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BMJ Open Sex differences and correlates of poor glycaemic control in type 2 diabetes: a cross-sectional study in Brazil and Venezuela

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ABSTRACT

Objective Examine whether glycaemic control varies according to sex and whether the latter plays a role in modifying factors associated with inadequate glycaemic control in patients with type 2 diabetes (T2D) in Brazil and Venezuela.

Design, setting and participants This was a cross-sectional, nationwide survey conducted in Brazil and Venezuela from February 2006 to June 2007 to obtain information about glycaemic control and its determinants in patients with diabetes mellitus attending outpatient clinics.

Main outcome measures Haemoglobin A1c (HbA1c) level was measured by liquid chromatography, and patients with HbA1c $\geq 7.0\%$ (53 mmol/mol) were considered to have inadequate glycaemic control. The association of selected variables with glycaemic control was analysed by multivariate linear regression, using HbA1c as the dependent variable.

Results A total of 9418 patients with T2D were enrolled in Brazil (n=5692) and in Venezuela (n=3726). They included 6214 (66%) women and 3204 (34%) men. On average, HbA1c levels in women were 0.13 (95% CI 0.03 to 0.24; p=0.015) higher than in men, after adjusting for age, marital status, education, race, country, body mass index, duration of disease, complications, type of healthcare, adherence to diet, adherence to treatment and previous measurement of HbA1c. Sex modified the effect of some factors associated with glycaemic control in patients with T2D in our study, but had no noteworthy effect in others.

Conclusions Women with T2D had worse glycaemic control than men. Possible causes for poorer glycaemic control in women compared with men include differences in glucose homeostasis, treatment response and psychological factors. In addition, sex modified factors associated with glycaemic control, suggesting the need to develop specific treatment guidelines for men and women.

INTRODUCTION

Diabetes mellitus (DM) is a chronic condition characterised by insulin deficiency or impaired response to insulin, leading to hyperglycaemia.¹ DM directly caused an

Strengths and limitations of this study

- The large multicentre sample, providing statistical power to examine the effects of many variables and to adjust for confounding.
- The measurement of haemoglobin A1c was performed using a reliable method in a central laboratory, avoiding problems with lack of standardisation reported by other authors.
- This study was conducted in health centres, consequently our conclusions may not apply to patients with type 2 diabetes who do not seek medical care or who have not yet been diagnosed.
- Patients' data were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers. However, self-reported data have been shown to have high agreement with medical records for several questions.
- The study design, a cross-sectional survey, is limiting because the temporal relationship between the exposure and the outcome cannot be determined with certainty.

estimated 1.5 million deaths in 2012, making it the world's eight leading cause of death among both sexes and the fifth leading cause among women.² In Latin America, DM is one of the main causes of death among the chronic, non-communicable diseases, only exceeded by myocardial infarction and stroke.³ According to the American Diabetes Association (ADA), the most prevalent form is type 2 diabetes (T2D), accounting for approximately 90% of all cases.⁴

People affected by T2D develop hyperglycaemia gradually and may only have symptoms once their DM is advanced.⁴ Late diagnosis, difficulty in adjusting individual treatment and non-adherence to treatment can lead to severe complications, such as retinopathy, neuropathy, nephropathy, amputation and stroke.⁵ These complications can

have a significant impact on the individual and at the population level. There is also a financial burden that not only has a significant effect on patients and their families, but on health systems worldwide. Overall, 12% of global health expenditures are directed at DM and consequent complications.¹

Complications of DM are avoidable and their likelihood of developing is directly correlated with level of glycaemic control. Evidence from key controlled studies has established the importance of tight and sustained glycaemic control among patients with DM.^{6–8} These studies have emphasised the central role of managing HbA1c levels in these patients, leading professional associations to propose targeting haemoglobin A1c (HbA1c) levels in the range of 6.5%–7.0% (48–53 mmol/mol).⁴

It has been shown that women with DM are generally less likely to reach target levels of HbA1c and, therefore, have more difficulties achieving adequate glycaemic control compared with men.^{9–16} Possible reasons for the different outcomes between men and women are differences in glucose and energy homeostasis (eg, hormones and visceral adipose distribution),¹⁷ treatment response (eg, side effects) and psychological factors (eg, acceptance of disease).¹⁸ Despite the potential role of sex on glycaemic control, currently, there are no specific treatment guidelines for men and women with T2D.

