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ORIGINAL RESEARCH

Non-pharmaceutical factors for poor glycemic control in 13,970 Chinese women with drugtreated type 2 diabetes: a cross-sectional survey in 77 tertiary hospitals in four Chinese cities

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http://dx.doi.org/10.2147/PPA.S66915

Background: Achieving good glycemic control improves clinical outcomes among patients with type 2 diabetes (T2D). This study aimed to explore non-pharmaceutical factors for poor glycemic control in Chinese women with T2D who used antidiabetic drug(s).

Methods: A cross-sectional survey was conducted in March to June 2011 in 77 top tertiary hospitals in Beijing, Shanghai, Tianjin, and Guangzhou, People's Republic of China (the coverage rates of the 3A hospitals: 74.4%, 76%, 55%, and 29.3%, respectively). Of 29,502 patients with T2D who used oral antidiabetic drugs (OADs) alone or combined with insulin, 13,970 were women and used in the analysis. Logistic regression analysis was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) of factors for hyperglycemia defined as HbA_{1c} (glycated hemoglobin) \geq 77 mmol/mol (7.0%).

Results: The mean age was 60.3 (standard deviation 11.0) years, with a median of 4 (interquartile range 2-9) years of duration of diabetes, and 65.1% had hyperglycemia. In multivariable analysis, body height of \geq 164 cm (OR 1.26, 95% CI 1.15–1.37) and obesity (OR 1.16, 95% CI 1.04-1.31) was associated with increased risk of hyperglycemia, while self-monitoring blood glucose (SMBG) decreased the risk of hyperglycemia (OR 0.78, 95% CI 0.73-0.84). Duration of diabetes ≥ 3 years (≥ 3 to < 6 years, OR 1.46, 95% CI 1.32–1.62; ≥ 6 to < 10 years, OR 1.65, 95% CI 1.44-1.89), especially ≥10 years (OR 1.95, 95% CI 1.73-2.19), was associated with higher risks of hyperglycemia.

Conclusion: Body height \geq 164 cm, obesity, and duration of diabetes \geq 3 years increased while SMBG decreased risk of hyperglycemia in Chinese women with OAD-treated T2D. **Keywords:** HbA_{1c} goal, hyperglycemia, oral antidiabetic drugs

Introduction

The prevalence of diabetes has been increasing worldwide, especially in the People's Republic of China.¹ Type 2 diabetes (T2D) increases the risk of micro- and macrovascular diseases^{2,3} and shortens life expectancy by 10-12 years.⁴ It is established that hyperglycemia increases the risk of diabetes complications, including microvascular diseases and macrovascular diseases, while hyperglycemia control decreases their risk. The United Kingdom Prospective Diabetes Study (UKPDS) showed that maintaining glycated hemoglobin (HbA_{1c}) around 77 mmol/mol (7.0%) by intensive blood-glucose control with sulfonylureas and/or insulin was able to reduce a 25% risk of microvascular endpoints over a 10-year period as compared with a conventional group whose HbA₁, was around 86 mmol/mol (7.9%),⁵ and achieved a 9% risk reduction in any diabetes-related endpoint, 24% risk reduction in the microvascular endpoint, a 15% risk

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Patient Preference and Adherence downloaded from https://www.dovepress.com/ For personal use only reduction in myocardial infarction over 10 years of further follow-up after the original trial.⁶ Although the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that further tight control of HbA_{1c} below 66 mmol/mol (6.0%) increased mortality risk,⁷ both the ACCORD trial and the Veterans Affairs Diabetes Trial found that tight control of HbA_{1c} below 66 mmol/mol (6.0%) did not achieve additional reduction in the risk of cardiovascular disease,^{7,8} the Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)9 did demonstrate that achievement of HbA_{1c} by intensive management below 71 mmol/mol (6.5%) was able to further reduce nephropathy by about 20%, which may be translated into cardiovascular disease (CVD) risk reduction in the long run.¹⁰ Nevertheless, achieving low HbA_{1c} targets by pharmaceutical intervention itself brings harm to patients. Such interventions may lead to more frequent hypoglycemia,^{7,8} which is related with high risk of CVD and all-cause mortality.11

