

Glycemic Control Rate in Type 2 Diabetes Mellitus Patients at a Public Referral Hospital in Rio de Janeiro, Brazil: Demographic and Clinical Factors

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Abstract

Background: The aim of the study was to determine the rate of satisfactory glycemic control among patients with type 2 diabetes (T2D) followed up at a tertiary referral hospital in Brazil.

Methods: A retrospective and observational study was conducted between September 2014 and September 2015, by collecting data from medical records.

Results: Data were obtained from 1,001 patients. The majority of patients were women (68%), with a median age of 61 years old (21 - 95). The median duration of disease was 10 years (1 - 58). Satisfactory glycemic control rate was found in 51% of patients. The strongest factors related to good control were: younger age ($P < 0.001$); absence of a T2D family history ($P = 0.04$), obesity ($P < 0.001$), overweight ($P < 0.001$), and absence of current alcohol consumption ($P = 0.006$); presence of fewer comorbidities ($P = 0.01$), chronic kidney disease ($P = 0.004$), and the treatment using only oral antidiabetic drugs (OADs) ($P < 0.001$).

Conclusions: The majority of patients obtained an adequate glycemic control rate, particularly among those using only OAD. Younger age, a negative family history of T2D, normal body mass index, absence of current alcohol consumption, presence of fewer comorbidities, and chronic kidney disease were associated with better glycemic control.

Keywords: Type 2 diabetes; Glycemic control; Glycated hemo-

globin; Brazil

Introduction

As stated by the International Diabetes Federation (IDF), 415 million individuals worldwide have diabetes mellitus, which is equivalent to 8.8% of the population. Brazil is the fourth largest country harboring diabetic patients, behind China, India and the United States, and the fifth regarding the highest costs. Brazil's adult population, aged between 20 and 79 years, accounts for approximately 134 million individuals, with a current prevalence of 10.2% of diabetes, and an estimated incidence of 23.3 million people in 2040 [1]. Type 2 diabetes (T2D) is considered an epidemic in both developed and in developing countries, and represents a social and economic burden, with a cost estimated in 2015 of 673 billion US dollars [1]. Microvascular and macrovascular complications are common, making diabetes mellitus an extremely onerous disease, leading to diminished life quality and productivity [2, 3].

Data from several epidemiological studies worldwide have shown that the majority of patients do not obtain, nor maintain glycemic control among satisfactory range defined by international societies [4-8]. Thus, diabetes' management remains challenging.

This study aimed to assess glycemic control rate and the demographic and clinical factors associated with glycemic control in patients with T2D in a public Brazilian referral hospital.

Materials and Methods

An observational, retrospective study was conducted between September 2014 and September 2015, at the Endocrinology Section of the Hospital Federal da Lagoa (HFL). All patients were seen by an endocrinologist in this tertiary referral center. Inclusion criteria were predefined as follows: patients with age more than 18 years old, diagnosed with T2D, with a regular follow-up and at least one available glycated hemoglobin (HbA1c) assessment during the studied period. Exclusion criteria included the following: 1) other types of diabetes (such as type 1 diabetes, latent autoimmune diabetes in adults, maturi-

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ty-onset of diabetes of the young, and gestational diabetes); 2) an uncertain diagnosis; 3) an irregular follow-up with no medical visits in the studied period; 4) patients with unavailable HbA1c measurement. First-visit patients were not included in this because they were not formerly followed up at our Endocrinology Department.

The following data were collected from medical records: gender, age at the last consultation, diabetes duration (in years), first degree family history of T2D, smoking, alcohol consumption, comorbidities (hypertension, dyslipidemia, overweight or obesity, chronic kidney disease (CKD)), nutritional therapy, type of treatment, body mass index (BMI; kg/m²), waist circumference (WC; cm) and HbA1c (%).

According to the American Diabetes Association (ADA), a diagnosis of diabetes can be established in the presence of any of the following (two tests are required): 1) fasting plasma glucose levels of ≥ 126 mg/dL; 2) random plasma glucose ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia; 3) 2-h plasma glucose level ≥ 200 mg/dL during a 75 g oral glucose tolerance test; 4) HbA1c level of $\geq 6.5\%$ [9].