There are few publications in the medical literature reporting on the factors associated with glycaemic control in patients with T2D in South American countries.^{19–21} There is also a dearth of studies describing the role sex differences may have on these factors.²² Here, we combined data collected in two large surveys on the prevalence of glycaemic control^{21 23} to further examine whether glycaemic control varies according to sex, and whether the latter modifies factors associated with glycaemic control in patients with T2D in Brazil and Venezuela.

METHODS

Study design and centre selection

We used data from two nationwide surveys on the prevalence of glycaemic control conducted in Brazil and Venezuela from February 2006 to June 2007. Detailed information on study design and methods has been published elsewhere.^{23 24} Briefly, the surveys were conducted in outpatient diabetes clinics and obtained detailed information about glycaemic control and its determinants in a large sample of adults with DM in Brazil and in Venezuela. Overall, 52 centres participated in the study in Brazil (n=20) and Venezuela (n=32). For the selection of diabetes centres, we asked the Brazilian Diabetes Association and two Venezuelan diabetes associations (Venezuelan Endocrinology Society and La Federación Nacional de Asociaciones y Unidades de Diabetes—FENADIABETES) to identify, in each of the regions studied, a minimum of four candidate centres from various registries, patient association lists and

professional information. These centres were to be chosen from those with longer experience in epidemiological research and where at least 100 adult patients with diabetes were followed per month. They were classified as university-affiliated hospitals (20), public general hospitals (15) or private not-for-profit hospitals (17).

Study population

A sample of all consecutive patients with DM attending each participating clinic during a 30-day period was selected. Eligible cases were adults aged ≥ 18 years who had been previously diagnosed by a physician with either type 1 diabetes or T2D before the survey (for the current analysis, only T2D were included). Patients who had participated in an intervention trial in the previous 3 months and women who reported a history of diabetes only during pregnancy were excluded. Each centre was asked to recruit at least 150 patients. Overall, the response rates were 84% (78%–95%) in Brazil and 92% (85%–98%) in Venezuela.

Ethical considerations

All patients were informed about the study aims, procedures and risks and signed an informed consent prior to inclusion. The study protocol was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Data collection

Data were collected using different strategies: a structured questionnaire (including self-reported items) and a blood sample to measure HbA1c. The information on sociodemographic characteristics (ie, age, sex, race, marital status and education), DM history, current medications, self-reported symptoms and comorbid conditions, complications and clinical parameters (ie, fasting blood glucose, HbA1c and body mass index (BMI)) were gathered using a structured questionnaire. In addition, data on factors related to treatment processes, such as self-reported adherence to diet and treatment, patient perception of treatment convenience and factors related to healthcare access (eg, number of consultations in the previous year, whether seen by the same physician, private or public healthcare) were obtained. Information was also collected on self-rated glycaemic control (using a scale with five levels: poor, fair, good, very good and excellent) and satisfaction with current diabetes treatment (using a single global question: 'If you were to spend the rest of your life with your diabetes treatment the way it is today, how would you feel about this? Very satisfied, somewhat satisfied, neither dissatisfied nor satisfied, somewhat dissatisfied, or very dissatisfied').

Patient and public involvement

A round of pilot testing was conducted prior to data collection on a sample of volunteer patients (n=30), in both Brazil and Venezuela, to assess and improve question wording and interviewer performance. The pilot interviews were recorded, and then four reviewers listened

to each interview and documented potential issues in question presentation or comprehension. Health survey experts assessed all items for face validity. The individual interviews lasted an average 20–25 min, and the sessions occurred in a private room. The study questionnaire was administered in person by a team of trained and certified interviewers (not part of the local centre staff).

Measurement of glycated haemoglobin

A peripheral blood sample was collected for the measurement of HbA1c in every patient. All measurements of HbA1c were made by automated high-performance liquid chromatography (Variant Turbo-BioRad) in a central laboratory for each country. The normal value range was 4.0%–6.0% (20–42 mmol/mol).

