]. A study that enrolled both DM1 and DM2, insulin-treated patients also found that better glycemic control was independently associated with adherence to a dietary plan that included greater daily ingestion of fruits and vegetables, but not with adherence to insulin therapy[16]. However, Gastal et al.[21] found that better scores in a diabetes self-care scale evaluating diabetes general management, diet, exercise, care with feet, glycemic monitoring, insulin administration, and detection, prevention or treatment of hypoglycemia/hyperglycemia were associated with lower HbA1c values. Thus, additional evidences support our findings that adherence to both diet and insulin regimens are essential for glycemic control and for subsequent prevention of disease complications and early death.

Unfortunately, we did not collect detailed data on diet and food consumption, which would allow a better understanding of its role on glycemic control. Even though, our finding of an inverse relation between the degree of self-perceived adherence to diet and HbA1c levels suggests that following specific alimentary recommendations have a direct contribution to glycemic control. Different actions may help reinforcing the role of diet adherence to glycemic control, such as a close follow up by a multidisciplinary health team (including nutritionists, social assistants, psychologists, and other professionals), provision of patients' education, spouse and family support, encouraging

diet adherence[22], and the use of digital media and electronic devices, such as smart phone self-care “apps”[23].

Some studies suggest that DM1 patients undergoing close monitoring of diabetes through regular HbA1c measurements, blood glucose self-monitoring, and regular medical appointments, had lower levels of HbA1c[12,24]. We found no association between self-monitoring of blood glucose and HbA1c in the multiple variable analysis; however, our finding of an independent correlation between not measuring the HbA1c level in the previous year and greater levels of HbA1c does support the notion that a careful disease monitoring is critical for an adequate glycemic control.

We also found that patients who had not received diabetes medical care at private services presented significantly higher HbA1c levels than their counterparts. This result raises concerns because the Brazilian public health system provides universal medical care for the majority of the population with diabetes in the country. Training the public health professionals for diabetes care and ensuring better infrastructure and access to universal assistance for patients with diabetes are critical collective actions that need to be attained in order to decrease the high percentage of DM1 patients with inadequate glycemic control. Specific actions may include providing multidisciplinary professional teams for diabetes care, and increasing access to the most advanced insulin therapies and to self-monitoring of blood glucose.

This study has some limitations. First, the cross-sectional design does not allow for establishing a temporal relation between the factors associated with high levels of HbA1c. Second, except for the HbA1c measurement, all the patients’ data, including the behavioral and clinical characteristics were collected through interviews, potentially

introducing a certain degree of inaccuracy for some answers. However, interviewers are widely used in epidemiological and clinical studies of diabetes and our results are consistent with those of previous studies that used self-reported answers [9]. In addition, self-reported data have been shown to have high agreement with medical records for several questions, such as type of diabetes, family history of diabetes, therapeutic regimen and disease complications[25]. Although inaccurate answers on type of diabetes might have led to inclusion of some insulin-treated DM2 patients in the study population, we expect this number to be small, having minimal impact on our findings and conclusions. Third, typical DM1 onset happens during childhood and adolescence, but our study sample only included patients ≥18 years of age and was obtained in reference diabetes care centers. Therefore, we might have introduced a selection bias, with participants likely having a longer disease duration, a greater number of complications and, possibly, worse glycemic control. However, as the sample was selected in ten large cities, from four different regions of Brazil, it is reasonable to assume that the factors associated with a poor glycemic control among the studied patients are representative of others DM1 patients in Brazil. On the other hand, in our study we measured the HbA1c levels for all participants in a single laboratory, and used the same reference method of liquid chromatography, thus avoiding problems with lack of standardization reported by other authors.

In summary, our findings support the concept that multiple and distinct factors, such as sociodemographic, behavioral and clinical drivers, act together to influence the glycemic control in DM1 patients. Encouraging patients' adherence to diet and to insulin treatment is critical for achieving optimum levels of HbA1c. Health education programs

to inform and engage patients in their treatment, as well as ensuring periodic medical monitoring and measurement of HbA1c, are important additional measures. Reinforcing these recommendations for public health policies and clinical guidelines may translate into improved glycemic control in DM1 patients.



**ACKNOWLEDGEMENTS**

The study was supported by an unconditional grant form Pfizer Inc. The authors would like to thank the team members in the collection of blood samples, interviews with patients and performing HbA1c tests, and the study investigators: Adriana C. Forti, MD; Ana B. V. Mendes, MD; Antônio R. Chacra, MD; Celio C. Borges, MD; Debora V. Soares, MD; Edson P. Brum, MD; Elza M. S. Constantino, MD; Francisco A. Oliveira, MD; Freddy Eliaschewitz, MD; Hermelinda Pedrosa, MD; João A. S. Fittipaldi, MD; Jorge Gross, MD; Jose E. P. Oliveira, MD; Lucia Cordeiro, MD; Lucia P. E. Souza, MD; Marcia Nery, MD; Marcos Tambascia, MD; Maria C. C. de Almeida, PhD; Maria R. Calsolari, MD; Reinaldo B. M. Machado, MD; Reine Chaves, MD; Rosane Kupfer, MD; Ruy Lyra, MD; Saulo Cavalcante, MD; and Silmara Leite, MD. We also thank Professor Uriel Kitron for his valuable review of the manuscript. Carine S. Andrade received scholarship from the Coordination for the Improvement of Higher Education Personnel (CAPES), Brazilian Ministry of Education. Guilherme S. Ribeiro and Edson D. Moreira Jr. received scholarships from the National Council for Scientific and Technological Development (CNPq).

## CONFLICT OF INTEREST

Carine S. Andrade has no conflicts of interest; Guilherme S. Ribeiro has no conflicts of interest; Carlos A.S.T. Santos has no conflicts of interest; Raimundo Celestino S. Neves has no conflicts of interest; Edson D. Moreira Jr. was a consultant for Pfizer Inc.

## AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: Edson D Moreira Jr; Carine S Andrade; Guilherme S Ribeiro. Analysis and interpretation of data: Carine S Andrade; Guilherme S Ribeiro; Carlos AST Santos; Raimundo Celestino S Neves; Edson D Moreira Jr. Wrote the paper: Carine S Andrade; Guilherme S Ribeiro. Reviewed and approved the final version of the manuscript: Carine S Andrade; Guilherme S Ribeiro; Carlos AST Santos; Raimundo Celestino S Neves; Edson D Moreira Jr.

## AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed during the current study may be available from the corresponding author on reasonable request.

## FUNDING

The Brazilian Study of Diabetes Control was funded by Pfizer Inc., Brazil.

## REFERENCE


1 Drouin P, Blickle JF, Charbonnel B, *et al.* Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;**33 Suppl 1**:S62-9. doi:10.2337/dc10-S062

2 Diaz-Valencia PA, Bougnères P, Valleron A-J. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. *BMC Public Health* 2015;**15**:255. doi:10.1186/s12889-015-1591-y

3 Tuomilehto J. The Emerging Global Epidemic of Type 1 Diabetes. *Curr Diab Rep* 2013;**13**:795–804. doi:10.1007/s11892-013-0433-5

4 DCCT. The New England Journal of Medicine Downloaded from nejm.org at FIOCRUZ on January 7, 2015. For personal use only. No other uses without permission. Copyright © 1993 Massachusetts Medical Society. All rights reserved. *N Engl J Med* 1993;**329**:977–86.http://www.nejm.org/doi/pdf/10.1056/NEJM199309303291401

5 George Bakris M, Lawrence Blonde, MD F, Andrew J.M. Boulton M, *et al.* Standards of Medical Care in Diabetes - 2015. *Diabetes Care J Clin Appl Res Educ* 2015;**38**:S1–99. doi:10.2337/dc15-S005

6 McCarthy M, Funk M, Grey M. Ideal Cardiovascular Health in Adults with Type 1 Diabetes. *Nurs Res* 2016;**65**:E65–E65 1/3p. doi:10.1016/j.ypmed.2016.08.019

7 Sastre J, Pines PJ, Moreno J, *et al.* Situacion de control metabolico y pautas de tratamiento en pacientes con diabetes tipo 1 en Castilla-La Mancha: estudio de diabetes tipo 1 en Castilla-La Mancha. *Endocrinol y Nutr* 2012;**59**:539–46. doi:10.1016/j.endonu.2012.07.003

8 Mendes ABV, Fittipaldi JAS, Neves RCS, *et al.* Prevalence and correlates of inadequate glycaemic control: results from a nationwide survey in 6,671 adults with diabetes in Brazil. *Acta Diabetol* 2010;**47**:137–45. doi:10.1007/s00592-009-0138-z

9 Braga de Souza ACC, Felício JS, Koury CC, *et al.* Health-related quality of life in people with type

1 Diabetes Mellitus: data from the Brazilian Type 1 Diabetes Study Group. *Health Qual Life Outcomes* 2015;**13**:204. doi:10.1186/s12955-015-0396-0

10 Paris CA, Imperatore G, Klingensmith G, *et al.* Predictors of Insulin Regimens and Impact on Outcomes in Youth with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr* 2009;**155**:183–189.e1. doi:10.1016/j.jpeds.2009.01.063

11 Nádas J, Putz Z, Fövényi J, *et al.* Cardiometabolic risk and educational level in adult patients with type 1 diabetes. *Acta Diabetol* 2009;**46**:159–62. doi:10.1007/s00592-008-0065-4

12 Pfützner A, Weissmann J, Mougiakakou S, *et al.* Glycemic Variability Is Associated with Frequency of Blood Glucose Testing and Bolus: Post Hoc Analysis Results from the ProAct Study. *Diabetes Technol Ther* 2015;**17**:150303065452008. doi:10.1089/dia.2014.0278

13 Davison K a K, Negrato C a, Cobas R, *et al.* Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: a nationwide survey in Brazil. *Nutr J* 2014;**13**:19. doi:10.1186/1475-2891-13-19

14 Petitti DB, Klingensmith GJ, Bell RA, *et al.* Glycemic Control in Youth with Diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr* 2009;**155**:668–672.e3. doi:10.1016/j.jpeds.2009.05.025

15 Patterson C, Guariguata L, Dahlquist G, *et al.* Diabetes in the young – a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract* 2014;**103**:161–75. doi:10.1016/j.diabres.2013.11.005

16 Angamo MT, Melese BH, Ayen WY. Determinants of glycemic control among insulin treated diabetic patients in Southwest Ethiopia: hospital based cross sectional study. *PLoS One* 2013;**8**:e61759. doi:10.1371/journal.pone.0061759

17 Colom C, Chico A, Carreras G, *et al.* Control glucémico y complicaciones crónicas a 20 años del comienzo de la diabetes tipo 1. Resultados de una unidad especializada. *Av en Diabetol* 2015;**31**:113–9. doi:10.1016/j.avdiab.2015.02.002

18 Ba-Essa E, Mobarak E. Intensified glucose self-monitoring with education in Saudi DM patients. *Int*

*J …* 2015;**8**:19374–80.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4694478/

19 Speight J, Holmes-Truscott E, Harvey DM, *et al.* Structured type 1 diabetes education delivered in routine care in Australia reduces diabetes-related emergencies and severe diabetes-related distress: The OzDAFNE program. *Diabetes Res Clin Pract* 2016;**112**:65–72. doi:10.1016/j.diabres.2015.11.002

20 Mehta SN, Volkening LK, Andreson BJ et al. Dietary behaviors predict glycemic control in youth with type 1 diabetes. *Diabetes Care* 2008;**31**:1318–20.http://care.diabetesjournals.org/content/31/7/1318.full.pdf+html

21 Gastal DA, Pinheiro RT, Vazquez DP. Self-efficacy scale for Brazilians with type 1 diabetes. *Sao Paulo Med J* 2007;**125**:96–101.http://www.ncbi.nlm.nih.gov/pubmed/17625707

22 Leong A, Rahme E, Dasgupta K. Spousal diabetes as a diabetes risk factor: a systematic review and meta-analysis. *BMC Med* 2014;**12**:12. doi:10.1186/1741-7015-12-12

23 Joshi R, Joshi D, Cheriyath P. Improving adherence and outcomes in diabetic patients. *Patient Prefer Adherence* 2017;**11**:271–5. doi:10.2147/PPA.S122490

24 Miller KM, Beck RW, Bergenstal RM, *et al.* Evidence of a Strong Association Between Frequency of Self-Monitoring of Blood Glucose and Hemoglobin A1c Levels in T1D Exchange Clinic Registry Participants. *Diabetes Care* 2013;**36**:2009–14. doi:10.2337/dc12-1770

25 Løvaas KF, Cooper JG, Sandberg S, *et al.* Feasibility of using self-reported patient data in a national diabetes register. *BMC Health Serv Res* 2015;**15**:553. doi:10.1186/s12913-015-1226-0

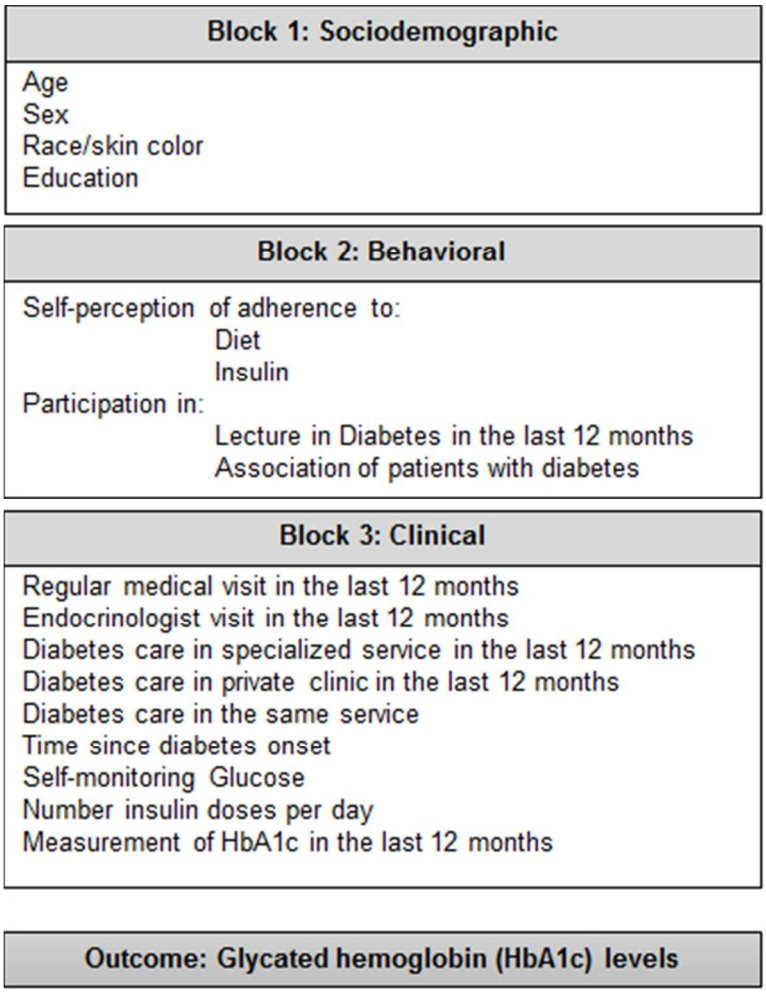


FIGURE 1. Hierarchical model for determinants of inadequate glycemic control.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | **1** |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | **2** |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | **4** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | **5** |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | **5** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | **5,6** |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | **6** |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | **6,7,8** |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | **7,8** |
| Bias | 9 | Describe any efforts to address potential sources of bias | **6,7** |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | **6,7** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | **7,8** |
| | | (*b*) Describe any methods used to examine subgroups and interactions | **7,8** |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | **7,8** |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | **9** |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | **9,10** |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | **11,12** |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | **11,12,13,14** |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | **16** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | **18,19** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | **17,18** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | **21,22** |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTER STUDY IN BRAZIL



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018094.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 25-Aug-2017 |
| Complete List of Authors: | ANDRADE, CARINE; Universidade Federal da Bahia, Escola de Nutrição<br>RIBEIRO, GUILHERME; Universidade Federal da Bahia, Institute of Collective Health; Oswaldo Cruz Foundation, Gonçalo Moniz Institute<br>SANTOS, CARLOS ANTONIO; Universidade Estadual de Feira de Santana; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute<br>NEVES, RAIMUNDO CELESTINO; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute<br>MOREIRA JR, EDSON; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute; Obras Sociais Irma Dulce |
| Primary Subject Heading: | Diabetes and endocrinology |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | type 1 diabetes, glycemic control, glycated hemoglobin, EPIDEMIOLOGY |
| | |

# FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTER STUDY IN BRAZIL

Carine Sousa Andrade, PhD[a,b], Guilherme Sousa Ribeiro, PhD[a,c], Carlos Antonio Souza Teles Santos, PhD[a,d], Raimundo Celestino Silva Neves, PhD[a], Edson Duarte Moreira Jr., PhD[a,e]*.

