Journal of
Cardiology and Vascular Medicine

JScholar
Fostering Scholarly Communication

Research Article Open Access

The Factors Affecting Glycemic Control Among Type 2 Diabetes Mellitus Patients with Higher Adherence to Prescription

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Received Date: February 20, 2021 **Accepted Date:** March 20, 2021 **Published Date:** March 22, 2021

Citation: Di Wu (2021) The Factors Affecting Glycemic Control Among Type 2 Diabetes Mellitus Patients with Higher Adherence to Prescription. J Cardio Vasc Med 7: 1-8.

Abstract

Aim: This study aimed to analyze the status of glycemic control in type 2 diabetes mellitus (T2DM) patients with higher adherence to prescription and explore the factors related to glycemic control.

Methods: A cross-sectional study was conducted in 569 T2DM patients who received routine health check-up at the community hospital. Risk factors related to glycemic control were assessed using logistic regression models.

Results: Of the total participants, 351 (61.7%) had poor glycemic control with fasting plasma glucose (FPG) >130 mg/dl. Higher levels of alanine transaminase (ALT) (OR: 1.024, 95% CI: 1.010-1.039, P = 0.001) and therapy regimens (P < 0.05) were significantly associated with poor glycemic control. The prevalence of hypertension was higher in patients with good glycemic control (P = 0.013). Gender (OR: 0.431, 95% CI: 0.213-0.872, P = 0.019), diabetes duration (OR: 1.073, 95% CI: 1.039-1.109, P < 0.001), body mass index (BMI) (OR: 1.185, 95% CI: 1.039-1.352, P = 0.011), and ALT (OR: 1.034, 95% CI: 1.015-1.055, P = 0.001) were significantly associated with poor glycemic control in patients with hypertension. However, diastolic blood pressure (DBP) (OR: 1.039, 95% CI: 1.005-1.073, P = 0.023) was the only risk factor for poor glycemic control in patients without hypertension.

Conclusion: The status of glycemic control is unsatisfactory, although there is good adherence to prescription. Liver function has an obvious influence on glycemic control. Hypertension complicates the factors of glycemic control in T2DM patients.

Keywords: Type 2 Diabetes Mellitus; Glycemic Control; Risk Factor; Hypertension

Introduction

Type 2 diabetes mellitus (T2DM) is a group of metabolic disorders characterized by abnormally elevated blood glucose level. Controlling blood glucose within the normal range is the main goal of diabetes treatment so as to prevent or delay the occurrence of microvascular and macrovascular complications. It was estimated that there were 451 million diabetes patients worldwide in 2017 [1]. Many patients have attained benefits from diet control, weight reduction, oral hypoglycaemic agents and insulin2. However, the overall status of glucose control is unsatisfactory from the perspectives of preventive, predictive and personalized medicine [2].

According to the data from Canada and America, about half of the diabetes patients meet the target of glycated hemoglobin (HbA1c) ≤7.0% for glycemic control, although more than 80% of the surveyed patients are prescribed antihyperglycemic therapy [3,4]. By measuring the level of fasting plasma glucose (FPG), a study found that about 30% of diabetes patients attained good glycemic control (FPG ≤130 mg/dl) in a community-based study in Taiwan [5]. In 2016, a study of 10590 patients with T2DM undergoing specialist care and coming from different nations and regions showed that only 38% of patients met the target of HbA1c ≤7.0%, and 15% had poor glycemic control with persistent HbA1c ≥9.0% [6].

Some factors have been found to influence glycemic control, regardless of the mechanisms, such as the age of onset, the level of biochemical indexes, exercise, therapy regimens and adherence to medication [6-10]. However, the conclusion is still unclear. This study used T2DM patients with higher adherence to prescription as the subjects to analyze the status of glycemic control, the factors related to glycemic control and the association between glycemic control and comorbidity. This study will facilitate the understanding of the factors related to glycemic control and thus improve the therapeutic effect of diabetes.