Statistical analysis

Patients with HbA1c $\geq 7.0\%$ (53 mmol/mol) were considered to have inadequate glycaemic control.⁴ Initially, a descriptive analysis was performed; the factors possibly associated with inadequate glycaemic control were evaluated using univariate linear regression, with the value of HbA1c as the dependent variable. Next, data from men and women were fit into multivariate linear regression models separately, starting with the same set of independent variables and using backwards elimination to fit the best model. In this step, variables with a value of $p < 0.10$ in either regression model (man or woman) were kept. Sociodemographic variables (eg, age, marital status, education and race) were kept in the model regardless of the significance level. To assess for effect modification by sex, we checked whether the point estimate of an independent variable in the regression model for one sex was not included in the respective 95% CI of the same variable in the regression model for the other sex. The statistical analyses were performed using the STATA statistical software V.12).

RESULTS

A total of 9418 patients with T2D were enrolled in Brazil ($n=5692$) and Venezuela ($n=3726$). They included 6214 (66%) women and 3204 (34%) men (table 1). Ages ranged from 18 to 98 years; most of the study participants were married or living with a partner, of white race and had completed primary school education or less. The distribution of BMI categories among male patients showed that 44.5% were overweight and 25.8% were obese compared with 36.2% and 35.2% among female patients, respectively. Less than one quarter of the study participants reported no complications of DM; approximately half reported poor/fair adherence to diet and self-rated their glycaemic control as very good/excellent; roughly three quarters (73.6%) were either satisfied or very satisfied with their current DM treatment.

The prevalence of inadequate glycaemic control was 74.2% and 73.0% among female and male patients with T2D, respectively. The average HbA1c level was higher

among women (8.8%) (73 mmol/mol) than in men (8.6%) (70 mmol/mol) ($p=0.002$). In the adjusted analysis, the average difference between HbA1c levels in women and men was 0.13 (95% CI 0.03 to 0.24; $p=0.015$). Table 2 shows the results of the multivariate analysis of factors potentially associated with glycaemic control according to sex. Increasing age in years was associated with better glycaemic control in both men and women. Non-white race was a predictor of worse control of DM. Subjects with a higher level of education (some college) or residing in Brazil were more likely to have a lower HbA1c level. Regarding BMI, men in the underweight category had worse glycaemic control than those of normal weight, but this difference was not observed among women. Obesity and overweight were predictors of lower HbA1c levels in both sexes. Duration of T2D was positively correlated with HbA1c in both men and women, as well as the number of complications in women with T2D. Men and women who sought a private healthcare service to treat their T2D in the past 12 months had lower HbA1c levels compared with those who used only public clinics. Better adherence to diet (self-reported) was also associated with improved glycaemic control, while adherence to treatment was not. Having had HbA1c measured in the past 12 months was associated with better glycaemic control in women, while men who perceived their diabetes treatment as convenient, compared with those who did not, were more likely to have a lower level of HbA1c. In both men and women, self-rated glycaemic control was associated with lower levels of HbA1c.

The magnitude of the association between some factors (ie, age, race, education, self-reported adherence to diet, and self-rated glycaemic control) and glycaemic control was similar in both men and women, while for other factors (ie, country of residence, BMI, T2D duration, number of complications, access to private healthcare, HbA1c measurement in the past year and perception of treatment convenience), the magnitude of the association seemed different for men as compared with women, therefore, suggesting that their effect was modified by sex.

DISCUSSION

We found that women with T2D had significantly higher HbA1c levels than men, after adjusting for several potential confounders. Furthermore, our results have shown that sex modifies determinants of glycaemic control, suggesting that specific treatment guidelines for men and women may be helpful. Some demographic and lifestyle characteristics might have changed in the study population since the data were collected, but the biological differences between sexes have likely remained. Thus, the correlates identified here might still be present.