(a) Gonçalo Moniz Institute, Oswaldo Cruz Foundation, Salvador, Brazil;

(b) School of Nutrition, Federal University of Bahia, Salvador, Brazil;

(c) Institute of Collective Health, Federal University of Bahia, Salvador, Brazil;

(d) State University of Feira de Santana, Feira de Santana, Brazil;

(e) Charitable Works Foundation of Sister Dulce, Salvador, Brazil.

*Address for correspondence: Dr. Edson D Moreira Jr.

Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Rua Waldemar Falcão 121, Salvador, Bahia, 40296-710, Brazil.

Tel .: +55 71 3176 2343; Fax: +55 71 3176 2243.

E-mail: edson@bahia.fiocruz.br (E. D. Moreira Jr.).

Word count: 3,555 words

## ABSTRACT

Objective: Long-term complications of type 1 diabetes mellitus (DM1) can be prevented with adequate glycemic control. However, high levels of glycated hemoglobin (HbA1c) occur in 60 to 90% of the DM1 patients. Thus, we aimed to investigate the role of sociodemographic, behavioral and clinical factors on the HbA1c levels of DM1 patients in Brazil.

Design, setting and participants: A cross-sectional study was conducted with ambulatory DM1 patients aged ≥18 years from 10 Brazilian cities. Sociodemographic, behavioral and clinical data were obtained through interviews.

Main outcome measures: HbA1c level was measured by liquid chromatography. Hierarchical multiple variable linear regression models were used to identify factors correlated with high levels of HbA1c.

Results: Of 979 DM1 patients, 63.8% were female and the mean age was 40 (SD: 14.6) years. The mean HbA1c level was 9.4% (SD: 2.2%), and 89.6% of the patients had HbA1c ≥7.0%. Factors independently correlated with increased HbA1c levels included: lower education, non-participation in diabetes classes/lecture during the year before, having a self-perception of poor adherence to diet and insulin, not having private medical care, and not measuring the HbA1c levels in the prior year. Of note, poor adherence to diet and insulin were the independent factors most strongly associated with high levels of HbA1c (mean increment in HbA1c levels of 0.88% and 1.25%, respectively).

Conclusion: Poor glycemic control, which is common among DM1 Brazilian patients, is associated with lower education, self-perception of insufficient adherence to diet and

insulin, and inadequate monitoring of HbA1c levels. Specific actions, particularly those targeting improving adherence to diet and insulin, may contribute to successful management of DM1 patients.

Keywords: type 1 diabetes, glycemic control, glycated hemoglobin, epidemiology.

**Strengths and limitations of this study**

- This cross-sectional, multicenter study included 979 type 1 diabetes mellitus patients from ten large Brazilian cities, representing four of the five regions of the country.
- We measured the HbA1c levels for all participants in a single laboratory, and used the same reference method of liquid chromatography, thus avoiding problems with lack of standardization reported by other authors.
- In order to identify independent factors associated with increased levels of HbA1c, we applied robust, multiple variable models, using a hierarchical approach according to a previously defined conceptual framework. This method accounts for hierarchical inter-relationships between variables and for the potential underestimation of the effects of distal determinants.
- Data on behavioral and clinical characteristics were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers.

## 1. INTRODUCTION

Type 1 diabetes mellitus (DM1) is characterized by the destruction of the insulin-producing pancreatic β cells, leading to an hyperglycemic state that requires continued reposition of exogenous insulin in order to prevent life-threatening acute and chronic complications[1]. The disease annual incidence varies greatly between countries, ranging from 1.1 to 39.9 per 100,000 persons 15-19 years of age[2], and is globally increasing at a rate of approximately 3% per year[3].

Patients with DM1 are at increased risk for cardiovascular disease, periphery nerve damage, nephropathy, and retinopathy, resulting in reduced life expectancy for those who are not properly treated[1]. This risk can be substantially reduced with intensive glycemic control, aiming for glycated hemoglobin (HbA1c) levels <6.0%[4]. However, most patients with DM1 have HbA1c values above the international recommendation of <7.0%[5]. Inadequate glycemic control (HbA1c levels >7.0% in DM1 patients was observed in 77% of the participants of a study in the United States in 2016[6], in 74% of the study patients in the region of Castilla-La Mancha, Spain in 2012[7], and in 84%-90% of the participants of national multicenter studies conducted in Brazil in 2010 and 2015[8,9].

A better understanding of the factors that determine glycemic control is critical to improved management of DM1 patients. However, the majority of studies investigating determinants of glycemic control enrolled patients with type 2 diabetes mellitus (DM2) or studied patients with DM1 and DM2 combined, despite the fact that challenges to achieve glycemic control differ between patients with DM1 and DM2, mainly due to the compulsory need of insulin use in DM1 patients. In the few published reports on

determinants of glycemic control in DM1 patients, high levels of HbA1c have been associated with younger age, low educational level, poor adherence to diet, mode of insulin administration, and infrequent monitoring of blood glucose[10–14]. Here, we describe the results of our study in which we investigated the role of sociodemographic, behavioral and clinical characteristics in the levels of HbA1c in a large sample of patients with DM1 in Brazil, a country where >31,000 persons <15 years of age have DM1[15].

## 2. SUBJECTS, MATERIAL AND METHODS

### 2.1. Study Design and Sample Selection:

This cross-sectional, multicenter study was conducted in ten large Brazilian cities, representing four of the five regions of the country (Southeast region: Belo Horizonte, Campinas, Rio de Janeiro, and São Paulo; South region: Curitiba, and Porto Alegre; Midwest region: Brasilia; and Northeast region: Salvador, Fortaleza and Recife). These cities are the largest in their respective regions, and nine of them were ranked among the most populous municipalities in Brazil. To pursue the selection of the diabetes medical centers, we requested the Brazilian Diabetes Association to identify in each of the study city a list of candidate centers, selected because of previous experience in conducting epidemiological research and where a large number of adult patients are treated for diabetes (minimum of 300 patients per month). In each city, two diabetes centers (20 centers in total) were invited to participate in the study: five university-

affiliated hospitals, eleven general public hospitals, and four not-for-profit private hospitals. All invited centers accepted and were included in the study.

From February 2006 to March 2007, we invited patients fulfilling the eligibility criteria to participate in the study during 30 consecutive days in each of the centers. To be eligible for study enrollment, patients had to be 18 years of age or older and report a prior medical diagnosis of DM1. Patients who had participated in other research in the three months preceding the study were excluded. All patients were informed about the study aims, procedures and risks, and signed an informed consent prior to inclusion. The study was approved by the Hospital Santo Antônio Ethics Committee (approval number 32/05).

### 2.2. Data Collection:

Trained interviewers who were not part of the medical centers staff interviewed the participants using a structured questionnaire to obtain data on demographic and socioeconomic indicators, self-perception of diet and insulin treatment adherence, attendance to diabetes education lectures, participation in associations of patients with diabetes, and clinical characteristics. The clarity of the questionnaire was assessed through pilot interviews in a sample of DM1 patients previously to study initiation. Data on education attainment (primary school or less, complete or incomplete secondary/high school, or at least some college level education) and on race/skin color were self-reported. Data on self-perception of diet adherence and of insulin adherence were collected using the following ordinal scale: poor/fair, good, or excellent. Clinical data included time since first diagnosis of diabetes, number of insulin doses per day,

frequency of self-monitoring of blood glucose, as well as frequencies, in the previous 12 months, of consultation in public and private medical service facilities, consultation with an endocrinologist, prior hypoglycemic episodes, prior hospitalizations due to ketoacidosis and HbA1c measurements. Interviews were conducted in a private room and lasted 20-25 minutes. The response rate was 84% (ranging from 78% to 95%).

### 2.3. Measurement of Glycated Hemoglobin (HbA1c):

A blood sample was collected from participants at enrollment and tested by automated high performance liquid chromatography to determine HbA1c levels. All exams were performed in the same laboratory, according to standard procedures. The HbA1c levels data were reported as mean and standard deviation (SD) and, categorically, as a frequency of <7.0%, 7.0-8.9%, 9.0-10.9%, or ≥11.0%. We considered glycemic control to be inadequate when the HbA1c concentration was ≥7.0%[5].

### 2.4. Statistical Analysis:

Data were double entered into a computerized database using the EPI INFO version 3.04 software system (Centers for Disease Control and Prevention, Atlanta, USA). Subsequently, the two databases were electronic compared to validate the accuracy and internal consistency of the data. Statistical analyses were performed using version 12 of STATA (StataCorp., College Station, USA).

Participants' characteristics were presented using means and standard deviation for continuous variables, and frequencies for categorical variables. We applied bivariate and multiple variables linear regression models to estimate the effect of the independent

variables on the level of HbA1c. Variables with a significant association at p value of ≤0.20 in the bivariate analyses were included in robust, multiple variable models using a hierarchical approach according to a previously defined conceptual framework (Figure 1). A conceptual framework is a theoretical model that describes the hierarchical relationships between explanatory variables and an outcome. This approach is considered an appropriate strategy for assessing disease determinants in multiple variable analyses because it handles complex hierarchical inter-relationships between variables and accounts for the potential underestimation of the effects of distal determinants (i.e. factors that typically do not determine the outcome directly, but do mediated by other intermediate factors)[16].

The hierarchical model grouped variables in three blocks (Figure 1). Block 1 contained socioeconomic variables, such as education level and race/skin color. Block 2 contained behavioral variables, such as attendance to diabetes class/lectures, participation in associations of patients with diabetes, and self-perception of adherence to diet and insulin treatment. Block 3 comprised of clinical characteristics, including time since first diagnosis of diabetes, number of insulin doses per day, and frequency of self-monitoring of blood glucose, consultation with an endocrinologist, and HbA1c measurement in the previous 12 months (Figure 1).

A backward elimination strategy was then performed for each block. Block 1 variables that were significantly correlated with HbA1c serum levels at a *p* value ≤0.05 were maintained in the subsequent backward elimination model with block 2 variables. Using the same approach, block 2 variables that were significantly correlated with HbA1c serum levels at a *p* value ≤0.05 were maintained in the subsequent backward

elimination model with block 3 variables. Finally, block 3 variables with a *p* value ≤0.05 were defined as factors independently correlated with the HbA1c levels. Variables from block 1 and block 2 that were selected to be included in following models were considered to be significantly correlated with HbA1c levels, regardless of their *p* value in the subsequent models. Sex and age were included in all models to ensure adjustments to these factors at all stages of the multiple variable analyses. We used the Akaike Information Criterion (AIC) to estimate the goodness of fit of the successive adjusted models.

## 3. RESULTS

Of the 979 DM1 patients enrolled in the study, 625 (63.8%) were female, and 296 (30.2%) were 18-29 years of age, 412 (42.1%) 30-49 years of age, and 271 (27.7%) ≥50 years of age (Table 1). About half (488, 49.8%) of the patients were white, and 398 (40.8%) had not studied beyond the primary school level. The Southeast region of Brazil accounted for 611 (62.4%) participants. Although all the diabetes centers were affiliated with the Brazilian public health care system, 95 (9.7%) of the patients reported they had also received private assistance during the past 12 months.

TABLE 1. Sociodemographic and clinical characteristics of 979 Brazilian patients with type 1 diabetes, Brazil.

| Characteristics | n (%) |
|---|---|
| SOCIODEMOGRAPHICS | |
| Age (years) | |
| 18 – 29 | 296 (30.2) |
| 30 – 49 | 412 (42.1) |
| ≥ 50 | 271 (27.7) |
| Sex Female | 625 (63.8) |
| Race/Skin color | |
| White | 488 (49.8) |
| Mixed | 286 (29.2) |
| Black | 122 (12.5) |
| Other | 83 (8.5) |
| Education[1] | |
| At least some College | 154 (15.8) |
| Secondary/High school | 424 (43.4) |
| Primary school or less | 398 (40.8) |
| Brazilian Region | |
| Southeast | 611 (62.4) |
| Northeast | 174 (17.8) |
| South | 104 (10.6) |
| Center-west | 90 (9.2) |
| Type of service for medical care in the last year | |
| Public | 884 (90.3) |
| Private | 95 (9.7) |
| CLINICAL COMPLICATIONS | |
| Hypoglycemic episodes in the last year | 497 (50.8) |
| Ketoacidosis hospitalization in the last year | 248 (25.3) |
| Reported complications | |
| Retinopathy | 427 (43.6) |
| Neuropathy[2] | 381 (39.2) |
| Nephropathy | 207 (21.1) |
| Angina[3] | 129 (13.2) |
| Vasculopathy[3] | 125 (12.8) |
| LABORATORY | |
| Glycated Hemoglobin (HbA1c) (%) | |
| <7.0 | 102 (10.4) |
| 7.0 – 8.9 | 366 (37.4) |
| 9.0 – 10.9 | 287 (29.3) |
| >11.0 | 224 (22.9) |

[1] Data available for 976 patients

[2] Data available for 973 patients

[3] Data available for 977 patients

The diabetes complications most frequently reported by the study participants were retinopathy (427, 43.6%), followed by neuropathy (381, 39.2%) and nephropathy (207, 21.1%). Episodes of ketoacidosis and hypoglycemia in the previous year were common, affecting 248 (25.3%) and 497 (50.8%) patients, respectively. The majority (887, 89.6%) of patients had inadequate glycemic control (HbA1c ≥7.0%), and the mean HbA1c level was 9.4% (SD: 2.2%).