Smoking was characterized by current smoking, associated to mental and behavioral disorder due to nicotine dependence syndrome. Patients were screened as positive if they reported any smoking practice in the past year. Alcohol consumption was considered positive if abusive, with behavioral and cognitive consequences, according to the 10th edition of the International Classification of Diseases and the World Health Organization [10]. Ex-smokers or ex-alcoholics were considered as former smokers or alcoholics if none of these habits were reported in the last medical visit. Regarding comorbidities, hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg in at least two measurements during consultation, or in patients already taking antihypertensive medication [11]; dyslipidemia was present if one or more of the following were observed: 1) low-density lipoprotein-cholesterol (LDL-c) ≥ 160 mg/dL, triglycerides ≥ 150 mg/dL, total cholesterol ≥ 400 mg/dL when triglyceride ≥ 400 mg/dL (due to inadequate LDL-c calculation with Friedewald's formula) or high-density lipoprotein-cholesterol (HDL-c) < 40 mg/dL in men and < 50 mg/dL for women [12]; CKD was considered positive if progressive, irreversible loss of kidney function with normal glomerular filtration rate (GFR; ≥ 90 mL/min/1.73 m²) was present, or abnormal GFR (≤ 89 mL/min/1.73 m²), or in patients already being followed up by a nephrologist, or those with a pre-established albuminuria [13].

Additionally, patients were divided into two treatment groups: those without medication (only lifestyle changes, such as low carbohydrate diets and regular physical exercise); and those taking medications: only oral antidiabetic drug (OAD); OAD + insulin; only basal insulin; or basal + bolus insulin.

A wide range of antidiabetic medications were prescribed, such as biguanides (metformin), sulfonylureas, thiazolidinediones, meglitinide derivatives, alpha-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase IV (DPP-4) inhibitors and selective sodium-glucose transporter-2 (SGLT-2) inhibitors. With respect to insulin therapy, intermediate insulin (NPH), rapid insulin (regular), long-acting insulin analogues (detemir, glargine or degludec) and ultra-rapid analogues (glulisine, lispro or aspart) were prescribed.

Table 1. Clinical and Demographic Data

Variables	Total, n (%)
Male/female	321 (32.0%)/680 (68.0%)
Age ^a (years)	61 (21 - 95)
Diabetes duration (years)	10 (1 - 58)
T2D family history (n = 527)	352 (66.8%)
Smoking (n = 639)	
Passed ^b /present	236 (37.0%)/69 (10.8%)
Alcohol consumption (n = 589)	
Previous ^b /Present	48 (8.1%)/11 (1.8%)
Hypertension	812 (81.1%)
Dyslipidemia	751 (75.0%)
CKD	185 (18.5%)
Treatment	
Only OAD	460 (46.0%)
OAD + insulin	363 (36.3%)
Only basal insulin	54 (5.4%)
Basal + bolus insulin	102 (10.2%)
Nutritional follow-up (n = 898)	331 (36.9%)
Waist circumference (cm) (n = 206)	100 (72 - 150)
BMI (kg/m ²)	29.50 (16.17 - 57.00)
Overweight/obesity	223 (22.3%)/302 (30.2%)
HbA1c (%)	7.3 (4.3 - 15.2)

^aAge, patient's age obtained at last evaluation. ^bFormer practice no longer present in the last medical visit. T2D: type 2 diabetes; CKD: chronic kidney disease; OAD: oral antidiabetic medication; BMI: body mass index; HbA1c: glycated hemoglobin.

BMI was determined by dividing the weight in kg by the square of the height in meters and classified as normal (18.5 - 24.9 kg/m²), overweight (25.0 - 29.9 kg/m²) or obese (≥ 30.0 kg/m²) [14]. WC was measured at midpoint between the inferior limit of the lowest rib and the superior limit of the iliac crest, with the measure tape placed horizontally [15], and considered abnormal if: ≥ 90 cm in men and ≥ 80 cm in women.

HbA1c was determined by high performance liquid chromatography, a certified method by the Glycohemoglobin Standardization Program, in the equipment Premier Hb9210™, with the software Affinity™, with an acceptable error range of 0.067. Adequate or satisfactory glycemic control target was defined according to the latest recommendations from ADA and from the Brazilian Diabetes Society (SBD) as a HbA1c lower than 7.0% for adults and below 8.0% for patients aged more than 70 years old, with serious microvascular or macrovascular complications, presence of severe hypoglycemia or several comorbidities, or with a limited life expectancy [9-17].