Thus, a research question should be asked: whether factors other than drug treatments also contribute to good glycemic control in T2D. In this regard, a study showed that women with T2D were at higher risk of poor glycemic control and abnormal lipid metabolism than men.¹² Obesity, insulin resistance, and metabolic syndrome are well established risk factors for diabetes^{13,14} but it is less certain whether obesity still plays a role in hyperglycemia control in drug-treated T2D. Low body height has been found associated with gestational diabetes mellitus (GDM) in Asian women,^{25,26} while no studies have attempted to examine the association between body height and glycemic control. Understanding associations of these factors with good glycemic control may help achieve better glycemic control and reduce the diabetes complications in the long run. Therefore, the current study aimed to explore non-drug factors for failure to achieve good glycemic control in Chinese women with T2D who used oral antidiabetic drugs (OADs) alone or combined with insulin.

Materials and methods Patients

The Chinese Diabetes Society launched an HbA_{1c} surveillance system among patients with T2D in mainland China in 2009. A total of 400 hospitals from 75 cities in 20 provinces, three autonomous regions, and four municipalities (Beijing, Shanghai, Tianjin, and Chongqing) directly under the central government agreed and participated in the surveillance system. The number of participating hospitals was increased to 414, with 81 cities in 30 provincial administrative regions of the People's Republic of China in 2011, from all the provincial administrative regions in the People's Republic of China except for Tibet. The ethics approval was obtained from People's Liberation Army (PLA) General Hospital, and informed consent was obtained before collecting data from the patients.

The survey in 2011 was conducted from March to June 2011. The inclusion criteria were 1) being an outpatient with T2D mellitus being treated with OADs alone, OADs combined with insulin, or OADs combined with glucagon-like peptide (GLP)-1 receptor agonists; 2) aged 18 years and more; 3) with at least one previous outpatient medical record pertaining to diabetes; and 4) being a local resident for at least 6 consecutive months prior to participation in the study. The exclusion criteria included 1) diabetes secondary to other diseases; 2) type 1 diabetes; 3) on diet and other life-style therapy and/or Chinese herbal medicine only; 4) being pregnant or breast-feeding an infant; and 5) being unable to complete the survey due to mental diseases, unconsciousness, or inability to communicate.

During the recruitment period, health professionals (junior doctors, nurses or postgraduate medical students) sequentially screened patients with T2D for their eligibility. Those who met the inclusion criteria and did not have any of the exclusion criteria were invited to participate in the survey. The process continued until seven patients were successfully recruited in a consecutive way in each day and until 400 patients were recruited in the pre-specified period. After obtaining informed consent, the health professional(s) reviewed the medical notes, including the results of laboratory assays, and recorded the related data in a form. The retrieved data included sex, height, weight, blood pressure, and date of diagnosis of diabetes. Laboratory data on HbA_{1c} and lipid profile were recorded. Specific information about the treatments used for the management of their T2D was documented, including the use of OADs (including dipeptidyl-peptidase (DPP) inhibitors and GLP-1 receptor agonists), and different types of insulin, as well as combinations of these antidiabetic drugs. Prior history of coronary heart disease, cerebrovascular disease, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, diabetes-related foot ulcers, and other complications diagnosed by secondary-care hospitals or tertiary hospitals were retrieved from medical notes, including dates of diagnosis of these medical conditions. A special staff member entered all the data and uploaded the entered data to the central database.

This analysis chose to analyze data of subjects recruited from the accredited 3A hospitals in four well-developed cities

in the People's Republic of China: Beijing, Shanghai, Tianjin, and Guangzhou. The 3A hospitals were the best hospitals that are assumed to provide quality care to patients with T2D. The reason to select 3A hospitals in four cities was that the coverage rates of the 3A hospitals were high and may be assumed to be representative of the population of patients with T2D cared by the top hospitals in the cities concerned. The coverage rates of the 3A hospitals were 74.4% for Beijing (n=32), 76% for Shanghai (n=22), 55% for Tianjin (n=11), and 29.3% for Guangzhou (n=12) after excluding those 3A hospitals that recruited less than 30 patients during the pre-specified recruitment period (n=2 for Beijing, n=2 for Tianjin, n=3 for Shanghai, and n=4 for Guangzhou). The recruitment goal was 400 patients by each hospital. A total of 13,970 women with T2D out of 29,502 patients recruited from the participating 3A hospitals from the four cities were used in the final analysis.