Bivariate analysis pointed to a correlation of higher levels of HbA1c with black race, lower education attainment, self-perception of fair/poor adherence to diet and to insulin treatment, not participating in diabetes class/lectures during the previous year, and never having participated in associations of patients with diabetes (Table 2). In addition, patients who reported that in the previous year had neither regular medical appointments, nor consultations with an endocrinologist, private consultations or health care delivered in the same diabetes center had significantly higher HbA1c. Finally, patients not performing regular self-monitoring of blood glucose, those with no measure of HbA1c during the previous year, and patients receiving less than four doses of insulin per day also had higher levels of HbA1c.

TABLE 2. Factors associated with glycated hemoglobin (HbA1c) levels in Brazilian patients with type 1 diabetes.

| Independent variable | Nº participants | HbA1c means in % (SD) | β Coefficient (CI 95%) | *p* value |
|---|---|---|---|---|
| BLOCK 1 – SOCIODEMOGRAPHIC | | | | |
| Age (years) | | | | |
| 18 – 29 | 296 | 9.35 (2.36) | Ref | 0.198 |
| 30 – 49 | 412 | 9.54 (2.28) | 0.186 (-0.146; 0.517) | |
| ≥ 50 | 271 | 9.24 (1.95) | -0.118 (-0.484; 0.248) | |
| Sex | | | | |
| Male | 354 | 9.25 (2.08) | Ref | 0.122 |
| Female | 625 | 9.48 (2.29) | 0.229 (-0.061; 0.518) | |
| Race/Skin color | | | | |
| White | 488 | 9.26 (2.10) | Ref | 0.058 |
| Mixed | 286 | 9.32 (2.33) | 0.133 (-0.191; 0.456) | |
| Black | 122 | 9.84 (2.34) | 0.576 (0.136; 1.017) | |
| Other | 83 | 9.62 (2.31) | 0.361 (-0.155; 0.877) | |
| Education | | | | |
| At least some College | 154 | 9.13 (1.82) | Ref | 0.002 |
| Secondary/High school | 424 | 9.21 (2.15) | 0.084 (-0.325; 0.492) | |
| Primary school or less | 398 | 9.70 (2.40) | 0.565 (0.154; 0.977) | |
| BLOCK 2 – BEHAVIORAL | | | | |
| Self-perception of adherence to diet | | | | |
| Excellent | 129 | 8.79 (2.22) | Ref | <0.001 |
| Good | 327 | 9.13 (2.09) | 0.344 (-0.103; 0.792) | |
| Fair / Poor | 523 | 9.72 (2.25) | 0.931 (0.508; 1.354) | |
| Self-perception of adherence to insulin | | | | |
| Excellent | 750 | 9.28 (2.12) | Ref | <0.001 |
| Good | 144 | 9.59 (2.30) | 0.315 (-0.074; 0.703) | |
| Fair / Poor | 62 | 10.82 (2.49) | 1.543 (0.978; 2.107) | |
| Participation in lecture for diabetes in the last year | | | | |
| Yes | 345 | 9.11 (2.09) | Ref | <0.001 |
| No | 540 | 9.67 (2.31) | 0.549 (0.247; 0.850) | |
| Participation in association of diabetics patients | | | | |
| Yes, still participate | 116 | 9.09 (1.88) | Ref | 0.023 |
| Yes, but no more participate | 124 | 9.02 (1.80) | -0.067 (-0.627; 0.492) | |
| No, I never participated | 713 | 9.51 (2.32) | 0.418 (-0.016; 0.851) | |
| BLOCK 3 – CLINICAL | | | | |
| Body mass index (kg/m$^2$) | | | | |
| <25 | 502 | 9.45 (2.29) | Ref | 0.273 |
| ≥25 | 455 | 9.30 (2.08) | -0.156 (-0.435; 0.123) | |
| Regular medical visit in the last year | | | | |
| Yes | 878 | 9.34 (2.19) | Ref | 0.020 |
| No | 101 | 9.89 (2.42) | 0.541 (0.084; 0.998) | |

| | | | | |
|---|---|---|---|---|
| Endocrinologist visit in the last year | | | | |
| Yes | 800 | 9.32 (2.15) | Ref | 0.014 |
| No | 177 | 9.77 (2.50) | 0.453 (0.091; 0.814) | |
| Diabetes care in specialized service in the last year | | | | |
| Yes | 661 | 9.32 (2.18) | Ref | 0.120 |
| No | 318 | 9.56 (2.29) | 0.236 (-0.061; 0.533) | |
| Diabetes care in private clinic in the last year | | | | |
| Yes | 95 | 8.87 (1.61) | Ref | 0.014 |
| No | 884 | 9.46 (2.27) | 0.586 (0.117; 1.055) | |
| Diabetes care in the same service | | | | |
| Yes | 921 | 9.36 (2.18) | Ref | 0.015 |
| No | 57 | 10.10 (2.64) | 0.735 (0.142; 1.328) | |
| Time since diabetes onset (years) | | | | |
| < 10 | 261 | 9.43 (2.66) | Ref | 0.326 |
| 10 – 19 | 307 | 9.52 (2.11) | 0.094 (-0.273; 0.460) | |
| ≥ 20 | 408 | 9.27 (1.97) | -0.115 (-0.497; 0.192) | |
| Self-monitoring glucose | | | | |
| Yes, regularly | 663 | 9.25 (2.14) | Ref | 0.008 |
| Yes, when decompensated | 160 | 9.72 (2.28) | 0.463 (0.080; 0.845) | |
| No | 151 | 9.74 (2.46) | 0.489 (0.097; 0.881) | |
| Number insulin doses per day | | | | |
| 4 times | 168 | 8.91 (1.97) | Ref | 0.001 |
| 3 times | 290 | 9.38 (2.10) | 0.477 (0.062; 0.892) | |
| 2 times or less | 505 | 9.61 (2.29) | 0.707 (0.326; 1.088) | |
| Measurement HbA1c in the last year | | | | |
| Yes | 533 | 9.10 (1.93) | Ref | <0.001 |
| No | 184 | 10.00 (2.48) | 0.901 (0.576; 1.226) | |
| Do not know | 261 | 9.40 (2.43) | 0.298 (-0.070; 0.665) | |

Bivariate linear regression analyses.

The first multiple variable model, built with the socioeconomic variables (Model A, Table 3), showed that for each one year rise in age, HbA1c level were, on average, reduced by 0.01% (β=-0.013, 95% CI: -0.025, -0.002) and that education level only up to primary school was correlated with higher HbA1c levels (β=0.565, 95% CI: 0.154, 0.977). The second multiple variable model, which combined the behavioral variables with the selected variables from model A (Model B, Table 3), found that not participating in diabetes class/lecture during the previous year (β=0.503, 95% CI: 0.208, 0.799) and a self-perception of fair/poor adherence to diet (β=0.889, 95% CI: 0.446, 1.332) and to insulin therapy (β=1.385, 95% CI: 0.764, 2.007) were also positively correlated with HbA1c levels. The third multiple variable model, which incorporated the clinical variables with those selected in model B (Model C, Table 3), found that not consulting at a private clinic during the previous year (β=0.545, 95% CI: 0.021, 1.069) and having no HbA1c measurement performed in the previous year (β=0.770, 95% CI: 0.418; 1.122) were positively correlated with the HbA1c levels. It is noteworthy to mention that the effect of education over HbA1c levels was reduced with the subsequent introduction of further variables from blocks 2 and 3 (Models B and C), indicating that the effect of education on glycemic control was mediated by the behavioral and clinical variables incorporated to the model.

TABLE 3. Hierarchical model of multiple linear regression analyses for determinants of inadequate glycemic control in 846 Brazilian patients with type 1 diabetes.

| Independent variable | Unadjusted | Model A | Model B | Model C |
|---|---|---|---|---|
| | β coefficient (95% IC) | β coefficient (95% IC) | β coefficient (95% IC) | β coefficient (95% IC) |
| BLOCK 1: SOCIODEMOGRAPHIC | | | | |
| Age (years) | -0.003 (-0.012; 0.007) | -0.013 (-0.025; -0.002) | -0.008 (-0.019; 0.002) | -0.009 (-0.020; 0.001) |
| Sex | | | | |
| Male | Ref | Ref | Ref | Ref |
| Female | 0.229 (-0.061; 0.518) | 0.243 (-0.065; 0.551) | 0.311 (0.012; 0.610) | 0.286 (-0.009; 0.582) |
| Education | | | | |
| At least some College | Ref | Ref | Ref | Ref |
| Secondary/High school | 0.084 (-0.325; 0.492) | 0.141 (-0.288; 0.572) | 0.081 (-0.336; 0.499) | -0.254 (-0.709; 0.199) |
| Primary school or less | 0.565 (0.154; 0.977) | 0.765 (0.313; 1.217) | 0.551 (0.106; 0.996) | 0.090 (-0.409; 0.590) |
| BLOCK 2: BEHAVIORAL | | | | |
| Self-perception of adherence to diet | | | | |
| Excellent | Ref | | Ref | Ref |
| Good | 0.344 (-0.103; 0.792) | | 0.401 (-0.062; 0.866) | 0.377 (-0.081; 0.836) |
| Fair / Poor | 0.931 (0.508; 1.354) | | 0.889 (0.446; 1.332) | 0.876 (0.439; 1.313) |
| Self-perception of adherence to insulin | | | | |
| Excellent | Ref | | Ref | Ref |
| Good | 0.315 (-0.074; 0.703) | | 0.295 (-0.112; 0.702) | 0.239 (-0.164; 0.642) |
| Fair / Poor | 1.543 (0.978; 2.107) | | 1.385 (0.764; 2.007) | 1.242 (0.625; 1.858) |
| Participation in lecture for diabetes in the last year | | | | |
| Yes | Ref | | Ref | Ref |
| No | 0.549 (0.247;0.850) | | 0.503 (0.208; 0.799) | 0.482 (0.184; 0.779) |
| BLOCK 3: CLINICAL | | | | |
| Diabetes care in private clinic in the last year | | | | |
| Yes | Ref | | | Ref |
| No | 0.586 (0.117; 1.055) | | | 0.545 (0.021; 1.069) |
| Measurement HbA1c in the last year | | | | |
| Yes | Ref | | | Ref |
| No | 0.901 (0.576; 1.226) | | | 0.770 (0.418; 1.122) |
| Do not know | 0.298 (-0.070; 0.665) | | | 0.243 (-0.170; 0.657) |
| AIC*: | Not Applicable | 3,735.893 | 3,685.672 | 3,666.879 |

Note: Model A shows associations between sociodemographic factors (block 1) and the levels of glycated hemoglobin (HbA1c). Model B shows associations between sociodemographic and behavioral factors (blocks 1 and 2) and HbA1c levels. Model C shows associations between sociodemographic, behavioral, and clinical factors (blocks 1, 2 and 3), and HbA1c levels. *Akaike Information Criteria.

## 4. DISCUSSION

Our results indicate that sociodemographic, behavioral and clinical factors in DM1 patients are independently associated with high levels of HbA1c. Of note, self-reported poor adherence to diet was strongly associated with elevated HbA1c levels. This finding is of special relevance because adherence to diet is a modifiable factor, possibly accomplished by specific actions targeting those noncompliant to dietary recommendations. These findings add valuable information for a better understanding of the barriers to achieve adequate glycemic control in adult patients with DM1.

The American Diabetes Association (ADA) recommends that patients with a recent diagnosis of diabetes and without major complications or prior history of severe hypoglycemic episodes should target HbA1c levels of <6.5%, while patients with advanced micro and macrovascular complications or comorbidities aim towards HbA1c levels of <8.0%[5]. This recommendation is supported by studies conducted over two decades ago, showing that poor glycemic control is associated with microvascular and macrovascular complications in patients with diabetes[4,5]. Despite that, the majority of DM1 patients worldwide have inadequate glycemic control[7,17,18]. In our study, we found that the mean HbA1c level was 9.4%, the same result observed in another multicenter, DM1 study, conducted in 20 Brazilian cities between 2008 and 2010[9]. This study also found that the quality of life of DM1 patients was inversely related to the levels of HbA1c.

In our multiple variable model including only the sociodemographic variables, we found that patients whose highest level of educational attainment was primary school had a mean level of HbA1c 0.77% greater than patients with at least some college level

education. The relation between lower educational attainment of DM1 patients and higher levels of HbA1c has been previously reported[7,11]. However, a noteworthy finding of our study is that the correlation coefficient between educational levels and HbA1c levels decreased after we incorporated the behavioral variables (Model B) and almost disappeared when the clinical factors were included (Model C). The differences observed in the education level correlation coefficients among these models indicate that the effect of lower education on the level of HbA1c is possibly mediated by behavioral (adherence to diet and insulin, and participation in lecture for diabetes in the last year) and, especially, by clinical factors (attendance to private clinics and measurement of HbA1c, both in the year before). This original finding is of relevance because it highlights that the influence of lower education on inadequate glycemic control can be surpassed if DM1 patients have good adherence to diet and treatment, and if receive proper monitoring of HbA1c levels.

Regarding the behavioral factors, we found that participation in diabetes education programs was associated with better glycemic control, consistent with previous studies. In a case-control study conducted in Saudi Arabia, patients with DM1 or DM2 who had received monthly counseling about the disease, had significantly reduced HbA1c levels compared to those who had received counseling only at the beginning of the study[19]. In another single-arm, pre-post cohort study, aiming to estimate the impact of improving the knowledge, skills and confidence in self-management of DM1, the average HbA1c levels was significantly reduced from baseline to follow-up measurements[20]. The mechanisms by which diabetes education programs help achieve a better glycemic control are likely diverse, and may include provision of

knowledge about the disease, aid in developing skills and techniques for disease self-management, and support for adoption of healthy eating and lifestyle habits. Our findings reinforce the importance of policies and practices that challenge the traditional medical care of DM1 and include educational activities to empower patients to achieve goals for glycemic control.

A lower degree of self-perceived adherence to diet and insulin therapy were also strongly associated with higher levels of HbA1c among our study patients. These findings are in accordance with other studies of DM1 patients, in which the average HbA1c was significantly lower among patients who followed dietary recommendations, compared to those who did not[13,21]. A study that enrolled both DM1 and DM2, insulin-treated patients also found after adjusting for confounders that better glycemic control was associated with adherence to a dietary plan that included greater daily ingestion of fruits and vegetables, but not with adherence to insulin therapy[17]. However, Gastal et al.[22] found that better scores in a diabetes self-care scale evaluating diabetes general management, diet, exercise, care with feet, glycemic monitoring, insulin administration, and detection, prevention or treatment of hypoglycemia/hyperglycemia were associated with lower HbA1c values. Thus, additional evidence supports our findings that adherence to both diet and insulin regimens are essential for glycemic control and for subsequent prevention of disease complications and early death. We recommend that health professional involved in DM1 care devote substantive efforts to motivate patients to follow diet recommendations and treatment prescriptions. Whenever possible, they should try to simplify the treatment regimen and work to guarantee a proper understanding of their patients about the disease and its management. Further

observational studies, aiming to identify factors that influence adherence to both diet and insulin, are warranted. In addition, experimental trials should compare the efficacy of different strategies to improve patients' compliance to diet and treatment. Such strategies may include different motivational approaches to improve adherence, as well as the use of different insulin delivery devices.