The statistical analyses were performed using SPSS version 20.0 for MacOS (SPSS Inc., Chicago, IL). None of the variables were found to follow a normal distribution using the Kolmogorov-Smirnov test. For the descriptive analysis, categorical variables were expressed as the percentage and frequency, and

Table 2. Factors Related to Satisfactory Glycemic Control Rate

Variables	HbA1c < target ^a (n = 510; 51.0%)	HbA1c > target ^a (n = 491; 49.0%)	P-value
Male/female	53.0%/50.0%	47.0%/50.0%	NS
Age ^b (years)	64 (33 - 95)	59 (21 - 91)	< 0.001
Diabetes duration (years)	10 (1 - 58)	11 (1 - 46)	0.057
T2D family history (n = 527)	45.5%	54.5%	0.042
Previous ^c /present smoking (n = 639)	53.8%/43.5%	46.2%/56.5%	NS
Previous ^c /present alcohol consumption (n = 589)	70.8%/36.4%	29.2%/63.6%	0.006
Hypertension	53.2%	46.8%	0.003
Dyslipidemia	52.1%	43.0%	NS
CKD	60.5%	39.5%	0.004
Overweight	45.7%	54.3%	< 0.001
Obesity	42.4%	56.6%	< 0.001
Treatment			
Only OAD	66.7%	33.3%	< 0.001
OAD + insulin	33.8%	66.2%	< 0.001
Only basal ^d insulin	49.0%	51.0%	NS
Basal + bolus ^e insulin	37.8%	62.2%	0.006
HbA1c (%)	6.3 (4.3 - 7.9)	8.7 (7.0 - 15.2)	< 0.001

^aFor this analysis, we considered ADA's goals for T2D patients as: HbA1c < 7.0% for young adults and < 8.0% for older than 70 years old, with serious microvascular or macrovascular complications, presence of severe hypoglycemia or several comorbidities, or with a limited life expectancy. ^bAge at last consultation. ^cFormer practice no longer present in the last medical visit. ^dIntermediate insulin (NPH) or long-acting analogues. ^eRapid insulin (regular) or ultra-rapid acting analogues. T2D: type 2 diabetes; CKD: chronic kidney disease; HbA1c: glycated hemoglobin; NS: not significant; OAD: oral antidiabetic medication.

numerical variables were expressed as median (minimum - maximum). The Mann-Whitney U test was performed to compare the numerical variables between the two groups. Fisher's exact test and Chi-square test were used to compare categorical variables. A P-value < 0.05 was considered statistically significant and P-values \geq 0.05 and \leq 0.09 were considered to indicate a tendency towards statistical significance.

Results

Clinical and epidemiological data of the 1,001 patients included in this study are shown in Table 1.

The majority of patients were women (68.0%), with a median age of 61 years old (21 - 95). The median time of disease was 10 years (1 - 58), with T2D family history found in 66.8% of cases. Regarding lifestyle habits, the majority did not abuse of alcohol or smoke. The median BMI and WC were 29.5 kg/m² (16.2 - 57.0) and 100 cm (72 - 150), respectively. Regarding comorbidities, 74% of patients had two or three comorbidities. Analyzed separately, 81.1% had hypertension, 75.0% had dyslipidemia, 52.5% were overweight or obese, and 18.5% had CKD (Table 1).

Medications were prescribed in approximately 98% of patients, of which 46% used only OAD, almost 37% used OAD + insulin, 10% used only insulin (including basal and bolus injections) and 5.4% used only basal insulin. Almost 37% had

regular follow-up with dieticians (Table 1).

The majority of patients (51.0%) had satisfactory glycemic control, with a median HbA1c of 7.3% (4.3-15.2%). Demographic and clinical factors associated with satisfactory glycemic control included older age at last consultation (P < 0.001), presence of hypertension (P = 0.003), and chronic kidney disease (P = 0.004). A shorter duration of diabetes tended to correlate with better glycemic control (P = 0.057).

Inadequate glycemic control was found in the presence of a positive family history of T2D (P = 0.04), current alcohol consumption (0.006), presence of overweight (P < 0.001) or obesity (P < 0.001). Additionally, the combination of three or four comorbidities was associated with an increased HbA1c, above satisfactory range in the majority of cases (P = 0.01). No statistical significance was found in relation to gender, smoking and dyslipidemia (Table 2).

Regarding medical treatment in the controlled group, almost 67.0% only used OAD and, in the uncontrolled group, 66.2% of patients used OAD + insulin and 62.2% used basal + bolus insulin. There was no statistical significance between HbA1c and the use of basal insulin only, or HbA1c and patients who took no medication (Table 2).

Discussion

This study evaluated the treatment of 1,001 T2D patients fol-

lowed up at a tertiary referral hospital in Brazil. Data analysis brought interesting and valuable information from a substantial number of patients. Only a few studies in Brazil analyzing glycemic control rate and its association with demographic and clinical characteristics are available. In this series, satisfactory glycemic control was present in the majority of patients, a finding not consistently observed in other studies in Brazil.