Our findings are consistent with those of previous studies. In 2002, a survey of 21 277 patients with diabetes between the ages of 45 and 64 years in Israel showed better glycaemic control in men, despite lower healthcare

Table 1 Characteristics (%) of 9418 patients with T2D in Brazil and Venezuela

	Men			Women		
	Brazil	Venezuela	Total	Brazil	Venezuela	Total
	n=1904 (59%)	n=1300 (41%)	n=3204 (100%)	n=3788 (61%)	n=2426 (39%)	n=6214 (100%)
Age (years)						
18–34	0.7	1.9	1.2	1.1	1.9	1.4
35–54	27	35	31	27	32	29
55–64	36	31	34	34	33	34
≥65	36	32	35	38	33	36
Marital status						
Married/living with partner	77	71	75	49	47	48
Single	10	18	13	16	26	20
Separated/divorced	8	6	7	9	9	9
Widowed	5	5	5	25	18	22
Race/ethnicity						
White	49	43	46	43	48	45
Mixed	29	52	39	29	48	37
Black	10	4	8	14	3	10
Others	12	0.1	7	14	1.0	9
Education						
Primary school or less	64	42	55	77	59	70
Middle school/high school	23	37	28	17	29	21
Some college	13	22	17	6	12	9
Body mass index (kg/m²)						
Underweight (≤18.5)	1.1	0.5	0.8	1.8	0.9	1.4
Normal weight (18.6–24.9)	30	27	29	28	25	27
Overweight (25.0–29.9)	46	43	45	36	37	36
Obesity (≥30.0)	23	30	26	34	37	35
Patients with HbA1c ≥7.0 (%)	72	75	73	74	75	74
Complications from diabetes						
None	24	24	24	24	21	23
1	30	30	30	31	29	31
2	25	26	26	25	28	26
≥3	20	21	21	20	22	21
Self-reported adherence to diet						
Poor	25	25	25	19	21	20
Fair	32	35	33	34	38	35
Good	28	30	29	29	32	30
Excellent	16	10	14	18	9	15
Self-rated glycaemic control						
Poor	6	5	6	7	3	5
Fair	5	5	5	8	4	6
Good	42	37	40	42	37	40
Very good	39	43	40	36	47	40
Excellent	8	11	9	8	9	8

Continued

Table 1 Continued

	Men			Women		
	Brazil	Venezuela	Total	Brazil	Venezuela	Total
	n=1904 (59%)	n=1300 (41%)	n=3204 (100%)	n=3788 (61%)	n=2426 (39%)	n=6214 (100%)
Global satisfaction with current treatment						
Very unsatisfied	1.7	2.0	1.8	1.9	1.0	1.6
Unsatisfied	8	6	7	10	6	8
Neutral	16	19	17	16	18	17
Satisfied	61	61	61	59	65	61
Very satisfied	14	13	14	13	11	12

T2D, type 2 diabetes.

utilisation.⁹ A study of 229 Swedish primary health-care centres, enrolling 9375 subjects (5082 men and 4293 women) with diabetes, found that men had better glycaemic control (HbA1c \leq 6.5%/48 mmol/mol) than women.¹² A cross-sectional study including 3849 patients with diabetes in the USA in 2003 found that women were less likely than men to have HbA1c <7% (53 mmol/mol) after adjusting for age, sociodemographic variables and clinic site.¹³ Data from the Health and Retirement Study of 1619 adults with T2D in 2010 also showed that women had worse glycaemic control compared with men, even though women reported better adherence to diet and blood glucose self-monitoring behaviours than men.¹¹

In contrast, other studies have found no significant relationship between sex and glycaemic control. For example, a study of 180 patients with T2D from two health clinics in Texas in 2007 found no sex differences in glycaemic control, after adjusting for self-management behaviours and quality of life indicators, suggesting that sex differences in glycaemic control outcomes might be related to less perceived social support, less acceptance of disease and more difficulty in self-management behaviour in women.²⁵ A cross-sectional study in the UK in 2002 of 10 663 patients with T2D aged 17–98 years⁵ and another one in Canada with 5569 patients²⁶ also found no association between sex and HbA1c levels.