Unfortunately, we did not collect detailed data on diet and food consumption, which would allow a better understanding of its role on glycemic control. Even though, our finding of an inverse relation between the degree of self-perceived adherence to diet and HbA1c levels suggests that following specific alimentary recommendations have a direct contribution to glycemic control. Several actions may help reinforcing the role of diet adherence to glycemic control, such as a close follow up by a multidisciplinary health team (including nutritionists, social assistants, psychologists, and other professionals), provision of patients' education, spouse and family support, encouraging diet adherence[23], and the use of digital media and electronic devices, such as smart phone self-care "apps"[24].

Some studies suggest that DM1 patients undergoing close monitoring of diabetes through regular HbA1c measurements, blood glucose self-monitoring, and regular medical appointments, had lower levels of HbA1c[12,25,26]. We found in bivariate analysis, but not in multiple variable analyses, that those self-monitoring blood glucose on a regular basis had lower HbA1c levels. The failure of our multiple variable analyses to show this association may derive from the method that we used to obtain data on blood glucose self-monitoring, which was self-reported, not relying on diaries or other more accurate sources to quantify the daily frequency of self-monitoring in a typical day.

However, our finding that patients who did not measure the HbA1c level in the previous year had greater levels of HbA1c, even after adjustment for other variables, does support the notion that a careful disease monitoring is critical for an adequate glycemic control. Thus, regular monitoring of glycemic levels should be an essential chapter of policies and programs designed to provide improved care for DM1 patients.

We also found that patients who had not received diabetes medical care at private services presented significantly higher HbA1c levels than those who had. This result raises concerns because the Brazilian public health system provides universal medical care for the majority of the population with diabetes in the country. Training the public health professionals for diabetes care and ensuring better infrastructure and access to universal assistance for patients with diabetes are critical collective actions that need to be attained in order to decrease the high percentage of DM1 patients with inadequate glycemic control. Specific actions may include providing multidisciplinary professional teams for diabetes care, and increasing access to the most advanced insulin therapies and to self-monitoring of blood glucose.

This study has some limitations. First, the cross-sectional design does not allow for establishing a temporal relation between the factors associated with high levels of HbA1c. Therefore, a thorough follow-up of DM1 patients through a cohort study is warranted and may help elucidate whether the factors we found to be associated with higher HbA1c levels are causally related to poor glycemic control. Second, except for the HbA1c measurement, all the patients' data, including the behavioral and clinical characteristics were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers. However, interviews are widely used in epidemiological

and clinical studies of diabetes and our results are consistent with those of previous studies that used self-reported answers [9]. In addition, self-reported data have been shown to have high agreement with medical records for several questions, such as type of diabetes, family history of diabetes, therapeutic regimen and disease complications[27]. Although inaccurate answers on type of diabetes might have led to inclusion of some insulin-treated DM2 patients in the study population, we expect this number to be small, having minimal impact on our findings and conclusions. Third, typical DM1 onset happens during childhood and adolescence, but our study sample only included patients ≥18 years of age and was obtained in reference diabetes care centers. Therefore, we might have introduced a selection bias, with participants likely having a longer disease duration, a greater number of complications and, possibly, worse glycemic control. In addition, the study patients were not randomly selected. However, as the DM1 patients sample was consecutively enrolled during 30 days in 20 diabetes centers from ten large cities in four different regions of Brazil, it is reasonable to assume that the factors associated with a poor glycemic control among the studied patients can be generalized to patients with DM1 seeking care in large urban centers in the country. On the other hand, in our study we measured the HbA1c levels for all participants in a single laboratory, and used the same reference method of liquid chromatography, thus avoiding problems with lack of standardization reported by other authors.

In summary, our findings support the concept that multiple and distinct factors, such as sociodemographic, behavioral and clinical drivers, act together to influence the glycemic control in DM1 patients. Encouraging patients' adherence to diet and to insulin

treatment is critical for achieving optimum levels of HbA1c. Health education programs to inform and engage patients in their treatment, as well as ensuring periodic medical monitoring and measurement of HbA1c, are important additional measures. Reinforcing these recommendations for public health policies and clinical guidelines may translate into improved glycemic control in DM1 patients.

**ACKNOWLEDGEMENTS**

The study was supported by an unconditional grant form Pfizer Inc. The authors would like to thank the team members in the collection of blood samples, interviews with patients and performing HbA1c tests, and the study investigators: Adriana C. Forti, MD; Ana B. V. Mendes, MD; Antônio R. Chacra, MD; Celio C. Borges, MD; Debora V. Soares, MD; Edson P. Brum, MD; Elza M. S. Constantino, MD; Francisco A. Oliveira, MD; Freddy Eliaschewitz, MD; Hermelinda Pedrosa, MD; João A. S. Fittipaldi, MD; Jorge Gross, MD; Jose E. P. Oliveira, MD; Lucia Cordeiro, MD; Lucia P. E. Souza, MD; Marcia Nery, MD; Marcos Tambascia, MD; Maria C. C. de Almeida, PhD; Maria R. Calsolari, MD; Reinaldo B. M. Machado, MD; Reine Chaves, MD; Rosane Kupfer, MD; Ruy Lyra, MD; Saulo Cavalcante, MD; and Silmara Leite, MD. We also thank Professor Uriel Kitron for his valuable review of the manuscript. Carine S. Andrade received scholarship from the Coordination for the Improvement of Higher Education Personnel (CAPES), Brazilian Ministry of Education. Guilherme S. Ribeiro and Edson D. Moreira Jr. received scholarships from the National Council for Scientific and Technological Development (CNPq).

## CONFLICT OF INTEREST

Carine S. Andrade has no conflicts of interest; Guilherme S. Ribeiro has no conflicts of interest; Carlos A.S.T. Santos has no conflicts of interest; Raimundo Celestino S. Neves has no conflicts of interest; Edson D. Moreira Jr. was a consultant for Pfizer Inc.

## AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: Edson D Moreira Jr; Carine S Andrade; Guilherme S Ribeiro. Analysis and interpretation of data: Carine S Andrade; Guilherme S Ribeiro; Carlos AST Santos; Raimundo Celestino S Neves; Edson D Moreira Jr. Wrote the paper: Carine S Andrade; Guilherme S Ribeiro. Reviewed and approved the final version of the manuscript: Carine S Andrade; Guilherme S Ribeiro; Carlos AST Santos; Raimundo Celestino S Neves; Edson D Moreira Jr.

## AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed during the current study may be available from the corresponding author on reasonable request.

## FUNDING

The Brazilian Study of Diabetes Control was funded by Pfizer Inc., Brazil.

## REFERENCE


1 Drouin P, Blickle JF, Charbonnel B, *et al.* Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;**33 Suppl 1**:S62-9. doi:10.2337/dc10-S062

2 Diaz-Valencia PA, Bougnères P, Valleron A-J. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. *BMC Public Health* 2015;**15**:255. doi:10.1186/s12889-015-1591-y

3 Tuomilehto J. The Emerging Global Epidemic of Type 1 Diabetes. *Curr Diab Rep* 2013;**13**:795–804. doi:10.1007/s11892-013-0433-5

4 DCCT. The New England Journal of Medicine Downloaded from nejm.org at FIOCRUZ on January 7, 2015. For personal use only. No other uses without permission. Copyright © 1993 Massachusetts Medical Society. All rights reserved. *N Engl J Med* 1993;**329**:977–86.http://www.nejm.org/doi/pdf/10.1056/NEJM199309303291401

5 George Bakris M, Lawrence Blonde, MD F, Andrew J.M. Boulton M, *et al.* Standards of Medical Care in Diabetes - 2015. *Diabetes Care J Clin Appl Res Educ* 2015;**38**:S1–99. doi:10.2337/dc15-S005

6 McCarthy M, Funk M, Grey M. Ideal Cardiovascular Health in Adults with Type 1 Diabetes. *Nurs Res* 2016;**65**:E65–E65 1/3p. doi:10.1016/j.ypmed.2016.08.019

7 Sastre J, Pines PJ, Moreno J, *et al.* Situacion de control metabolico y pautas de tratamiento en pacientes con diabetes tipo 1 en Castilla-La Mancha: estudio de diabetes tipo 1 en Castilla-La Mancha. *Endocrinol y Nutr* 2012;**59**:539–46. doi:10.1016/j.endonu.2012.07.003

8 Mendes ABV, Fittipaldi JAS, Neves RCS, *et al.* Prevalence and correlates of inadequate glycaemic control: results from a nationwide survey in 6,671 adults with diabetes in Brazil. *Acta Diabetol* 2010;**47**:137–45. doi:10.1007/s00592-009-0138-z

9 Braga de Souza ACC, Felício JS, Koury CC, *et al.* Health-related quality of life in people with type

1 Diabetes Mellitus: data from the Brazilian Type 1 Diabetes Study Group. *Health Qual Life Outcomes* 2015;**13**:204. doi:10.1186/s12955-015-0396-0

10 Paris CA, Imperatore G, Klingensmith G, *et al.* Predictors of Insulin Regimens and Impact on Outcomes in Youth with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr* 2009;**155**:183–189.e1. doi:10.1016/j.jpeds.2009.01.063

11 Nádas J, Putz Z, Fövényi J, *et al.* Cardiometabolic risk and educational level in adult patients with type 1 diabetes. *Acta Diabetol* 2009;**46**:159–62. doi:10.1007/s00592-008-0065-4

12 Pfützner A, Weissmann J, Mougiakakou S, *et al.* Glycemic Variability Is Associated with Frequency of Blood Glucose Testing and Bolus: Post Hoc Analysis Results from the ProAct Study. *Diabetes Technol Ther* 2015;**17**:150303065452008. doi:10.1089/dia.2014.0278

13 Davison K a K, Negrato C a, Cobas R, *et al.* Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: a nationwide survey in Brazil. *Nutr J* 2014;**13**:19. doi:10.1186/1475-2891-13-19

14 Petitti DB, Klingensmith GJ, Bell RA, *et al.* Glycemic Control in Youth with Diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr* 2009;**155**:668–672.e3. doi:10.1016/j.jpeds.2009.05.025

15 Patterson C, Guariguata L, Dahlquist G, *et al.* Diabetes in the young – a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract* 2014;**103**:161–75. doi:10.1016/j.diabres.2013.11.005

16 Victora CG, Huttly SR, Fuchs SC, *et al.* The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. *Int J Epidemiol* 1997;**26**:224–7. doi:10.1093/ije/26.1.224

17 Angamo MT, Melese BH, Ayen WY. Determinants of glycemic control among insulin treated diabetic patients in Southwest Ethiopia: hospital based cross sectional study. *PLoS One* 2013;**8**:e61759. doi:10.1371/journal.pone.0061759

18 Colom C, Chico A, Carreras G, *et al.* Control glucémico y complicaciones crónicas a 20 años del comienzo de la diabetes tipo 1. Resultados de una unidad especializada. *Av en Diabetol*

2015;**31**:113–9. doi:10.1016/j.avdiab.2015.02.002

19 Ba-Essa E, Mobarak E. Intensified glucose self-monitoring with education in Saudi DM patients. *Int J …* 2015;**8**:19374–80.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4694478/

20 Speight J, Holmes-Truscott E, Harvey DM, *et al.* Structured type 1 diabetes education delivered in routine care in Australia reduces diabetes-related emergencies and severe diabetes-related distress: The OzDAFNE program. *Diabetes Res Clin Pract* 2016;**112**:65–72. doi:10.1016/j.diabres.2015.11.002

21 Mehta SN, Volkening LK, Andreson BJ et al. Dietary behaviors predict glycemic control in youth with type 1 diabetes. *Diabetes Care* 2008;**31**:1318–20.http://care.diabetesjournals.org/content/31/7/1318.full.pdf+html

22 Gastal DA, Pinheiro RT, Vazquez DP. Self-efficacy scale for Brazilians with type 1 diabetes. *Sao Paulo Med J* 2007;**125**:96–101.http://www.ncbi.nlm.nih.gov/pubmed/17625707

23 Leong A, Rahme E, Dasgupta K. Spousal diabetes as a diabetes risk factor: a systematic review and meta-analysis. *BMC Med* 2014;**12**:12. doi:10.1186/1741-7015-12-12

24 Joshi R, Joshi D, Cheriyath P. Improving adherence and outcomes in diabetic patients. *Patient Prefer Adherence* 2017;**11**:271–5. doi:10.2147/PPA.S122490

25 Miller KM, Beck RW, Bergenstal RM, *et al.* Evidence of a Strong Association Between Frequency of Self-Monitoring of Blood Glucose and Hemoglobin A1c Levels in T1D Exchange Clinic Registry Participants. *Diabetes Care* 2013;**36**:2009–14. doi:10.2337/dc12-1770

26 Jin S-M, Baek JH, Suh S, *et al.* Factors Associated with Greater Benefit of a National Reimbursement Policy for Blood Glucose Test Strips in Adult Patients with Type 1 Diabetes: A Prospective Cohort Study. *J Diabetes Investig* 2017;:0–2. doi:10.1111/jdi.12728

27 Løvaas KF, Cooper JG, Sandberg S, *et al.* Feasibility of using self-reported patient data in a national diabetes register. *BMC Health Serv Res* 2015;**15**:553. doi:10.1186/s12913-015-1226-0

FIGURE 1. Hierarchical model for determinants of high levels of glycated hemoglobin in patients with type 1 diabetes.