Compared to our study, other Brazilian studies by Malerbi and Franco [18] and Borges et al [19] showed similar results to our epidemiological profile: higher prevalence of diabetes in patients aged 60 - 69 years old, in female patients and with a positive family history of T2D. Malerbi and Franco found a two-fold increase in the prevalence of diabetes if a family history was present [18]. Regarding gender, the IDF mentions that T2D is more common in men worldwide, but in South and Central America the prevalence is higher in women [1]. Among comorbidities, the association between T2D and hypertension is well known, as are the abuse of alcohol and dyslipidemia, as well as BMI and WC above normal range, regardless of gender or age [18, 20-23]. Obesity, especially central obesity, is a key factor in the pathophysiology of insulin resistance and diabetes [24]. A wider WC alone leads to increased risk of metabolic syndrome and cardiovascular disease [1].

The objective of this study was to analyze the satisfactory glycemic control rate of patients treated in HFL, based on the latest recommendations of international and national societies - Brazilian Diabetes Society (SBD), ADA and American Association of Clinical Endocrinologists [17, 25, 26].

The majority of patients had adequate glycemic control (51%), with a median HbA1c of 6.3% (4.3-7.9%), showing more excellent glycemic control as compared with Tunisia (16.7%) [4], United Kingdom (24%) [5], Canada (27%) [27], Lithuania (34.5%) [28] and Denmark (49%) [29]. A meta-analysis of 137 randomized controlled trials, conducted in 2011, with a total of 39,845 patients, found a satisfactory control rate of 25.9-48.6%, considered a wide range depending on the OAD taken [30]. Another study conducted in 2008 with 2,023 patients in seven European countries revealed a glycemic control rate of 20-29.6% of cases only [31]. Lopez et al, in a multicenter Latin American study, found a satisfactory glycemic control rate in 43.2% of patients [7].

With respect to Brazilian studies, much lower control rates are seen compared to those found in our study: 26% in a study conducted between 2006 and 2007 by Borges et al [19] and 40% in a multicenter study in 2007 with 878 patients [7]. Another Brazilian study performed between 2006 and 2011, with 5,750 diabetic patients seen in a public health system found mean HbA1c of 8.1% (8.6±2.2%) [6]. However, in our study, 49% of our patients were above glycemic control target, with a median HbA1c of 8.7%, a worse percentage than encountered in, for example, Germany (40%) [32], the Netherlands (42%) [33] and USA (43%) [34].

Analyzing glycemic control rate factors, Borges et al also found a worse control as diabetes' duration progressed [19]. The presence of alcohol abuse was a poor control factor, as well as overweight and obesity and the presence of multiple comorbidities. T2D and hypertension alone increase cardiovascular and CKD risks [20]. Visceral adiposity has been researched more intensively in recent years, with several stud-

ies showing its relationship as a determinant of hypertension, insulin resistance and dyslipidemia, all defining comorbidities of the metabolic syndrome, with a significant increase in morbidity and mortality from cardiovascular disease [35, 36]. In Switzerland, in a study conducted in 2002, 42.5% of T2D's cases were attributed to obesity [37].

The presence of systemic arterial hypertension, when analyzed separately in our study, was a factor of good glycemic control rate, possibly because these patients have more frequent medical visits and, apart from endocrinologists, they are followed up by general practitioner or cardiologist, and take more seriously lifestyle changes and have better adherence to drug treatment. Similarly, a satisfactory control rate was found in CKD patients (60.5% vs. 39.5%), which could be explained by decreased progressive renal gluconeogenesis, worse insulin clearance and increased insulin sensitivity in CKD patients, which may even lead to severe and frequent hypoglycemia [38, 39]. Another possible explanation is the shorter half-life of red blood cells (RBC), leading to lower HbA1c level, either by hemolysis in patients on hemodialysis, or by anemia due to deficiency in the production of erythropoietin, or by folic acid deficiency. Any of these reasons can interfere with HbA1c's measurement, leading to erroneous low values. Furthermore, the increase in turnover of RBC due to the use of recombinant erythropoietin may be also associated with lower HbA1c levels in patients with CKD [40, 41].