Statistical analysis

The Statistical Analysis System (SAS) release 9.3 (SAS Institute Inc., Cary, NC, USA) was used in all the data analysis. Data were expressed as mean (standard deviation [SD]) if normal distribution could not be rejected or median (25th to 75th percentile) if normal distribution was rejected by checking the Q-Q plot of the variable concerned. Chi-square test or Fisher's exact test where appropriate was used to compare categorical variables, and Student's t-test or Wilcoxon two-sample test where appropriate was used to compare continuous variables between two groups. Body mass index (BMI) was calculated as body weight in kilograms divided by squared body height in meters. Overweight and obesity were defined based on recommendations of the Chinese Diabetes Association (ie, BMI \geq 24.0 but < 28.0 kg/m² being used to defined overweight, and $\geq 28.0 \text{ kg/m}^2$ being used to define obesity).¹⁵ Duration of diabetes was calculated as the period from the date of diagnosis of diabetes to that of measurement of HbA_{1c}. Quintiles of duration of diabetes and body height were used to check their V-shaped or J-shaped relations, if any, with hyperglycemia. The American Diabetes Association (ADA) recommended that the treatment target of HbA_{1c} was <77 mmol/mol (7.0%),¹⁶ and HbA_{1c} \geq 77 mmol/mol (7.0%) was used to define hyperglycemia or poor glycemic control.

Logistic regression analysis on cities and 3A hospitals was used to obtain odds ratio (OR) of factors of interest for hyperglycemia in univariable and multivariable analysis. *P*-values <0.05 were considered to be statistically significant.

Results

The mean age of the women surveyed was 60.3 (SD 11.0) years, and they had a median duration of diabetes of 4 (25th to 75th percentiles: 2 to 9) years. The percentage of patients with poor glycemic control was 65.1% in the four cities combined, and also varied from city to city, with the highest percentage in Tianjin (76.3%), followed by Shanghai (69.2%), Beijing (62.4%), and Guangzhou (54.7%) (P<0.0001). Women with hyperglycemia had higher body height, higher BMI, longer duration of diabetes, and higher blood pressure, higher lipids (total cholesterol, triglyceride, and low-density lipoprotein (LDL)-cholesterol) and were less likely to use self-monitoring blood glucose (SMBG) (Table 1).

In univariable analysis, obesity and body height \geq 164 cm were associated with a higher risk of poor glycemic control, while SMBG in the last week was associated with lower risk of poor glycemic control. Duration of diabetes was associated with poor glycemic control in a J-shaped relation. Below 1 year and above 3 years of disease duration were all associated with increased risk of hyperglycemic control, with a marked increase for 10 and more years of duration of diabetes (Table 2).

After adjusting for covariates, the statistical significance for the association between obesity and poor glycemic control persisted, with an OR of 1.16 (95% confidence interval [CI] 1.04–1.31). Body height of \geq 164 cm was also significantly associated with poor glycemic control (OR 1.26, 95% CI 1.15–1.37). Duration of diabetes \geq 3 years but not <1 year increased the risk of poor hyperglycemia control, while SMBG was associated with lower risk of hyperglycemia (OR 0.78, 95% CI 0.73–0.84) (Table 2).

Age was not significant in univariable analysis, but in multivariable analysis, older age tended to reduce the risk of poor glycemic control. As compared with patients residing in Guangzhou, those patients residing in other cities were all at higher risk of poor glycemic control (Table 2).

Discussion

Although pharmaceutical treatment is the cornerstone in hyperglycemia control, we found that obesity, a body height of \geq 164 cm and long duration of diabetes in OAD-treated T2D were independently associated with hyperglycemia, and use of SMBG helped achieve good glycemic control, highlighting the importance of obesity control and use of SMBG in the management of T2D.