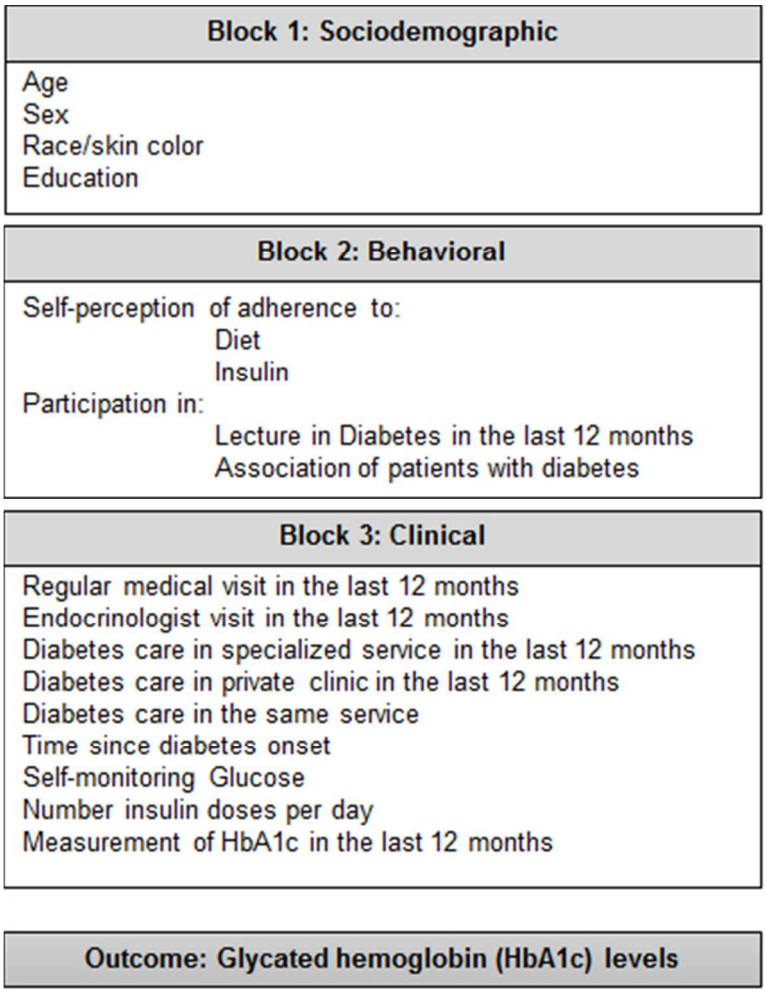


FIGURE 1. Hierarchical model for determinants of high levels of glycated hemoglobin in patients with type 1 diabetes.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | **1** |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | **2** |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | **4** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | **5** |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | **5** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | **5,6** |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | **6** |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | **6,7,8** |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | **7,8** |
| Bias | 9 | Describe any efforts to address potential sources of bias | **6,7** |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | **6,7** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | **7,8** |
| | | (*b*) Describe any methods used to examine subgroups and interactions | **7,8** |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | **7,8** |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | **9** |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | **9,10** |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | **11,12** |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | **11,12,13,14** |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | **16** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | **18,19** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | **17,18** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | **21,22** |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTER STUDY IN BRAZIL



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018094.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 16-Oct-2017 |
| Complete List of Authors: | ANDRADE, CARINE; Universidade Federal da Bahia, Escola de Nutrição<br>RIBEIRO, GUILHERME; Universidade Federal da Bahia, Institute of Collective Health; Oswaldo Cruz Foundation, Gonçalo Moniz Institute<br>SANTOS, CARLOS ANTONIO; Universidade Estadual de Feira de Santana; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute<br>NEVES, RAIMUNDO CELESTINO; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute<br>MOREIRA JR, EDSON; Fundacao Oswaldo Cruz, Gonçalo Moniz Institute; Obras Sociais Irma Dulce |
| Primary Subject Heading: | Diabetes and endocrinology |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | type 1 diabetes, glycemic control, glycated hemoglobin, EPIDEMIOLOGY |
| | |

# FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTER STUDY IN BRAZIL

Carine Sousa Andrade, PhD[a,b], Guilherme Sousa Ribeiro, PhD[a,c], Carlos Antonio Souza Teles Santos, PhD[a,d], Raimundo Celestino Silva Neves, PhD[a], Edson Duarte Moreira Jr., PhD[a,e]*.

(a) Gonçalo Moniz Institute, Oswaldo Cruz Foundation, Salvador, Brazil;

(b) School of Nutrition, Federal University of Bahia, Salvador, Brazil;

(c) Institute of Collective Health, Federal University of Bahia, Salvador, Brazil;

(d) State University of Feira de Santana, Feira de Santana, Brazil;

(e) Charitable Works Foundation of Sister Dulce, Salvador, Brazil.

*Address for correspondence: Dr. Edson D Moreira Jr.

Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Rua Waldemar Falcão 121, Salvador, Bahia, 40296-710, Brazil.

Tel .: +55 71 3176 2343; Fax: +55 71 3176 2243.

E-mail: edson@bahia.fiocruz.br (E. D. Moreira Jr.).

Word count: 3,669 words

## ABSTRACT

Objective: Long-term complications of type 1 diabetes mellitus (DM1) can be prevented with adequate glycemic control. However, high levels of glycated hemoglobin (HbA1c) occur in 60 to 90% of the DM1 patients. Thus, we aimed to investigate the role of sociodemographic, behavioral and clinical factors on the HbA1c levels of DM1 patients in Brazil.

Design, setting and participants: A cross-sectional study was conducted with ambulatory DM1 patients aged ≥18 years from 10 Brazilian cities. Sociodemographic, behavioral and clinical data were obtained through interviews.

Main outcome measures: HbA1c level was measured by liquid chromatography. Hierarchical multiple variable linear regression models were used to identify factors correlated with high levels of HbA1c.

Results: Of 979 DM1 patients, 63.8% were female and the mean age was 40 (SD: 14.6) years. The mean HbA1c level was 9.4% (SD: 2.2%), and 89.6% of the patients had HbA1c ≥7.0%. Factors independently correlated with increased HbA1c levels included: lower education, non-participation in diabetes classes/lecture during the year before, having a self-perception of poor adherence to diet and insulin, not having private medical care, and not measuring the HbA1c levels in the prior year. Of note, poor adherence to diet and insulin were the independent factors most strongly associated with high levels of HbA1c (mean increment in HbA1c levels of 0.88% and 1.25%, respectively).

Conclusion: Poor glycemic control, which is common among DM1 Brazilian patients, is associated with lower education, self-perception of insufficient adherence to diet and

insulin, and inadequate monitoring of HbA1c levels. Specific actions, particularly those targeting improving adherence to diet and insulin, may contribute to successful management of DM1 patients.

Keywords: type 1 diabetes, glycemic control, glycated hemoglobin, epidemiology.

**Strengths and limitations of this study**

- This cross-sectional, multicenter study included 979 type 1 diabetes mellitus patients from ten large Brazilian cities, representing four of the five regions of the country.
- We measured the HbA1c levels for all participants in a single laboratory, and used the same reference method of liquid chromatography, thus avoiding problems with lack of standardization reported by other authors.
- In order to identify independent factors associated with increased levels of HbA1c, we applied robust, multiple variable models, using a hierarchical approach according to a previously defined conceptual framework. This method accounts for hierarchical inter-relationships between variables and for the potential underestimation of the effects of distal determinants.
- Data on behavioral and clinical characteristics were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers.

## 1. INTRODUCTION

Type 1 diabetes mellitus (DM1) is characterized by the destruction of the insulin-producing pancreatic β cells, leading to an hyperglycemic state that requires continued reposition of exogenous insulin in order to prevent life-threatening acute and chronic complications[1]. The disease annual incidence varies greatly between countries, ranging from 1.1 to 39.9 per 100,000 persons 15-19 years of age[2], and is globally increasing at a rate of approximately 3% per year[3].

Patients with DM1 are at increased risk for cardiovascular disease, periphery nerve damage, nephropathy, and retinopathy, resulting in reduced life expectancy for those who are not properly treated[1]. This risk can be substantially reduced with intensive glycemic control, aiming for glycated hemoglobin (HbA1c) levels <6.0%[4]. However, most patients with DM1 have HbA1c values above the international recommendation of <7.0%[5]. Inadequate glycemic control (HbA1c levels >7.0%) in DM1 patients was observed in 77% of the participants of a study in the United States in 2016[6], in 74% of the study patients in the region of Castilla-La Mancha, Spain in 2012[7], in 87% of patients surveyed in Venezuela[8], and in 84%-90% of the participants of national multicenter studies conducted in Brazil in 2010 and 2015[9,10].

A better understanding of the factors that determine glycemic control is critical to improved management of DM1 patients. However, the majority of studies investigating determinants of glycemic control enrolled patients with type 2 diabetes mellitus (DM2) or studied patients with DM1 and DM2 combined, despite the fact that challenges to achieve glycemic control differ between patients with DM1 and DM2, mainly due to the compulsory need of insulin use in DM1 patients. In the few published reports on

determinants of glycemic control in DM1 patients, high levels of HbA1c have been associated with younger age, low educational level, poor adherence to diet, mode of insulin administration, and infrequent monitoring of blood glucose[11–15]. Here, we describe the results of our study in which we investigated the role of sociodemographic, behavioral and clinical characteristics in the levels of HbA1c in a large sample of patients with DM1 in Brazil, a country where >31,000 persons <15 years of age have DM1 and where the disease burden in adults had not been estimated[16].

## 2. SUBJECTS, MATERIAL AND METHODS

### 2.1. Study Design and Sample Selection:

Detailed information on this cross-sectional, multicenter study was published before[9]. Briefly, the study was conducted in ten large Brazilian cities, representing four of the five regions of the country (Southeast region: Belo Horizonte, Campinas, Rio de Janeiro, and São Paulo; South region: Curitiba, and Porto Alegre; Midwest region: Brasilia; and Northeast region: Salvador, Fortaleza and Recife). These cities are the largest in their respective regions, and nine of them were ranked among the most populous municipalities in Brazil. To pursue the selection of the diabetes medical centers, we requested the Brazilian Diabetes Association to identify in each of the study city a list of candidate centers, selected because of previous experience in conducting epidemiological research and where a large number of adult patients are treated for diabetes (minimum of 300 patients per month). In each city, two diabetes centers (20 centers in total) were invited to participate in the study: five university-affiliated hospitals,

eleven general public hospitals, and four not-for-profit private hospitals. All invited centers accepted and were included in the study.

From February 2006 to March 2007, we invited patients fulfilling the eligibility criteria to participate in the study during 30 consecutive days in each of the centers. To be eligible for study enrollment, patients had to be 18 years of age or older and report a prior medical diagnosis of DM1. Patients who had participated in other research in the three months preceding the study were excluded. All patients were informed about the study aims, procedures and risks, and signed an informed consent prior to inclusion. The study was approved by the Hospital Santo Antônio Ethics Committee (approval number 32/05).

### 2.2. Data Collection:

Trained interviewers who were not part of the medical centers staff interviewed the participants using a structured questionnaire (supplementary file) to obtain data on demographic and socioeconomic indicators, self-perception of diet and insulin treatment adherence, attendance to diabetes education lectures, participation in associations of patients with diabetes, and clinical characteristics. The clarity of the questionnaire was assessed through pilot interviews in a sample of DM1 patients previously to study initiation. Data on education attainment (primary school or less, complete or incomplete secondary/high school, or at least some college level education) and on race/skin color were self-reported. Data on self-perception of diet adherence and of insulin adherence were collected using the following ordinal scale: poor/fair, good, or excellent. Clinical data included self-referred height and weight, time since first diagnosis of diabetes,

number of insulin doses per day, frequency of self-monitoring of blood glucose, as well as frequencies, in the previous 12 months, of consultation in public and private medical service facilities, consultation with an endocrinologist, prior hypoglycemic episodes, prior hospitalizations due to ketoacidosis and HbA1c measurements. Interviews were conducted in a private room and lasted 20-25 minutes. The response rate was 84% (ranging from 78% to 95%).

### 2.3. Measurement of Glycated Hemoglobin (HbA1c):

A blood sample was collected from participants at enrollment and tested by automated high performance liquid chromatography to determine HbA1c levels. All exams were performed in the same laboratory, according to standard procedures. The HbA1c levels data were reported as mean and standard deviation (SD) and, categorically, as a frequency of <7.0%, 7.0-8.9%, 9.0-10.9%, or ≥11.0%. We considered glycemic control to be inadequate when the HbA1c concentration was ≥7.0%[5].

### 2.4. Statistical Analysis:

Data were double entered into a computerized database using the EPI INFO version 3.04 software system (Centers for Disease Control and Prevention, Atlanta, USA). Subsequently, the two databases were electronic compared to validate the accuracy and internal consistency of the data. Statistical analyses were performed using version 12 of STATA (StataCorp., College Station, USA).

Participants' characteristics were presented using means and standard deviation for continuous variables, and frequencies for categorical variables. Patients' body mass

index (BMI) was calculated (by dividing weight in kilograms by the square of height in meters) and classified as eutrophic (<25.0 kg/m$^2$) and overweight/obese (≥25.0 kg/m$^2$), according to the World Health Organization criteria[17].

We applied bivariate and multiple variables linear regression models to estimate the effect of the independent variables on the level of HbA1c. Variables with a significant association at p value of ≤0.20 in the bivariate analyses were included in robust, multiple variable models using a hierarchical approach according to a previously defined conceptual framework (Figure 1). A conceptual framework is a theoretical model that describes the hierarchical relationships between explanatory variables and an outcome. This approach is considered an appropriate strategy for assessing disease determinants in multiple variable analyses because it handles complex hierarchical inter-relationships between variables and accounts for the potential underestimation of the effects of distal determinants (i.e. factors that typically do not determine the outcome directly, but do determine by other intermediate factors)[18].

The hierarchical model grouped variables in three blocks (Figure 1). Block 1 contained socioeconomic variables, such as education level and race/skin color. Block 2 contained behavioral variables, such as attendance to diabetes class/lectures, participation in associations of patients with diabetes, and self-perception of adherence to diet and insulin treatment. Block 3 comprised of clinical characteristics, including BMI, time since first diagnosis of diabetes, number of insulin doses per day, and frequency of self-monitoring of blood glucose, consultation with an endocrinologist, and HbA1c measurement in the previous 12 months (Figure 1).

A backward elimination strategy was then performed for each block. Block 1 variables that were significantly correlated with HbA1c serum levels at a *p* value ≤0.05 were maintained in the subsequent backward elimination model with block 2 variables. Using the same approach, block 2 variables that were significantly correlated with HbA1c serum levels at a *p* value ≤0.05 were maintained in the subsequent backward elimination model with block 3 variables. Finally, block 3 variables with a *p* value ≤0.05 were defined as factors independently correlated with the HbA1c levels. Variables from block 1 and block 2 that were selected to be included in following models were considered to be significantly correlated with HbA1c levels, regardless of their *p* value in the subsequent models. Sex and age were included in all models to ensure adjustments to these factors at all stages of the multiple variable analyses. We used the Akaike Information Criterion (AIC) to estimate the goodness of fit of the successive adjusted models.

## 3. RESULTS

Of the 979 DM1 patients enrolled in the study, 625 (63.8%) were female, and 296 (30.2%) were 18-29 years of age, 412 (42.1%) 30-49 years of age, and 271 (27.7%) ≥50 years of age (Table 1). About half (488, 49.8%) of the patients were white, and 398 (40.8%) had not studied beyond the primary school level. The Southeast region of Brazil accounted for 611 (62.4%) participants. Although all the diabetes centers were affiliated with the Brazilian public health care system, 95 (9.7%) of the patients reported they had also received private assistance during the past 12 months.

TABLE 1. Sociodemographic and clinical characteristics of 979 Brazilian patients with type 1 diabetes, Brazil.

| Characteristics | n (%) |
|---|---|
| SOCIODEMOGRAPHICS | |
| Age (years) | |
| 18 – 29 | 296 (30.2) |
| 30 – 49 | 412 (42.1) |
| ≥ 50 | 271 (27.7) |
| Sex Female | 625 (63.8) |
| Race/Skin color | |
| White | 488 (49.8) |
| Mixed | 286 (29.2) |
| Black | 122 (12.5) |
| Other | 83 (8.5) |
| Education[1] | |
| At least some College | 154 (15.8) |
| Secondary/High school | 424 (43.4) |
| Primary school or less | 398 (40.8) |
| Brazilian Region | |
| Southeast | 611 (62.4) |
| Northeast | 174 (17.8) |
| South | 104 (10.6) |
| Center-west | 90 (9.2) |
| CLINICAL | |
| Type of service for medical care in the last year | |
| Public | 884 (90.3) |
| Private | 95 (9.7) |
| Body mass index (kg/m$^2$)[2] | |
| <25.0 | 502 (52.5) |
| ≥25.0 | 455 (47.5) |
| CLINICAL COMPLICATIONS | |
| Hypoglycemic episodes in the last year | 497 (50.8) |
| Ketoacidosis hospitalization in the last year | 248 (25.3) |
| Reported complications | |
| Retinopathy | 427 (43.6) |
| Neuropathy[3] | 381 (39.2) |
| Nephropathy | 207 (21.1) |
| Angina[4] | 129 (13.2) |
| Vasculopathy[4] | 125 (12.8) |
| LABORATORY | |
| Glycated Hemoglobin (HbA1c) (%) | |
| <7.0 | 102 (10.4) |
| 7.0 – 8.9 | 366 (37.4) |
| 9.0 – 10.9 | 287 (29.3) |
| >11.0 | 224 (22.9) |

[1] Data available for 976 patients

[2] Data available for 957 patients

[3] Data available for 973 patients

[4] Data available for 977 patients

The diabetes complications most frequently reported by the study participants were retinopathy (427, 43.6%), followed by neuropathy (381, 39.2%) and nephropathy (207, 21.1%). Episodes of ketoacidosis and hypoglycemia in the previous year were common, affecting 248 (25.3%) and 497 (50.8%) patients, respectively. The majority (887, 89.6%) of patients had inadequate glycemic control (HbA1c ≥7.0%), and the mean HbA1c level was 9.4% (SD: 2.2%).