Regarding treatment, an adequate glycemic control rate was observed in most patients using OAD alone. In contrast, only one-third of patients using insulin + OAD had satisfactory glycemic control rate, regardless of the type of insulin, and only 37.8% had HbA1c below target with the use of basal + bolus insulin. Therefore, these combinations show a worsening in T2D's control, as reported in another Brazilian study conducted in 2007 by Borges et al [19] and a Greek study in 2012 [42]. Some plausible explanations could be that possibly the patients using insulin have worse T2D, with more difficulties found in achieving good glycemic control and using several combinations of antidiabetic and insisting on it could have postponed a proper T2D control. Maybe these patients should have been intensively treated with insulin earlier. Patients with mild T2D can be treated by only OADs; however, patients with severe T2D whose pancreatic beta cells were severely disturbed cannot be treated by only OAD, and need the insulin therapy. Other studies proclaim that introducing basal insulin or basal + bolus led to significant weight gain, perhaps leading to worse glucose control [43]. Also, Borges et al mentioned that treatment with oral medications may be simpler and easier, therefore being more efficient in T2D's control [19]. Clearly, more studies are needed regarding T2D's treatment to elucidate these uncertainties.

Treatment regimens that reduce HbA1c target below 7% and 8% (in pre-defined cases) have been associated with lower incidence of macrovascular and microvascular complications over time. In the era of intensive glycemic control, the Diabetes Control and Complications Trial (DCCT) showed that effective glucose control contributes to a decrease in the risk of microvascular complications in T1D [16]. The United Kingdom Prospective Diabetes Study (UKPDS) initially showed no statistical significance in reducing vascular events with inten-

sive glycemic control in T2D, but after 10 years of follow-up, evidence showed that for every 1% reduction in mean HbA1c, there was a decrease of 37% in microvascular complications, 14% in fatal and non-fatal myocardial infarction and 43% in amputation rate or death from peripheral vascular disease. This protective factor underlying metabolic memory still remained effective after the study was concluded [44].

Our study had some limitations. Since it was carried out in a single care center, data may not be transferable to all endocrine centers in the country. The regional distribution of patients, access to health care centers and the severity of the disease in each population could also be different, apart from the divergence in methods of data collection, the measurement of HbA1c and the definition of the T2D control target.

In conclusion, achieving adequate control in T2D is difficult but manageable. In this study, the majority of T2D patients obtained satisfactory glycemic control. The treatment using only OADs was more effective in reaching target HbA1c compared to insulin alone or associated with OAD, perhaps because of a milder T2D. Other important positive factors of good metabolic control were younger age at the last consultation, the absence of a positive family history of T2D, absence of current alcohol consumption, normal BMI, the presence of fewer comorbidities, and the presence of CKD.

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Conflicts of Interest

The authors have nothing to declare.

Author Contributions

Study design: Leonardo Vieira Neto. Study conduct: Leonardo Vieira Neto and Natasha Reis Lozovey. Literature review: Leonardo Vieira Neto, Natasha Reis Lozovey, Elisa Baranski Lamback, Raissa Barros Mota and Michelle Botelho Caarls. Data collection: Natasha Reis Lozovey and Raissa Barros Mota. Data analysis: Leonardo Vieira Neto, Natasha Reis Lozovey and Raissa Barros Mota. Data interpretation: Leonardo Vieira Neto, Natasha Reis Lozovey, Elisa Baranski Lamback, Raissa Barros Mota and Michelle Botelho Caarls. Drafting manuscript: Natasha Reis Lozovey and Elisa Baranski Lamback. Revising manuscript content: Leonardo Vieira Neto and Michelle Botelho Caarls. Approving final version of manuscript: Leonardo Vieira Neto, Natasha Reis Lozovey, Elisa Baranski Lamback, Raissa Barros Mota and Michelle Botelho Caarls. Leonardo Vieira Neto takes responsibility for the integ-

rity of the data analysis.

Abbreviations

ADA: American Diabetes Association; BMI: body mass index; CKD: chronic kidney disease; DCCT: Diabetes Control and Complications Trial; F: female; HbA1c: glycated hemoglobin; HDL-c: high-density lipoprotein-cholesterol; HFL: Hospital Federal da Lagoa; IDF: International Diabetes Federation; LADA: latent autoimmune diabetes in adults; LDL-c: low-density lipoprotein-cholesterol; M: male; MODY: maturity-onset of diabetes of the young; NGSP: National Glycohemoglobin Standardization Program; NPH: intermediate insulin; RBC: red blood cells; SBD: Brazilian Diabetes Society; T2D: type 2 diabetes; UKPDS: United Kingdom Prospective Diabetes Study; WC: waist circumference; WHO: World Health Organization

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