Possible causes for poorer glycaemic control in women compared with men include differences in regulation of glucose homeostasis,¹⁷ treatment response and psychological factors.¹⁸ A survey of 201 Pakistani patients with T2D living in Manchester, UK, showed that women were worse than men in performing glucose self-measurements and in managing persistent hyperglycaemia, and consequently, had poorer glycaemic control overall.¹⁵ Salcedo-Rocha *et al* in Mexico suggested that women had several social and economical disadvantages (ie, lower education, lower participation in paid work, and reduced wages or economic dependence) that might decrease their ability to achieve glycaemic control successfully.¹⁶ Women and men differ in the distribution of body fat and in hormonal production, both of which are likely to alter

the risk of developing T2D and its complications. Obesity and being overweight are two of the strongest risk factors for developing T2D in both sexes,²² and women are even more vulnerable, as they have a higher percentage of body fat than men.²⁷ In addition, 40% of men with T2D have abdominal obesity, compared with 70% of women, suggesting a stronger association between T2D and abdominal obesity in women than in men.²⁸

Sex hormones not only regulate sex characteristics and fertility, but are essential in regulating glucose homeostasis and are responsible for fundamental biological differences between men and women.^{29–30} Testosterone in men stimulates lipolysis in adipose tissue, so low testosterone levels are associated with abdominal obesity and insulin resistance.²⁹ A meta-analysis in 2006 that reviewed 80 articles examining sex differences in endogenous hormones and the risk of T2D found that men with higher testosterone levels (15.6–21.0 nmol/L) had a 42% lower risk of developing T2D. They found the opposite was true for women, for whom, increased androgen levels were associated with insulin resistance and an increased risk of T2D.³¹ Oestrogen is the primary female hormone, is synthesised in the ovaries in women before menopause and in adipose tissue in both men and women via conversion from testosterone.³² In women, the decrease in oestrogen levels after menopause occurs concurrently with increased elevated blood glucose levels, whereas in men, elevated oestrogen levels may be a risk factor for insulin resistance.³³

There are also metabolic differences between men and women in the pharmacodynamics of the medications used to treat T2D. Metformin, an oral hypoglycaemic drug, has been shown to have more beneficial effects on myocardial fatty acid and glucose metabolism in men than in women.³⁴ Women were found to report more adverse effects than men when treated with this medication (15% vs 10%) and were also less adherent to treatment.³⁵ Women may also be more likely to experience side effects from thiazolidinediones (insulin-sensitising drugs), experiencing more hypoglycaemia³⁶ and bone fractures.³⁷ In patients treated with insulin, hypoglycaemia is not only more

Table 2 Multivariate linear regression of HbA1c level in men and women with T2D in Brazil and Venezuela

	Men				Women			
	β	95% CI		P value	β	95% CI		P value
		Lower limit	Upper limit			Lower limit	Upper limit	
Age	-0.03	-0.04	-0.03	<0.01	-0.03	-0.04	-0.03	<0.01
Married/living with partner (vs other)	-0.06	-0.23	0.12	0.54	0.03	-0.09	0.15	0.60
Non-white race (vs white)	0.18	0.02	0.34	0.03	0.14	0.02	0.27	0.02
Education								
≤4 years	Reference				Reference			
5–8 years	-0.22	-0.46	0.03	0.09	0.09	-0.09	0.27	0.31
9–11 years	-0.17	-0.37	0.02	0.08	-0.04	-0.20	0.12	0.60
≥12 years	-0.40	-0.64	-0.16	<0.01	-0.34	-0.58	-0.11	<0.01
Venezuela (vs Brazil)	0.45	0.27	0.62	<0.01	0.71	0.57	0.85	0.00
Body mass index (kg/m²)								
Normal weight (18.6–24.9)	Reference				Reference			
Underweight (≤18.5)	1.40	0.55	2.25	<0.01	0.35	-0.15	0.86	0.17
Overweight (25.0–29.9)	-0.44	-0.62	-0.26	<0.01	-0.22	-0.37	-0.07	<0.01
Obesity (≥30.0)	-0.43	-0.64	-0.22	<0.01	-0.21	-0.36	-0.05	0.01
Duration of disease								
Up to 5 years	Reference				Reference			
5–9 years	0.77	0.56	0.98	<0.01	0.96	0.79	1.13	<0.01
≥10 years	0.97	0.78	1.17	<0.01	1.37	1.22	1.52	<0.01
1 or more complications from diabetes (vs none)	0.03	-0.15	0.22	0.72	0.19	0.04	0.33	0.01
Have used private healthcare in the past 12 mo (vs not)	-0.52	-0.94	-0.10	0.02	-0.29	-0.48	-0.09	0.01
Self-reported adherence to diet								
Poor/fair	Reference				Reference			
Good	0.06	-0.15	0.27	0.56	-0.09	-0.26	0.08	0.32
Very good	-0.15	-0.37	0.07	0.18	-0.21	-0.39	-0.03	0.02
Excellent	-0.26	-0.54	0.01	0.06	-0.22	-0.43	0.00	0.05
Self-reported adherence to treatment								
Poor/fair	Reference				Reference			
Good	-0.10	-0.60	0.41	0.70	-0.50	-0.89	0.10	0.14
Very good	-0.24	-0.73	0.24	0.32	-0.30	-0.68	0.07	0.12
Excellent	-0.15	-0.62	0.32	0.53	-0.25	-0.62	0.12	0.19
HbA1c measured in past 12 mo (vs not)	-0.08	-0.26	0.10	0.38	-0.19	-0.33	-0.05	0.01
Perceived treatment as convenient (vs not)	-0.20	-0.36	-0.03	0.02	-0.06	-0.19	0.07	0.35
Self-rated glycaemic control								
Poor/fair	Reference				Reference			
Good	-1.05	-1.32	-0.77	<0.01	-0.87	-1.08	-0.67	<0.01
Very good	-1.51	-1.79	-1.22	<0.01	-1.51	-1.73	-1.29	<0.01
Excellent	-1.77	-2.15	-1.39	<0.01	-1.73	-2.02	-1.45	<0.01