Bivariate analysis pointed to a correlation of higher levels of HbA1c with black race, lower education attainment, self-perception of fair/poor adherence to diet and to insulin treatment, not participating in diabetes class/lectures during the previous year, and never having participated in associations of patients with diabetes (Table 2). In addition, patients who reported that in the previous year had neither regular medical appointments, nor consultations with an endocrinologist, private consultations or health care delivered in the same diabetes center had significantly higher HbA1c. Finally, patients not performing regular self-monitoring of blood glucose, those with no measure of HbA1c during the previous year, and patients receiving less than four doses of insulin per day also had higher levels of HbA1c.

TABLE 2. Factors associated with glycated hemoglobin (HbA1c) levels in Brazilian patients with type 1 diabetes.

| Independent variable | Nº participants | HbA1c means in % (SD) | β Coefficient (CI 95%) | *p* value |
|---|---|---|---|---|
| BLOCK 1 – SOCIODEMOGRAPHIC | | | | |
| Age (years) | | | | |
| 18 – 29 | 296 | 9.35 (2.36) | Ref | 0.198 |
| 30 – 49 | 412 | 9.54 (2.28) | 0.186 (-0.146; 0.517) | |
| ≥ 50 | 271 | 9.24 (1.95) | -0.118 (-0.484; 0.248) | |
| Sex | | | | |
| Male | 354 | 9.25 (2.08) | Ref | 0.122 |
| Female | 625 | 9.48 (2.29) | 0.229 (-0.061; 0.518) | |
| Race/Skin color | | | | |
| White | 488 | 9.26 (2.10) | Ref | 0.058 |
| Mixed | 286 | 9.32 (2.33) | 0.133 (-0.191; 0.456) | |
| Black | 122 | 9.84 (2.34) | 0.576 (0.136; 1.017) | |
| Other | 83 | 9.62 (2.31) | 0.361 (-0.155; 0.877) | |
| Education | | | | |
| At least some College | 154 | 9.13 (1.82) | Ref | 0.002 |
| Secondary/High school | 424 | 9.21 (2.15) | 0.084 (-0.325; 0.492) | |
| Primary school or less | 398 | 9.70 (2.40) | 0.565 (0.154; 0.977) | |
| BLOCK 2 – BEHAVIORAL | | | | |
| Self-perception of adherence to diet | | | | |
| Excellent | 129 | 8.79 (2.22) | Ref | <0.001 |
| Good | 327 | 9.13 (2.09) | 0.344 (-0.103; 0.792) | |
| Fair / Poor | 523 | 9.72 (2.25) | 0.931 (0.508; 1.354) | |
| Self-perception of adherence to insulin | | | | |
| Excellent | 750 | 9.28 (2.12) | Ref | <0.001 |
| Good | 144 | 9.59 (2.30) | 0.315 (-0.074; 0.703) | |
| Fair / Poor | 62 | 10.82 (2.49) | 1.543 (0.978; 2.107) | |
| Participation in lecture for diabetes in the last year | | | | |
| Yes | 345 | 9.11 (2.09) | Ref | <0.001 |
| No | 540 | 9.67 (2.31) | 0.549 (0.247; 0.850) | |
| Participation in association of diabetics patients | | | | |
| Yes, still participate | 116 | 9.09 (1.88) | Ref | 0.023 |
| Yes, but no more participate | 124 | 9.02 (1.80) | -0.067 (-0.627; 0.492) | |
| No, I never participated | 713 | 9.51 (2.32) | 0.418 (-0.016; 0.851) | |
| BLOCK 3 – CLINICAL | | | | |
| Body mass index (kg/m$^2$) | | | | |
| <25.0 | 502 | 9.45 (2.29) | Ref | 0.273 |
| ≥25.0 | 455 | 9.30 (2.08) | -0.156 (-0.435; 0.123) | |
| Regular medical visit in the last year | | | | |
| Yes | 878 | 9.34 (2.19) | Ref | 0.020 |
| No | 101 | 9.89 (2.42) | 0.541 (0.084; 0.998) | |

| | | | | |
|---|---|---|---|---|
| Endocrinologist visit in the last year | | | | |
| Yes | 800 | 9.32 (2.15) | Ref | 0.014 |
| No | 177 | 9.77 (2.50) | 0.453 (0.091; 0.814) | |
| Diabetes care in specialized service in the last year | | | | |
| Yes | 661 | 9.32 (2.18) | Ref | 0.120 |
| No | 318 | 9.56 (2.29) | 0.236 (-0.061; 0.533) | |
| Diabetes care in private clinic in the last year | | | | |
| Yes | 95 | 8.87 (1.61) | Ref | 0.014 |
| No | 884 | 9.46 (2.27) | 0.586 (0.117; 1.055) | |
| Diabetes care in the same service | | | | |
| Yes | 921 | 9.36 (2.18) | Ref | 0.015 |
| No | 57 | 10.10 (2.64) | 0.735 (0.142; 1.328) | |
| Time since diabetes onset (years) | | | | |
| < 10 | 261 | 9.43 (2.66) | Ref | 0.326 |
| 10 – 19 | 307 | 9.52 (2.11) | 0.094 (-0.273; 0.460) | |
| ≥ 20 | 408 | 9.27 (1.97) | -0.115 (-0.497; 0.192) | |
| Self-monitoring glucose | | | | |
| Yes, regularly | 663 | 9.25 (2.14) | Ref | 0.008 |
| Yes, when decompensated | 160 | 9.72 (2.28) | 0.463 (0.080; 0.845) | |
| No | 151 | 9.74 (2.46) | 0.489 (0.097; 0.881) | |
| Number insulin doses per day | | | | |
| 4 times | 168 | 8.91 (1.97) | Ref | 0.001 |
| 3 times | 290 | 9.38 (2.10) | 0.477 (0.062; 0.892) | |
| 2 times or less | 505 | 9.61 (2.29) | 0.707 (0.326; 1.088) | |
| Measurement HbA1c in the last year | | | | |
| Yes | 533 | 9.10 (1.93) | Ref | <0.001 |
| No | 184 | 10.00 (2.48) | 0.901 (0.576; 1.226) | |
| Do not know | 261 | 9.40 (2.43) | 0.298 (-0.070; 0.665) | |

Bivariate linear regression analyses.

The first multiple variable model, built with the socioeconomic variables (Model A, Table 3), showed that for each one year rise in age, HbA1c level were, on average, reduced by 0.01% (β=-0.013, 95% CI: -0.025, -0.002) and that education level only up to primary school was correlated with higher HbA1c levels (β=0.565, 95% CI: 0.154, 0.977). The second multiple variable model, which combined the behavioral variables with the selected variables from model A (Model B, Table 3), found that not participating in diabetes class/lecture during the previous year (β=0.503, 95% CI: 0.208, 0.799) and a self-perception of fair/poor adherence to diet (β=0.889, 95% CI: 0.446, 1.332) and to insulin therapy (β=1.385, 95% CI: 0.764, 2.007) were also positively correlated with HbA1c levels. The third multiple variable model, which incorporated the clinical variables with those selected in model B (Model C, Table 3), found that not consulting at a private clinic during the previous year (β=0.545, 95% CI: 0.021, 1.069) and having no HbA1c measurement performed in the previous year (β=0.770, 95% CI: 0.418; 1.122) were positively correlated with the HbA1c levels. It is noteworthy to mention that the effect of education over HbA1c levels was reduced with the subsequent introduction of further variables from blocks 2 and 3 (Models B and C), indicating that the effect of education on glycemic control was mediated by the behavioral and clinical variables incorporated into the model.

TABLE 3. Hierarchical model of multiple linear regression analyses for determinants of inadequate glycemic control in 846 Brazilian patients with type 1 diabetes.

| Independent variable | Unadjusted | Model A | Model B | Model C |
|---|---|---|---|---|
| | β coefficient (95% IC) | β coefficient (95% IC) | β coefficient (95% IC) | β coefficient (95% IC) |
| BLOCK 1: SOCIODEMOGRAPHIC | | | | |
| Age (years) | -0.003 (-0.012; 0.007) | -0.013 (-0.025; -0.002) | -0.008 (-0.019; 0.002) | -0.009 (-0.020; 0.001) |
| Sex | | | | |
| Male | Ref | Ref | Ref | Ref |
| Female | 0.229 (-0.061; 0.518) | 0.243 (-0.065; 0.551) | 0.311 (0.012; 0.610) | 0.286 (-0.009; 0.582) |
| Education | | | | |
| At least some College | Ref | Ref | Ref | Ref |
| Secondary/High school | 0.084 (-0.325; 0.492) | 0.141 (-0.288; 0.572) | 0.081 (-0.336; 0.499) | -0.254 (-0.709; 0.199) |
| Primary school or less | 0.565 (0.154; 0.977) | 0.765 (0.313; 1.217) | 0.551 (0.106; 0.996) | 0.090 (-0.409; 0.590) |
| BLOCK 2: BEHAVIORAL | | | | |
| Self-perception of adherence to diet | | | | |
| Excellent | Ref | | Ref | Ref |
| Good | 0.344 (-0.103; 0.792) | | 0.401 (-0.062; 0.866) | 0.377 (-0.081; 0.836) |
| Fair / Poor | 0.931 (0.508; 1.354) | | 0.889 (0.446; 1.332) | 0.876 (0.439; 1.313) |
| Self-perception of adherence to insulin | | | | |
| Excellent | Ref | | Ref | Ref |
| Good | 0.315 (-0.074; 0.703) | | 0.295 (-0.112; 0.702) | 0.239 (-0.164; 0.642) |
| Fair / Poor | 1.543 (0.978; 2.107) | | 1.385 (0.764; 2.007) | 1.242 (0.625; 1.858) |
| Participation in lecture for diabetes in the last year | | | | |
| Yes | Ref | | Ref | Ref |
| No | 0.549 (0.247;0.850) | | 0.503 (0.208; 0.799) | 0.482 (0.184; 0.779) |
| BLOCK 3: CLINICAL | | | | |
| Diabetes care in private clinic in the last year | | | | |
| Yes | Ref | | | Ref |
| No | 0.586 (0.117; 1.055) | | | 0.545 (0.021; 1.069) |
| Measurement HbA1c in the last year | | | | |
| Yes | Ref | | | Ref |
| No | 0.901 (0.576; 1.226) | | | 0.770 (0.418; 1.122) |
| Do not know | 0.298 (-0.070; 0.665) | | | 0.243 (-0.170; 0.657) |
| AIC*: | Not Applicable | 3,735.893 | 3,685.672 | 3,666.879 |

Note: Model A shows associations between sociodemographic factors (block 1) and the levels of glycated hemoglobin (HbA1c). Model B shows associations between sociodemographic and behavioral factors (blocks 1 and 2) and HbA1c levels. Model C shows associations between sociodemographic, behavioral, and clinical factors (blocks 1, 2 and 3), and HbA1c levels. *Akaike Information Criteria.

## 4. DISCUSSION

Our results indicate that sociodemographic, behavioral and clinical factors in DM1 patients are independently associated with high levels of HbA1c. Of note, self-reported poor adherence to diet was strongly associated with elevated HbA1c levels. This finding is of special relevance because adherence to diet is a modifiable factor, possibly accomplished by specific actions targeting those noncompliant to dietary recommendations. These findings add valuable information for a better understanding of the barriers to achieve adequate glycemic control in adult patients with DM1.

The American Diabetes Association (ADA) recommends that patients with a recent diagnosis of diabetes and without major complications or prior history of severe hypoglycemic episodes should target HbA1c levels of <6.5%, while patients with advanced micro and macrovascular complications or comorbidities aim towards HbA1c levels of <8.0%[5]. This recommendation is supported by studies conducted over two decades ago, showing that poor glycemic control is associated with microvascular and macrovascular complications in patients with diabetes[4,5]. Despite that, the majority of DM1 patients worldwide have inadequate glycemic control[7,19,20]. In our study, we found that the mean HbA1c level was 9.4%, the same result observed in another multicenter, DM1 study, conducted in 20 Brazilian cities between 2008 and 2010[10]. This study also found that the quality of life of DM1 patients was inversely related to the levels of HbA1c.

In our multiple variable model including only the sociodemographic variables, we found that patients whose highest level of educational attainment was primary school had a mean level of HbA1c 0.77% greater than patients with at least some college level

education. The relation between lower educational attainment of DM1 patients and higher levels of HbA1c has been previously reported[7,12]. However, a noteworthy finding of our study is that the correlation coefficient between educational levels and HbA1c levels decreased after we incorporated the behavioral variables (Model B) and almost disappeared when the clinical factors were included (Model C). The differences observed in the education level correlation coefficients among these models indicate that the effect of lower education on the level of HbA1c is possibly mediated by behavioral (adherence to diet and insulin, and participation in lecture for diabetes in the last year) and, especially, by clinical factors (attendance to private clinics and measurement of HbA1c, both in the year before). This original finding is of relevance because it highlights that the influence of lower education on inadequate glycemic control can be surpassed if DM1 patients have good adherence to diet and treatment, and if receive proper monitoring of HbA1c levels.

Regarding the behavioral factors, we found that participation in diabetes education programs was associated with better glycemic control, consistent with previous studies. In a case-control study conducted in Saudi Arabia, patients with DM1 or DM2 who had received monthly counseling about the disease, had significantly reduced HbA1c levels compared to those who had received counseling only at the beginning of the study[21]. In another single-arm, pre-post cohort study, aiming to estimate the impact of improving the knowledge, skills and confidence in self-management of DM1, the average HbA1c levels was significantly reduced from baseline to follow-up measurements[22]. The mechanisms by which diabetes education programs help achieve a better glycemic control are likely diverse, and may include provision of

knowledge about the disease, aid in developing skills and techniques for disease self-management, and support for adoption of healthy eating and lifestyle habits. Our findings reinforce the importance of policies and practices that challenge the traditional medical care of DM1 and include educational activities to empower patients to achieve goals for glycemic control.