Recent mega-trials caused concerns over the safety of intensive pharmaceutical intervention to achieve the further tight glycemic control, including increased risk of death and hypoglycemia, which itself may increase the risk of CVD and

Variable	HbA _{ıc} <77 mmol/mol (7.0%) (n=4,880) Mean/number (SD or %)	HbA _{ıc} ≥77 mmol/mol (7.0%) [↑] (n=9,090) Mean/number (SD or %)	<i>P</i> -value
Body height, cm	159.5 (5.3)	159.8 (5.7)	<0.001
<155	745 (15.3%)	1,306 (14.4%)	
≥155 to <158	856 (17.5%)	1,551 (17.1%)	
≥158 to <161	1,363 (27.9%)	2,422 (26.6%)	
≥ 6 to < 64	931 (19.1%)	1,652 (18.2%)	
≥164	985 (20.2%)	2,159 (23.8%)	
BMI, kg/m ²	24.3 (3.4)	24.6 (3.7)	<0.0001
Overweight	1,972 (40.4%)	3,648 (40.1%)	< 0.0001
Obesity	587 (12.0%)	1,325 (14.6%)	
Duration of diabetes, years	3 (1–7)*	5 (2–10)*	<0.0001
<	735 (15.1%)	1,026 (11.3%)	
\geq I to $<$ 3	1,410 (28.9%)	1,738 (19.1%)	
\geq 3 to <6	1,117 (22.9%)	2,051 (22.6%)	
≥6 to <10	785 (16.1%)	1,866 (20.5%)	
≥10	833 (17.1%)	2,406 (26.5%)	
Systolic BP, mmHg	129 (13.5)	133 (14.7)	<0.0001
Diastolic BP, mmHg	78 (9.1)	80 (12.1)	<0.0001
Low density lipoprotein cholesterol, mmol/L	2.9 (1.03)	3.0 (1.08)	<0.0001
Triglyceride, mmol/L	1.49 (1.08–2.14)*	1.69 (1.23–2.40)*	<0.0001
Total cholesterol, mmol/L	4.72 (1.21)	4.83 (1.55)	<0.0001
SMBG	2,158 (44.8%)	3,744 (41.2%)	<0.0001
Location			<0.0001
Beijing	2,441 (50.0%)	4,054 (44.6%)	
Tianjin	544 (11.2%)	1,221 (13.4%)	
Shanghai	755 (15.5%)	2,436 (26.8%)	
Guangzhou	1,140 (23.4%)	1,379 (15.2%)	
Drug treatment schemes			<0.0001
One OAD	1,659 (34%)	1,671 (18.4%)	
Two OADs	1,824 (37.4%)	3,509 (38.6%)	
Three OADs	396 (8.1%)	974 (10.7%)	
Four and more OADs	19 (0.4%)	51 (0.6%)	
OAD(s) plus insulin	982 (20.1%)	2,885 (31.7%)	

Notes: *P*-values were derived from chi-square test or Student's *t*-test; *Median (25th percentile to 75th percentile) and their *P*-values were derived from two-sample Wilcoxon test; †Hyperglycemia was defined as HbA_{1c} \geq 77 mmol/mol (7.0%).

Abbreviations: BMI, body mass index; BP, blood pressure; HbA_{1c}, glycated hemoglobin; OAD, oral antidiabetic drug; SD, standard deviation; SMBG, self-monitoring of blood glucose.

death.^{7–9,17} Epidemiological analysis of the ADVANCE trial data¹⁸ reconfirms the benefit to control HbA_{1c} below 77 mmol/ mol (7.0%) for macrovascular events and death, and below 71 mmol/mol (6.5%) for microvascular events. The ADA recommendation endorsed maintenance of the HbA_{1c} target of 77 mmol/mol (7.0%).¹⁶ Pharmaceutical intervention plays an essential role in achieving the glycemic control target in T2D. Although tighter glycemic control was achievable in clinical trial settings,⁹ it is very difficult to achieve and maintain HbA_{1c} <77 mmol/mol (7.0%) in real practice,¹⁹ as reflected by up to 65.1% of women with T2D in the survey not reaching the HbA_{1c} target. These figures are consistent