HbA1c, haemoglobin A1c; T2D, type 2 diabetes. Statistically significant values are shown in bold.

common, but also more severe in women.³⁸ This difference may, in part, be explained by women having lower counter-regulatory responses to hypoglycaemia.³⁹ One of the reasons for poorer adherence to more intensive insulin treatment and other antidiabetic medications in women may be due to fear of these side effects.⁴⁰

Psychological factors, such as depression, stress and anxiety, affect men and women differently and potentially contribute to poor glycaemic control. A cross-sectional study of 8871 subjects in Germany in 2013 showed that social class and psychosocial stress were stronger predictors of T2D in women than in men.⁴¹ According to a study

in 2013 by Siddiqui *et al*, which reviewed the differences between men and women in coping with DM, men with DM were more satisfied with the management of their disease and experienced less depression and anxiety, compared with women with DM.⁴² Women with T2D were also found to have a higher prevalence of depression than women without T2D.⁴³

Given that women tend to have worse control of their T2D, it is important to assess whether determinants of glycaemic control affect men and women differently. Sex modified the effect of some factors associated with glycaemic control in patients with T2D in our study but had no noteworthy effect in others. Patients with T2D living in Venezuela had worse glycaemic control than those living in Brazil. Healthcare disparities between these countries may account for this difference, and our results suggest that women are affected by these inequalities to a higher extent than men. The relationship between BMI and glycaemic control was also modified by sex. It is plausible that differences of body fat distribution in men and women may lead to a different impact on outcomes of glycaemic control.²⁷ Predictors of worse glycaemic control (eg, longer duration of disease and presence of complications) also seemed to affect women to a higher degree than men. Menopause predisposes women to hyperglycaemia^{33 44} and is more prone to drug side effects.³⁴ Therefore, they may be more affected by diabetes duration and related complications. Predictors of better glycaemic control were modified by sex in different ways. While access to private care and perception of treatment as convenient seemed to have a greater effect in men as compared with women, the opposite was observed for another predictor of better glycaemic control (HbA1c measurement in the past year). More studies are warranted to better assert these findings.

This study had limitations. It was conducted in health centres, consequently our conclusions may not apply to patients with T2D who do not seek medical care or who have not yet been diagnosed. Patients' data were collected through interviews, potentially introducing a certain degree of inaccuracy for some answers. However, 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.⁴⁵ Finally, the study design, a cross-sectional survey, is limiting because the temporal relationship between the exposure and the outcome cannot be determined with certainty. The strengths of this study are the large multicentre sample, providing statistical power to examine the effects of many variables and to adjust for confounding. Another merit was the collection of data by trained and certified interviewers, who were not part of the staff at the study centres, avoiding patients feeling uncomfortable about truthfully reporting on adherence to diet or treatment. Last, the measurement of HbA1c was performed using a reliable method in a central laboratory.