A lower degree of self-perceived adherence to diet and insulin therapy were also strongly associated with higher levels of HbA1c among our study patients. These findings are in accordance with other studies of DM1 patients, in which the average HbA1c was significantly lower among patients who followed dietary recommendations, compared to those who did not[14,23]. A study that enrolled both DM1 and DM2, insulin-treated patients also found after adjusting for confounders that better glycemic control was associated with adherence to a dietary plan that included greater daily ingestion of fruits and vegetables, but not with adherence to insulin therapy[19]. However, Gastal et al.[24] found that better scores in a diabetes self-care scale evaluating diabetes general management, diet, exercise, care with feet, glycemic monitoring, insulin administration, and detection, prevention or treatment of hypoglycemia/hyperglycemia were associated with lower HbA1c values. Thus, additional evidence supports our findings that adherence to both diet and insulin regimens are essential for glycemic control and for subsequent prevention of disease complications and early death. We recommend that health professional involved in DM1 care devote substantive efforts to motivate patients to follow diet recommendations and treatment prescriptions. Whenever possible, they should try to simplify the treatment regimen and work to guarantee a proper understanding of their patients about the disease and its management. Further

observational studies, aiming to identify factors that influence adherence to both diet and insulin, are warranted. In addition, experimental trials should compare the efficacy of different strategies to improve patients' compliance to diet and treatment. Such strategies may include different motivational approaches to improve adherence, as well as the use of different insulin delivery devices.

Unfortunately, we did not collect detailed data on diet and food consumption, which would allow a better understanding of its role on glycemic control. Even though, our finding of an inverse relation between the degree of self-perceived adherence to diet and HbA1c levels suggests that following specific alimentary recommendations have a direct contribution to glycemic control. Several actions may help reinforcing the role of diet adherence to glycemic control, such as a close follow up by a multidisciplinary health team (including nutritionists, social assistants, psychologists, and other professionals), provision of patients' education, spouse and family support, encouraging diet adherence[25], and the use of digital media and electronic devices, such as smart phone self-care "apps"[26].

Some studies suggest that DM1 patients undergoing close monitoring of diabetes through regular HbA1c measurements, blood glucose self-monitoring, and regular medical appointments, had lower levels of HbA1c[13,27,28]. We found in bivariate analysis, but not in multiple variable analyses, that those self-monitoring blood glucose on a regular basis had lower HbA1c levels. The failure of our multiple variable analyses to show this association may derive from the method that we used to obtain data on blood glucose self-monitoring, which was self-reported, not relying on diaries or other more accurate sources to quantify the daily frequency of self-monitoring in a typical day.

However, our finding that patients who did not measure the HbA1c level in the previous year had greater levels of HbA1c, even after adjustment for other variables, does support the notion that a careful disease monitoring is critical for an adequate glycemic control. Thus, regular monitoring of glycemic levels should be an essential chapter of policies and programs designed to provide improved care for DM1 patients.

We also found that patients who had not received diabetes medical care at private services presented significantly higher HbA1c levels than those who had. This result raises concerns because the Brazilian public health system provides universal medical care for the majority of the population with diabetes in the country. Training the public health professionals for diabetes care and ensuring better infrastructure and access to universal assistance for patients with diabetes are critical collective actions that need to be attained in order to decrease the high percentage of DM1 patients with inadequate glycemic control. Specific actions may include providing multidisciplinary professional teams for diabetes care, and increasing access to the most advanced insulin therapies, such as insulin pump, and to self-monitoring of blood glucose. Use of insulin pumps in Brazil is not covered by the public national health system and it is incipient even for patients treated at private health services because insulin pumps are not produced in the country and the imported product is sold at an unaffordable price (>US$ 4,000.00)[29,30].

This study has some limitations. First, the cross-sectional design does not allow for establishing a temporal relation between the factors associated with high levels of HbA1c. Therefore, a thorough follow-up of DM1 patients through a cohort study is warranted and may help elucidate whether the factors we found to be associated with

higher HbA1c levels are causally related to poor glycemic control. Second, except for the HbA1c measurement, all the patients' data, including the behavioral and clinical characteristics were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers. However, interviews are widely used in epidemiological and clinical studies of diabetes and our results are consistent with those of previous studies that used self-reported answers [10]. In addition, self-reported data have been shown to have high agreement with medical records for several questions, such as type of diabetes, family history of diabetes, therapeutic regimen and disease complications[31]. Although inaccurate answers on type of diabetes might have led to inclusion of some insulin-treated DM2 patients in the study population, we expect this number to be small, having minimal impact on our findings and conclusions. Third, typical DM1 onset happens during childhood and adolescence, but our study sample only included patients ≥18 years of age and was obtained in reference diabetes care centers. Therefore, we might have introduced a selection bias, with participants likely having a longer disease duration, a greater number of complications and, possibly, worse glycemic control. In addition, the study patients were not randomly selected. However, as the DM1 patients sample was consecutively enrolled during 30 days in 20 diabetes centers from ten large cities in four different regions of Brazil, it is reasonable to assume that the factors associated with a poor glycemic control among the studied patients can be generalized to patients with DM1 seeking care in large urban centers in the country. On the other hand, in our study we measured the HbA1c levels for all participants in a single laboratory, and used the same reference method of liquid

chromatography, thus avoiding problems with lack of standardization reported by other authors.

In summary, our findings support the concept that multiple and distinct factors, such as sociodemographic, behavioral and clinical drivers, act together to influence the glycemic control in DM1 patients. Encouraging patients' adherence to diet and to insulin treatment is critical for achieving optimum levels of HbA1c. Health education programs to inform and engage patients in their treatment, as well as ensuring periodic medical monitoring and measurement of HbA1c, are important additional measures. Reinforcing these recommendations for public health policies and clinical guidelines may translate into improved glycemic control in DM1 patients.

**ACKNOWLEDGEMENTS**

The study was supported by an unconditional grant form Pfizer Inc. The authors would like to thank the team members in the collection of blood samples, interviews with patients and performing HbA1c tests, and the study investigators: Adriana C. Forti, MD; Ana B. V. Mendes, MD; Antônio R. Chacra, MD; Celio C. Borges, MD; Debora V. Soares, MD; Edson P. Brum, MD; Elza M. S. Constantino, MD; Francisco A. Oliveira, MD; Freddy Eliaschewitz, MD; Hermelinda Pedrosa, MD; João A. S. Fittipaldi, MD; Jorge Gross, MD; Jose E. P. Oliveira, MD; Lucia Cordeiro, MD; Lucia P. E. Souza, MD; Marcia Nery, MD; Marcos Tambascia, MD; Maria C. C. de Almeida, PhD; Maria R. Calsolari, MD; Reinaldo B. M. Machado, MD; Reine Chaves, MD; Rosane Kupfer, MD; Ruy Lyra, MD; Saulo Cavalcante, MD; and Silmara Leite, MD. We also thank Professor

Uriel Kitron for his valuable review of the manuscript. Carine S. Andrade received scholarship from the Coordination for the Improvement of Higher Education Personnel (CAPES), Brazilian Ministry of Education. Guilherme S. Ribeiro and Edson D. Moreira Jr. received scholarships from the National Council for Scientific and Technological Development (CNPq).

## CONFLICT OF INTEREST

Carine S. Andrade has no conflicts of interest; Guilherme S. Ribeiro has no conflicts of interest; Carlos A.S.T. Santos has no conflicts of interest; Raimundo Celestino S. Neves has no conflicts of interest; Edson D. Moreira Jr. was a consultant for Pfizer Inc.

## AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: Edson D Moreira Jr; Carine S Andrade; Guilherme S Ribeiro. Analysis and interpretation of data: Carine S Andrade; Guilherme S Ribeiro; Carlos AST Santos; Raimundo Celestino S Neves; Edson D Moreira Jr. Wrote the paper: Carine S Andrade; Guilherme S Ribeiro. Reviewed and approved the final version of the manuscript: Carine S Andrade; Guilherme S Ribeiro; Carlos AST Santos; Raimundo Celestino S Neves; Edson D Moreira Jr.

## AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed during the current study may be available from the corresponding author on reasonable request.

## FUNDING

The Brazilian Study of Diabetes Control was funded by Pfizer Inc., Brazil.

## REFERENCE

1 Drouin P, Blickle JF, Charbonnel B, *et al.* Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33 Suppl 1:S62-9. doi:10.2337/dc10-S062

2 Diaz-Valencia PA, Bougnères P, Valleron A-J. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. *BMC Public Health* 2015;15:255. doi:10.1186/s12889-015-1591-y

3 Tuomilehto J. The Emerging Global Epidemic of Type 1 Diabetes. *Curr Diab Rep* 2013;13:795–804. doi:10.1007/s11892-013-0433-5

4 DCCT. The New England Journal of Medicine Downloaded from nejm.org at FIOCRUZ on January 7, 2015. For personal use only. No other uses without permission. Copyright © 1993 Massachusetts Medical Society. All rights reserved. *N Engl J Med* 1993;329:977–86.http://www.nejm.org/doi/pdf/10.1056/NEJM199309303291401

5 George Bakris M, Lawrence Blonde, MD F, Andrew J.M. Boulton M, *et al.* Standards of Medical Care in Diabetes - 2015. *Diabetes Care J Clin Appl Res Educ* 2015;38:S1–99. doi:10.2337/dc15-S005

6 McCarthy M, Funk M, Grey M. Ideal Cardiovascular Health in Adults with Type 1 Diabetes. *Nurs Res* 2016;65:E65–E65 1/3p. doi:10.1016/j.ypmed.2016.08.019

7 Sastre J, Pines PJ, Moreno J, *et al.* Situacion de control metabolico y pautas de tratamiento en pacientes con diabetes tipo 1 en Castilla-La Mancha: estudio de diabetes tipo 1 en Castilla-La Mancha. *Endocrinol y Nutr* 2012;59:539–46. doi:10.1016/j.endonu.2012.07.003

8 Moreira ED, Neves RCS, Nunes ZO, *et al.* Glycemic control and its correlates in patients with

diabetes in Venezuela: Results from a nationwide survey. *Diabetes Res Clin Pract* 2010;87:407–14. doi:10.1016/j.diabres.2009.12.014

9 Mendes ABV, Fittipaldi JAS, Neves RCS, *et al.* Prevalence and correlates of inadequate glycaemic control: results from a nationwide survey in 6,671 adults with diabetes in Brazil. *Acta Diabetol* 2010;47:137–45. doi:10.1007/s00592-009-0138-z

10 Braga de Souza ACC, Felício JS, Koury CC, *et al.* Health-related quality of life in people with type 1 Diabetes Mellitus: data from the Brazilian Type 1 Diabetes Study Group. *Health Qual Life Outcomes* 2015;13:204. doi:10.1186/s12955-015-0396-0

11 Paris CA, Imperatore G, Klingensmith G, *et al.* Predictors of Insulin Regimens and Impact on Outcomes in Youth with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr* 2009;155:183–189.e1. doi:10.1016/j.jpeds.2009.01.063

12 Nádas J, Putz Z, Fövényi J, *et al.* Cardiometabolic risk and educational level in adult patients with type 1 diabetes. *Acta Diabetol* 2009;46:159–62. doi:10.1007/s00592-008-0065-4

13 Pfützner A, Weissmann J, Mougiakakou S, *et al.* Glycemic Variability Is Associated with Frequency of Blood Glucose Testing and Bolus: Post Hoc Analysis Results from the ProAct Study. *Diabetes Technol Ther* 2015;17:150303065452008. doi:10.1089/dia.2014.0278

14 Davison K a K, Negrato C a, Cobas R, *et al.* Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: a nationwide survey in Brazil. *Nutr J* 2014;13:19. doi:10.1186/1475-2891-13-19

15 Petitti DB, Klingensmith GJ, Bell RA, *et al.* Glycemic Control in Youth with Diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr* 2009;155:668–672.e3. doi:10.1016/j.jpeds.2009.05.025

16 Patterson C, Guariguata L, Dahlquist G, *et al.* Diabetes in the young – a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract* 2014;103:161–75. doi:10.1016/j.diabres.2013.11.005

17 Bailey K V., Ferro-Luzzi A. Use of body mass index of adults in assessing individual and

community nutritional status. *Bull World Health Organ* 1995;73:673–8.

18 Victora CG, Huttly SR, Fuchs SC, *et al.* The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. *Int J Epidemiol* 1997;26:224–7. doi:10.1093/ije/26.1.224

19 Angamo MT, Melese BH, Ayen WY. Determinants of glycemic control among insulin treated diabetic patients in Southwest Ethiopia: hospital based cross sectional study. *PLoS One* 2013;8:e61759. doi:10.1371/journal.pone.0061759

20 Colom C, Chico A, Carreras G, *et al.* Control glucémico y complicaciones crónicas a 20 años del comienzo de la diabetes tipo 1. Resultados de una unidad especializada. *Av en Diabetol* 2015;31:113–9. doi:10.1016/j.avdiab.2015.02.002

21 Ba-Essa E, Mobarak E. Intensified glucose self-monitoring with education in Saudi DM patients. *Int J …* 2015;8:19374–80.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4694478/

22 Speight J, Holmes-Truscott E, Harvey DM, *et al.* Structured type 1 diabetes education delivered in routine care in Australia reduces diabetes-related emergencies and severe diabetes-related distress: The OzDAFNE program. *Diabetes Res Clin Pract* 2016;112:65–72. doi:10.1016/j.diabres.2015.11.002

23 Mehta SN, Volkening LK, Andreson BJ et al. Dietary behaviors predict glycemic control in youth with type 1 diabetes. *Diabetes Care* 2008;31:1318–20.http://care.diabetesjournals.org/content/31/7/1318.full.pdf+html

24 Gastal DA, Pinheiro RT, Vazquez DP. Self-efficacy scale for Brazilians with type 1 diabetes. *Sao Paulo Med J* 2007;125:96–101.http://www.ncbi.nlm.nih.gov/pubmed/17625707

25 Leong A, Rahme E, Dasgupta K. Spousal diabetes as a diabetes risk factor: a systematic review and meta-analysis. *BMC Med* 2014;12:12. doi:10.1186/1741-7015-12-12

26 Joshi R, Joshi D, Cheriyath P. Improving adherence and outcomes in diabetic patients. *Patient Prefer Adherence* 2017;11:271–5. doi:10.2147/PPA.S122490

27 Miller KM, Beck RW, Bergenstal RM, *et al.* Evidence of a Strong Association Between Frequency

of Self-Monitoring of Blood Glucose and Hemoglobin A1c Levels in T1D Exchange Clinic Registry Participants. *Diabetes Care* 2013;36:2009–14. doi:10.2337/dc12-1770

28 Jin S-M, Baek JH, Suh S, *et al.* Factors Associated with Greater Benefit of a National Reimbursement Policy for Blood Glucose Test Strips in Adult Patients with Type 1 Diabetes: A Prospective Cohort Study. *J Diabetes Investig* 2017;:0–2. doi:10.1111/jdi.12728

29 Minicucci WJ. Uso de bomba de infusão subcutânea de insulina e suas indicações. *Arq Bras Endocrinol Metabol* 2008;52:340–8. doi:10.1590/S0004-27302008000200022

30 Cocolo AC. Bomba de insulina nacional facilitará controle do diabetes tipo 1. *Entre Teses* 2017;8:38–41.http://www.unifesp.br/reitoria/dci/entreteses/item/2854-bomba-de-insulina-nacional-facilitara-controle-do-diabetes-tipo-1

31 Løvaas KF, Cooper JG, Sandberg S, *et al.* Feasibility of using self-reported patient data in a national diabetes register. *BMC Health Serv Res* 2015;15:553. doi:10.1186/s12913-015-1226-0

FIGURE 1. Hierarchical model for determinants of high levels of glycated hemoglobin in patients with type 1 diabetes.