with a report that showed that 62.7% in Asia, 64% in Eastern Europe, and 64% in Latin America of patients with T2D failed to reach the HbA_{1c} target.²⁰ In that multi-region survey,²⁰ old age, obesity (defined as BMI >30 kg/m²), longer duration of diabetes, and nonuse of SMBG were determinants of poor glycemic control as defined as HbA_{1c} \geq 77 mmol/mol (7.0%). The association between age and hyperglycemia appeared after the adjustment suggests that old age seemed to be a protective factor, probably through increased awareness with age. Obesity is associated with insulin resistance. Large diabetes prevention trials have shown that lifestyle intervention aiming at normalizing

Table 2 Determinants of hyperglycemia in Chinese women with type 2 diabetes

- - 4,117 (64.0%) 3,648 (64.9%) 1,325 (69.3%)	1.02 (0.99–1.05) 1.03 (1.02–1.04) Reference 1.04 (0.97–1.12)	0.2255 <0.0001
- 4,117 (64.0%) 3,648 (64.9%)	1.03 (1.02–1.04) Reference	
3,648 (64.9%)	Reference	<0.0001
3,648 (64.9%)		
	1.04 (0.97-1.12)	<0.0001
1,325 (69.3%)		
	1.27 (1.14–1.42)	
		<0.0001
1,306 (63.7%)	0.99 (0.88-1.12)	
1,551 (64.4%)	1.02 (0.91-1.15)	
2,422 (64.0%)		
1,652 (64.0%)	Reference	
	1.24 (1.11–1.38)	
, (,		<0.0001
1.026 (58.3%)	1.13 (1.01–1.27)	~0.0001
	· · · · · ·	
	· · · · · ·	
		<0.0001
3,744 (63.2%) versus 3,346 (66.3%)	0.86 (0.81-0.73)	< 0.0001
1 379 (54 7%)	Poforonco	
2,100 (70.070)	2.07 (2.00 2.77)	
_	0.95 (0.92-0.99)	0.0053
		<0.0001
4,117 (64,0%)	Reference	<0.0001
,,		<0.0001
6.931 (64.0%)	Reference	
_,		<0.0001
1,026 (58,3%)	1.04(0.92 - 1.17)	<0.0001
	,	<0.0001
3,744 (63.2%) versus 3,346 (66.5%)	0.78 (0.73-0.84)	<0.0001
1 270 (64 7%)	Defense	<0.0001
	,	
	1,551 (64.4%)	1,551 (64.4%) 1.02 (0.91–1.15) $2,422$ (64.0%) 1.00 (0.90–1.11) $1,652$ (64.0%)Reference $2,159$ (68.7%) 1.24 (1.11–1.38) $1,026$ (58.3%) 1.13 (1.01–1.27) $1,738$ (55.2%)Reference $2,051$ (64.7%) 1.49 (1.35–1.65) $1,866$ (70.4%) 1.93 (1.73–2.15) $2,406$ (74.3%) 2.34 (2.11–2.60) $3,744$ (63.2%) versus 5,346 (66.5%) 0.86 (0.81–0.93) $1,379$ (54.7%)Reference $4,054$ (62.4%) 1.37 (1.25–1.51) $1,221$ (69.2%) 1.86 (1.63–2.11) $2,436$ (76.3%) 2.67 (2.38–2.99) $ 0.95$ (0.92–0.99) $4,117$ (64.0%)Reference $3,648$ (64.9%) 0.99 (0.91–1.07) $1,325$ (69.3%) 1.04 (0.92–1.17) $1,738$ (55.2%)Reference $2,159$ (68.7%) 1.26 (1.15–1.37) $1,026$ (58.3%) 1.04 (0.92–1.17) $1,738$ (55.2%)Reference $2,051$ (64.7%) 1.35 (1.22–1.50) $1,866$ (70.4%) 1.68 (1.50–1.88) $2,406$ (74.3%) 1.95 (1.73–2.19) $3,744$ (63.2%) versus 5,346 (66.5%) 0.78 (0.73–0.84) 1.379 (54.7%) 1.46 (1.32–1.62) $1,221$ (69.2%) 1.65 (1.44–1.89)

Notes: Hyperglycemia was defined as $HbA_{1c} \ge 77 \text{ mmol/mol} (7.0\%)$; [†]No other variables were adjusted in the univariable analyses; [‡]Variables adjusted for in the multivariable analysis included age, BMI, self home glucose monitoring and treatment schemes (one OAD only, two OADs only, three OADs only, four and more OADs, and OADs plus insulin).