CONCLUSIONS

We have shown that women with T2D had worse glycaemic control than men. In addition, sex modified factors associated with glycaemic control suggesting the need of specific treatment guidelines for men and women. These data may be helpful to improve strategies and policies aimed at minimising the complications of T2D in men and women with T2D. Longitudinal studies are warranted and may help elucidate whether the factors we found to be associated with higher HbA1c levels are indeed causally related to poor glycaemic control.

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Contributors Conceived and designed the study: EDM and FGD. Analysis and interpretation of data: FGD, SdSM, ALR, CAdST and EDM. Wrote the first draft: FGD. Reviewed and approved the final version of the manuscript: All authors.

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Competing interests EDM reports having received grant support through his institution from Pfizer Inc.

Ethics approval The study protocol was approved by the Hospital Santo Antônio Ethics Committee (approval number 32/05).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets analysed during the current study may be available from the corresponding author on reasonable request.

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REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 7 edn, 2015.
2. WHO. *Mortality Database*: WHO, 2014.
3. WHO. *Global Report on Diabetes*, 2016.
4. American Diabetes Association. Standards of medical care in diabetes-2016. *Diabetes Care* 2016;39:S1-112.
5. Fox KM, Gerber Pharmd RA, Bolinder B, *et al*. Prevalence of inadequate glycaemic control among patients with type 2 diabetes in the United Kingdom general practice research database: A series of retrospective analyses of data from 1998 through 2002. *Clin Ther* 2006;28:388-95.
6. Reichard P, Berglund B, Britz A, *et al*. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837-53.
7. Nathan DM, Genuth S, Lachin J, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
8. Sousa Andrade C, Sousa Ribeiro G. Factors associated with high levels of glycated haemoglobin in patients with type 1 diabetes: a multicentre study in Brazil. *BMJ Open* 2017.
9. Shalev V, Chodick G, Heymann AD, *et al*. Gender differences in healthcare utilization and medical indicators among patients with diabetes. *Public Health* 2005;119:45-9.
10. Tang YH, Pang SM, Chan MF, *et al*. Health literacy, complication awareness, and diabetic control in patients with type 2 diabetes mellitus. *J Adv Nurs* 2008;62:74-83.
11. Chiu CJ, Wray LA. Gender differences in functional limitations in adults living with type 2 diabetes: biobehavioral and psychosocial mediators. *Ann Behav Med* 2011;41:71-82.