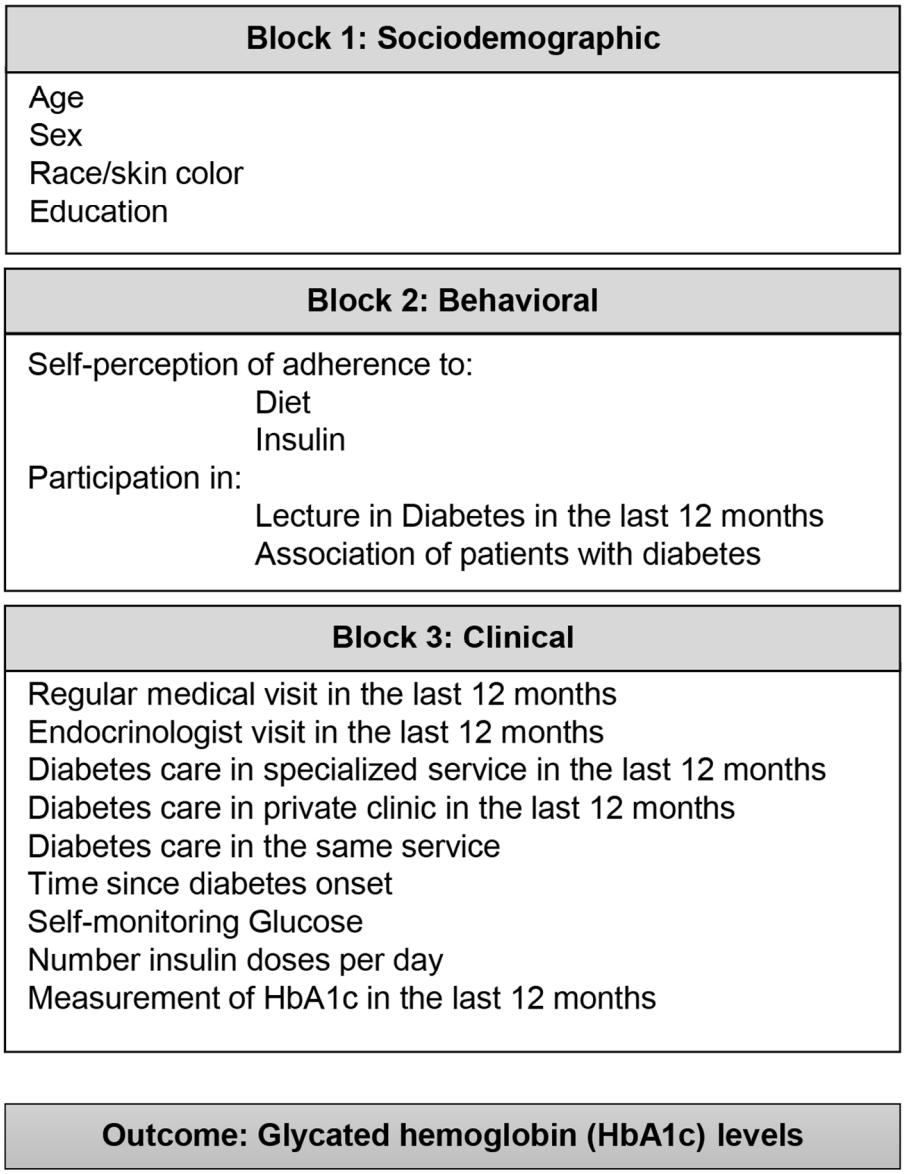


FIGURE 1. Hierarchical model for determinants of high levels of glycated hemoglobin in patients with type 1 diabetes.

103x133mm (300 x 300 DPI)

# NATIONAL DIABETES RESEARCH

| | | |
|---|---|---|
| **Interviewer:**_____ | | **Interview date:** ___ / ___ / _____ |
| **City:**_____ | **Center:**_____ | **Record #:** [ TAG ] |

## SECTION A: PERSONAL INFORMATION

**A1. How old are you?** ☐☐ **years old**

**A2. [MARK ANSWER WITHOUT ASKING]:** 1. ( ) Male 2. ( ) Female

**A3. What is yours marital status?**
1. ( ) Single
2. ( ) Married
3. ( ) Divorced
4. ( ) Widower
5. ( ) Living with a partner

**A4. What is your skin color (race/ethnicity)?**
1. ( ) White
2. ( ) Mixed
3. ( ) Black
4. ( ) Asian
5. ( ) Other (specify) _____

**A5. What is your educational attainment? [ILLITERATE: SCORE "0"]**
1. I studied up to ☐☐ grade, or
2. ( ) Secondary/High school or
3. ( ) At least some College
4. ( ) Primary school or less

**A6. What is your current working situation?**
1. ( ) Full-time or part-time work
2. ( ) Retired or pensioner
3. ( ) Unemployed
4. ( ) Medical license due to illness or physical disability
5. ( ) Housewife
6. ( ) Student
7. ( ) Does not work

## SECTION B: DATA ON HEALTH HISTORY AND LIFE HABITS

**B1. What is your height?** ☐, ☐☐ **m**

**B2. How much do you weigh?** ☐☐☐, ☐ **Kg**

**B3. Has any doctor ever told you that you have or have had any of these problems....?**

| | (Yes) | (No) | (Do not know) |
|---|---|---|---|
| **B3a. Angina or heart attack (chest pain).....** | **( Y )** | **( N )** | **( DNK )** |
| **B3b. Change in the fundus of the eye (or have had a laser treatment), cataracts, or significant loss or decrease in vision.....** | **( Y )** | **( N )** | **( DNK )** |
| **B3c. Renal function impairment (kidney disease).....** | **( Y )** | **( N )** | **( DNK )** |
| **B3d. Neuropathy / neuritis (numbness, "twinges" in the legs / feet).....** | **( Y )** | **( N )** | **( DNK )** |
| **B3e. Peripheral vasculopathy ("diabetic foot", chronic leg ulcers / sores)…....** | **( Y )** | **( N )** | **( DNK )** |
| **B3f. Stroke .....** | **( Y )** | **( N )** | **( DNK )** |
| **B3g. Other (What? _____).....** | **( Y )** | **( N )** | **( DNK )** |

# NATIONAL DIABETES RESEARCH

**B4. Do you have other family members with diabetes (parents, grandparents, children, siblings)?. ( Y ) ( N ) (DNK )**

**B5. Compared to other people your age, you would say that your level of physical activity is:**

1. ( ) Less than most people
2. ( ) Same as most people
3. ( ) More than most people

## SECTION C: DIABETES DATA (TYPE, TREATMENT AND CONTROL)

**C1. What was your age when your diabetes was diagnosed?** | | | **years old**

**C2. What type of diabetes is it?**

1. ( ) Type 1 (usually starts at a young age, almost always without previous cases of diabetes in the family, and treated with insulin)
2. ( ) Type 2 (usually begins at age 40 years or more, associated with obesity, often with previous cases in the family and treated with oral medication associated or not with insulin)
3. ( ) Gestational (occurred during pregnancy)

**C3. Indicate which treatment(s) you currently use:**

**C3.1. Do you follow a specific diet?**

1. ( ) NO [GO TO C3.2]
2. ( ) YES

**C3.1a. Honestly, how would you say it is your diet adherence? [READ ALL OPTIONS]**

1. [ ] Poor (I never follow the diet)
2. [ ] Bad (I rarely follow the diet)
3. [ ] Regular (Sometimes I follow the diet)
4. [ ] Good (I almost always follow the diet)
5. [ ] Excellent (I always follow the diet)

**C3.2. Do you use oral medication for diabetes?**

1. ( ) NO [GO TO C3.3]
2. ( ) YES. Which are they?

SIGN THE TIME (S) YOU TAKE MEDICATION:

| | Breakfast | Lunch | Dinner | Before bed / at night |
|---|---|---|---|---|
| **C3.2a.** _____ | \|___\| | \|___\| | \|___\| | \|___\| |
| **C3.2b.** _____ | \|___\| | \|___\| | \|___\| | \|___\| |
| **C3.2c.** _____ | \|___\| | \|___\| | \|___\| | \|___\| |

**C3.2d. Honestly, how would you say that is your adherence to the use of medication? [READ ALL OPTIONS]**

1. [ ] Poor (I use medication only when I feel bad)
2. [ ] Bad (I use medication very irregularly)
3. [ ] Regular (Sometimes I forget / stop taking the medication)
4. [ ] Good (I rarely forget / stop taking the medication)
5. [ ] Excellent (I almost never forget / stop taking the medication)

**C3.3. Do you use insulin?**

1. ( ) NO [GO TO C4]
3. ( ) YES Which type (s) of insulin?

SIGN THE TIME (S) YOU TAKE MEDICATION

| | Breakfast | Lunch | Dinner | Before bed / at night |
|---|---|---|---|---|
| **C3.3a.** _____ | \|___\| | \|___\| | \|___\| | \|___\| |
| **C3.3b.** _____ | \|___\| | \|___\| | \|___\| | \|___\| |
| **C3.3c.** _____ | \|___\| | \|___\| | \|___\| | \|___\| |

**C3.3d. Honestly, how would you say that is your adherence to the use of insulin? [READ ALL OPTIONS]**

1. [ ] Poor (I use insulin only when I feel bad)
2. [ ] Bad (I use insulin very irregularly)
3. [ ] Regular (Sometimes I forget / stop taking insulin)
4. [ ] Good (I rarely forget / stop taking insulin)
5. [ ] Excellent (I almost never forget / stop taking insulin)

**C4. Currently, what test (s) do you use to evaluate your diabetes control:**

# NATIONAL DIABETES RESEARCH

**C4.1. Capillary blood glucose test (droplet of blood from the tip of the finger)?**

1. ( ) No
2. ( ) Yes, occasionally (when I feel bad, or when I go to the doctor's office, etc.)
3. ( ) Yes, regularly. **C4.1a. How many times do you do the test?** |___|___| per DAY OR |___|___| per WEEK

**C4.2. Urine glucose strip?**

1. ( ) No
2. ( ) Yes, occasionally (when I feel bad, when I go to the doctor's office, etc.)
3. ( ) Yes, regularly. **C4.2a. How many times do you do the test?** |___|___| per DAY OR |___|___| per WEEK

**C5. In the last 12 months, have you had any glycated (or glycosylated) hemoglobin test?**

1. ( ) No
2. ( ) Do not know
3. ( ) Yes. **C5.1. How many times did you take this test in the last 12 months?** |___|___|
   **C5.2. What is the most recent result? _____ |___| Do not know**

**C6. In the past 12 months, have you had any other medical visits to control your diabetes (in addition to this visit)?**

1. ( ) No
2. ( ) Yes, but not regularly (only when I felt bad or thought diabetes was uncontrolled)
3. ( ) Yes, regularly (regardless of whether I feel well controlled) **C6.1. In this case, how many times?** |___|___|

**C7. In the last 12 months, what type of doctor did you consult for your diabetes? [READ ALL OPTIONS]**

1. ( ) I did not see a doctor during this period
2. ( ) General doctor
3. ( ) Endocrinologist or diabetes specialist
4. ( ) Other (specify which:_____)

**C8. Generally, do you always consult for diabetes with the same doctor?**

1. ( ) No, I consult with the doctor who is available.
2. ( ) Yes, always with the same doctor

**C9. In the last 12 months, where did you go to consult for diabetes? [READ ALL OPTIONS]**

1. ( ) I did not consult myself during this period
2. ( ) General public service (not specialized in diabetes)
3. ( ) Diabetes Specialized Public Service (Reference Center)
4. ( ) Private clinic
5. ( ) Other (Which?_____)

**C10. Generally, do you always care for your diabetes in the same place / medical service?**

1. ( ) No, I consult different medical clinics / services, depending on availability.
2. ( ) Yes, always in the same clinic / medical service.

**C11. In the past 12 months, have you had any hypoglycemia (low blood sugar) episodes that required medical assistance or family / friends / neighbors help?**

1. ( ) NO [GO TO C12]
2. ( ) YES **C11.1. How many times?** |___|___|

**C12. In the past 12 months, have you had to go to emergency room because of diabetic ketoacidosis (diabetes decompensation or very high blood sugar)?**

1. ( ) NO [GO TO C13]
2. ( ) YES **C12.1. How many times?** |___|___|

**C13a. In the last 12 months, have you participated in any lecture, class or course on diabetes?**

1. ( ) NO [GO TO C13b]
2. ( ) YES **C12.1. How many times?** |___|___|

**C13b. Do you participate in any diabetic group or association?**

# NATIONAL DIABETES RESEARCH

1. ( ) No, I never participated.
2. ( ) Yes, but I do not participate anymore.
3. ( ) Yes, I still participate.

**C14. In the last 12 months, you would say that controlling your diabetes has been ... (Answer honestly!)**

| Terrible | Bad | Average | Good | Excellent |
|---|---|---|---|---|
| [ 1 ] | [ 2 ] | [ 3 ] | [ 4 ] | [ 5 ] |

**C15. Recently, how much have you found the treatment of your diabetes (medications, control exams, etc.) convenient / practical / easy? (use this scale from 0 to 10 [SHOW SCALE], where "0" means "very inconvenient" and "10" means "very convenient")**

Very inconvenient or impractical **0** — **10** Very convenient or practical

**C16. Recently, how much have you found that treating your diabetes (medications, checkups, etc.) fits your life? (use this scale from 0 to 10 [SHOW SCALE], where "0" means "does not adapt very easily to my life" and "10" means "adapts very easily to my life")**

It does not adapt very easily to my life **0** — **10** It adapts very easily to my life

**C17. How satisfied are you with what you know about your diabetes? (use this scale from 0 to 10 [SHOW SCALE], where "0" means "very dissatisfied" and "10" means "very satisfied")**

Very dissatisfied or unhappy 0 — 10 Very satisfied or happy

**C18. How satisfied would you be with continuing your current routine of treatment (medications, medications, control tests, etc.)? [READ ALL OPTIONS]**

| Very dissatisfied | Dissatisfied | Neither satisfied nor dissatisfied | Satisfied | Very Satisfied |
|---|---|---|---|---|
| [ 1 ] | [ 2 ] | [ 3 ] | [ 4 ] | [ 5 ] |

**THANK YOU FOR YOUR PARTICIPATION!**

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | **1** |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | **2** |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | **4** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | **5** |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | **5** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | **5,6** |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | **6** |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | **6,7,8** |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | **7,8** |
| Bias | 9 | Describe any efforts to address potential sources of bias | **6,7** |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | **6,7** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | **7,8** |
| | | (*b*) Describe any methods used to examine subgroups and interactions | **7,8** |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | **7,8** |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | **9** |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | **9,10** |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | **11,12** |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | **11,12,13,14** |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | **16** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | **18,19** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | **17,18** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | **21,22** |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.