Abbreviations: BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated hemoglobin; OAD, oral antidiabetic drug; OR, odds ratio; SMBG, self-monitoring of blood glucose.

obesity reduces incidence of diabetes, establishing a causal role of obesity in T2D occurrence.^{21–23} In our study, obesity was associated with poor glycemic control in Chinese women with OAD-treated T2D, highlighting importance of

maintaining normal body weight for achieving good glycemic control in T2D. Our study also quantified duration of diabetes for the risk of poor glycemic control and reported that hyperglycemia worsened from the third year of diagnosis of diabetes and deteriorated over time. Similar with the findings from UKPDS,²⁴ the small increased risk of poor glycemic control in the first year of diagnosis of diabetes was likely to be confounded by other factors. On the other hand, gradual increase in the risk of hyperglycemia with increasing duration of diabetes since the third year of diagnosis of diabetes may reflect deterioration of beta-cell function.

Our study was the first reporting that body height of \geq 164 cm was associated with poor glycemic control among women with T2D. Shorter body height, eg, <159 cm for Chinese pregnant women²⁵ and <157 cm for Korean pregnant women,²⁶ was associated with increased risk of GDM. Other studies reported that short leg length was related to insulin resistance and diabetes in multiple adult populations,^{27,28} suggesting a role of prepubertal growth in the etiology of diabetes.²⁷ Differently from the relationship between body height and diabetes or GDM reported in other studies, we found that higher rather than shorter body height was associated with poor glycemic control. This group of women needs special attention, and more diabetes education is needed to help them to achieve the glycemic control target given to its benefits for micro- and macrovascular outcomes.^{5,6,9} The importance of SMBG for good glycemic control has been demonstrated by several observational²⁹ and randomized controlled trials,³⁰ which itself may be associated with reduced risk of morbidity and mortality.³¹ Our study reaffirmed that SMBG was useful for achieving good glycemic control among Chinese women with OAD-treated T2D.

Our study has strengths and limitations. The strength of the study is that the sample size was large and could detect factors for poor glycemic control with high sensitivity and accuracy. The OR reported in this study ranged from 1.35 to 1.95 for duration of diabetes and 0.78 for SMBG and 1.26 for body height, which may not be detectable by small sample sized studies. The first limitation was that the patients were outpatient female subjects with T2D who were seeking care from top tertiary hospitals in the four well-developed cities in the People's Republic of China. They were not representative of all the women with T2D in the People's Republic of China, especially those women under the care of community or primary-care hospitals. The findings cannot be extrapolated to patients with T2D under care by primary-care hospitals. The second limitation was that this study was a cross-sectional survey; time-relationships and causal relationships between these factors and hyperglycemia could not be established. Further cohort studies and trials are needed to verify our findings. The third limitation was that physical activity and diet data were not collected. It is unknown whether physical activity and diet mediated these associations.

In conclusion, the study found that obesity, body height of ≥ 164 cm, and duration of diabetes ≥ 3 years, especially ≥ 10 years, were associated with hyperglycemia, while use of SMBG decreased the risk of poor glycemic control. Our study highlights the importance of maintaining normal body weight and use of SMBG, and special attention needs to be given to patients with a longer duration of disease and/or a higher body height. Given the epidemic of diabetes in the world and a huge number of patients with T2D in the People's Republic of China,¹ understanding these non-drug treatment factors related with poor glycemic control may help control hyperglycemia and reduce the burden of T2D.

Acknowledgments

The authors thank those who were involved in the surveillance system for their efforts in data collection and quality control. This study was supported by a research grant from Novo Nordisk, People's Republic of China.

Disclosure

All the authors except for XY received a grant from Novo Nordisk, People's Republic of China. The authors have no other conflicts of interest in this work.

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