12. Nilsson PM, Theobald H, Journath G, *et al.* Gender differences in risk factor control and treatment profile in diabetes: a study in 229 swedish primary health care centres. *Scand J Prim Health Care* 2004;22:27–31.
13. Wexler DJ, Grant RW, Meigs JB, *et al.* Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care* 2005;28:514520:514–20.
14. Kamuhabwa AR, Charles E. Predictors of poor glycemic control in type 2 diabetic patients attending public hospitals in Dar es Salaam. *Drug Healthc Patient Saf* 2014;6:155–65.
15. Hawthorne K, Tomlinson S. Pakistani moslems with Type 2 diabetes mellitus: effect of sex, literacy skills, known diabetic complications and place of care on diabetic knowledge, reported self-monitoring management and glycaemic control. *Diabet Med* 1999;16:591–7.
16. Salcedo-Rocha AL, García de Alba-García JE, Frayre-Torres MJ, *et al.* [Gender and metabolic control of type 2 diabetes among primary care patients]. *Rev Med Inst Mex Seguro Soc* 2008;46:73–81.
17. Mauvais-jarvis F. Physiology & Behavior Gender differences in glucose homeostasis and diabetes. 2018;187:20–3.
18. Arnetz L, Ekberg NR, Alvarsson M. Sex differences in type 2 diabetes: focus on disease course and outcomes. *Diabetes Metab Syndr Obes* 2014;7:409.
19. 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.
20. Moreira ED, Silveira PC, Neves RC, *et al.* Glycemic control and diabetes management in hospitalized patients in Brazil. *Diabetol Metab Syndr* 2013;5:62.
21. Mendes AB, Fittipaldi JA, Neves RC, *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.
22. Legato MJ, Gelzer A, Goland R, *et al.* Gender-specific care of the patient with diabetes: review and recommendations. *Gend Med* 2006;3:131–58.
23. Moreira ED, Neves RC, 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.
24. Bahia LR, Araujo DV, Schaan BD, *et al.* The costs of type 2 diabetes mellitus outpatient care in the Brazilian public health system. *Value Health* 2011;14:S137–S140.
25. Misra R, Lager J, Aalto AM. Ethnic and gender differences in psychosocial factors, glycemic control, and quality of life among adult type 2 diabetic patients. *J Diabetes Complications* 2009;23:54–64.
26. Shah BR, Hux JE, Laupacis A, *et al.* Diabetic patients with prior specialist care have better glycaemic control than those with prior primary care. *J Eval Clin Pract* 2005;11:568–75.
27. Mattsson C, Olsson T. Estrogens and glucocorticoid hormones in adipose tissue metabolism. *Curr Med Chem* 2007;14:2918–24.
28. Pasquali R, Vicennati V, Gambineri A, *et al.* Sex-dependent role of glucocorticoids and androgens in the pathophysiology of human obesity. *Int J Obes* 2008;32:1764–79.
29. Navarro G, Allard C, Xu W, *et al.* The role of androgens in metabolism, obesity, and diabetes in males and females. *Obesity* 2015;23:713–9.
30. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev* 2013;34:309–38.
31. Ding EL, Song Y, Malik VS, *et al.* Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006;295:1288–99.
32. Regitz-Zagrosek V, Lehmkühl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend Med* 2007;4 Suppl B:S162–S177.
33. Szalat A, Aryan S, Raz I, *et al.* Gender-specific care of diabetes mellitus: particular considerations in the management of diabetic women. *Diabetes Obes Metab* 2008;10:080520205432340–???
34. Lyons MR, Peterson LR, McGill JB, *et al.* Impact of sex on the heart's metabolic and functional responses to diabetic therapies. *Am J Physiol Heart Circ Physiol* 2013;305:H1584–H1591.
35. Walker EA, Molitch M, Kramer MK, *et al.* Adherence to preventive medications: predictors and outcomes in the diabetes prevention program. *Diabetes Care* 2006;29:1997–2002.
36. Vickova V, Cornelius V, Kasliwal R, *et al.* Hypoglycaemia with pioglitazone: analysis of data from the prescription-event monitoring study. *J Eval Clin Pract* 2010;16:1124–8.
37. Kahn SE, Zinman B, Lachin JM, *et al.* Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2008;31:845–51.
38. Rincon J, Holmäng A, Wahlström EO, *et al.* Mechanisms behind insulin resistance in rat skeletal muscle after oophorectomy and additional testosterone treatment. *Diabetes* 1996;45:615–21.
39. Amiel SA, Maran A, Powrie JK, *et al.* Gender differences in counterregulation to hypoglycaemia. *Diabetologia* 1993;36:460–4.
40. Körner A, Wabitsch M, Seidel B, *et al.* Adiponectin expression in humans is dependent on differentiation of adipocytes and down-regulated by humoral serum components of high molecular weight. *Biochem Biophys Res Commun* 2005;337:540–50.
41. Müller G, Hartwig S, Greiser KH, *et al.* Gender differences in the association of individual social class and neighbourhood unemployment rate with prevalent type 2 diabetes mellitus: a cross-sectional study from the DIAB-CORE consortium. *BMJ Open* 2013;3:e002601.
42. Siddiqui MA, Khan MF, Carline TE. Gender differences in living with diabetes mellitus. *Mater Sociomed* 2013;25:140–2.
43. Anderson RJ, Freedland KE, Clouse RE, *et al.* The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069–78.
44. Mauvais-Jarvis F, Manson JE, Stevenson JC, *et al.* Menopausal hormone therapy and type 2 diabetes prevention: evidence, mechanisms, and clinical implications. *Endocr Rev* 2017;38:173–88.
45. 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.