Materials and Methods

Patients

A cross-sectional study was conducted in 569 T2DM patients who received routine health check-up at the community hospital, at Harbin city, China from March 2016 to August 2017. Their medical information was collected from medical records and a self-report questionnaire. Inclusion criteria: (1) Chinese Han individuals. (2) patients who were diagnosed with T2DM according to 1999 WHO criteria [11]. (3) patients who kept higher adherence to prescription in the past year. The assessment of adherence was performed referring to the questionnaire developed by Lu, *et al.* [12,13]. The mean of three indices of adherence was calculated on the basis of three questions: "Did you take all your medications all the time?", "What percent of the time were you able to take your medications exactly as your doctor prescribed them?", and "Rate your ability to take all your medications as prescribed." All the patients with mean scores ≥80 were included in this study. Exclusion criteria: (1) patients who were type 1 diabetes and secondary diabetes. (2) patients who were unable to complete the questionnaire. This study was approved by the Ethics Committee of Harbin Medical University. Informed consent was obtained from each patient before initiating this study.

Data collection

All the information was collected by well-trained nurses in the community hospital (Table 1). We collected the information of these patients, including age, gender, duration of diabetes, education (low: junior high school or below, mid-low: senior high school or secondary vocational education, mid-high: junior college, high: university), marital status, smoke, drinking (moderate: up to 15 g/day of ethanol for women and 30 g/day for men, heavy: beyond the moderate dose). Physical activity was estimated by the weekly calorie expenditure as metabolic equivalents per week (MET-min/wk). It was calculated on the basis of physical activity duration and mode [14]. Anthropometric measurements included systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, waist circumstance and body mass index (BMI). The biochemical indexes of check-up data included alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), creatinine (Cr), blood urea nitrogen (BUN), total cholesterol (TC), total triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and fasting plasma glucose (FPG). The status of glycemic control was assessed according to the level of FPG (good glycemic control: FPG ≤130 mg/dl, poor glycemic control: FPG >130 mg/dl) [15].

Table 1: Characteristics between T2DMpatients with good and poor glycemic control

Characteristics	Poor glycemic control (n = 351)	Good glycemic control (n = 218)	*P* value
Age (years)	66.00 (62.00-71.00)	66.00 (62.00-72.00)	0.213
Gender (male/female)	163/188	83/135	0.050
Diabetes Duration (years)	8.00 (4.00-14.00)	5.00 (2.00-12.00)	<0.001
SBP (mmHg)	134.00 (120.00-150.00)	132.00 (120.00-144.00)	0.288
DBP (mmHg)	80.00 (74.00-84.00)	78.00 (70.00-84.00)	0.248
Weight (kg)	68.6.00 (61.80-77.00)	67.45 (60.08-76.03)	0.127
Waist (cm)	89.00 (82.00- 95.00)	88.00 (82.93-94.00)	0.375

BMI (kg/m2)	26.10 (24.20-28.36)	25.73 (23.48-27.82)	0.082
MET Value (MET/wk)	840.00 (0.00-1386.00)	840.00 (0.00-1386.00)	0.363
FPG (mg/dl)	162.70 (142.70-186.13)	113.42 (98.34-122.34)	<0.001
ALT (U/L)	23.00 (16.00-33.00)	19.00 (14.00-25.33)	<0.001
AST (U/L)	17.00 (14.00-22.00)	18.00 (15.00-22.00)	0.276
TB (U/L)	12.30 (9.40-15.80)	11.18 (8.38-14.33)	0.004
Cr (umol/L)	74.80 (63.20-89.80)	73.90 (65.30-90.50)	0.822
BUN (mmol/L)	5.54 (4.63-6.08)	5.60 (4.56 -6.69)	0.727
TC (mmol/L)	5.30 (4.60-5.90)	5.20 (4.41-5.83)	0.031
TG (mmol/L)	1.50 (1.10-2.20)	1.47 (1.00-1.95)	0.095
LDL (mmol/L)	2.80 (2.20-3.43)	2.96 (2.29-3.73)	0.044
HDL (mmol/L)	1.37 (1.19-1.57)	1.38 (1.16-1.58)	0.614
Education			
Low	184 (52.4%)	124 (56.9%)	0.733
Mid-low	112 (31.9%)	65 (29.8%)	
Mid-high	42 (12.0%)	23 (10.5%)	
High	13 (3.7%)	6 (2.8%)	
Marital Status			
Married/ Remarried	279 (79.5%)	166 (76.1%)	0.348
Divorced/ Widowed/ Single	72 (20.5%)	52 (23.9%)	
Smoke			
Never	266 (75.8%)	165 (75.7%)	0.536
Former	37 (10.5%)	18 (8.3%)	
Current	48 (13.7%)	35 (16.0%)	
Drinking			
None	263 (74.9%)	173 (79.4%)	0.097
Moderate	50 (14.3%)	18 (8.2%)	
Heavy	38 (10.8%)	27 (12.4%)	
Prescription			<0.001
Diet and exercise	77 (21.9%)	82 (37.6%)	
OAD alone	112 (31.9%)	70 (32.1%)	
Insulin alone	106 (30.2%)	45 (20.7%)	
OAD and Insulin	56 (16.0%)	21 (9.6%)	

*SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; MET: metabolic equivalents; FPG: fasting plasma glucose; ALT: alanine transaminase; AST: aspartate aminotransferase; TB: total bilirubin; Cr: creatinine; BUN: blood urea nitrogen; TC: total cholesterol; TG: total triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein; OAD: oral antidiabetes drug

Statistically analysis

Normality distribution of all variables was tested by the Kolmogorov-Smirnov test. Non-normally distributed continuous variables were represented as medians and interquartile ranges (IQR). Categorical variables were represented as frequencies and percentages. The descriptive analysis was performed in two subgroups. The comparison of quantitative data between the two groups was performed using Student's t-tests for normal distribution or Mann–Whitney U tests for skewed distribution. Chi-square tests were used to analyze categorical variables. All variables with $P < 0.05$ were entered into multivariable logistic regression models to evaluate the risk factors adjusted for the influence of confounders. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. A P-value of <0.05 was considered to be statistically significant. SPSS software version 24.0 (SPSS, Chicago, IL, USA) was used to complete all the analysis.

Results

Description and analysis of basic information

A total of 569 patients with T2DM were recruited in this study. The median age of the patients was 66 years with an interquartile range of 62-72 years, 246 male and 323 females. In this sampled population, 218 (38.3%) had good glycemic control (FPG ≤130 mg/dl) whereas 351 (61.7%) had poor glycemic control (FPG >130 mg/dl). The basic characteristics of patients with good and with poor glycemic control were described and compared (Table 1). Patients with poor glycemic control had a longer diabetes duration than those with good glycemic control ($P < 0.001$). The proportion of males was higher in patients with poor glycemic control, although with only a marginal significance ($P = 0.050$). Higher levels of ALT, TB, TC, and lower LDL presented in patients with poor glycemic control ($P < 0.050$). There was a significant difference between patients prescribed with different therapy regimens although higher adherence to prescription ($P < 0.001$). Glycemic control was significantly better in patients prescribed with diet and exercise than those with medication.

The significant variables were entered into multivariable logistic regression models to investigate the risk factors for poor glycemic control. As shown in Table 2, higher levels of ALT (OR: 1.024, 95% CI: 1.010-1.039, $P = 0.001$) and therapy regimens ($P < 0.05$) were significantly associated with poor glycemic control. The OR successively increased in the oral antidiabetes drug (OAD) group, insulin group, and combined group.

Table 2: Multivariate analysis of the factors related to poor glycemic control

Characteristics	OR	95% CI	P value
Diabetes Duration (years)	1.023	0.996-1.051	0.091
ALT (U/L)	1.024	1.010-1.039	0.001
TB (U/L)	1.022	0.995-1.048	0.108
TC (mmol/L)	1.004	0.994-1.015	0.400
LDL (mmol/L)	0.989	0.977-1.001	0.078
Prescription			
Diet and exercise	Ref	Ref	Ref
OAD alone	1.632	1.039-2.562	0.033
Insulin alone	2.391	1.426-4.011	0.001
OAD and Insulin	2.595	1.350-4.989	0.004

* ALT: alanine transaminase; TB: total bilirubin; TC: total cholesterol; LDL: low-density lipoprotein; OAD: oral antidiabetes drug

The association between glycemic control and comorbidity

Many patients in this study had accompanying diseases. Of them, 210 (36.9%) cases had coronary heart disease (CHD), 323 (56.8%) cases had hypertension and 220 (38.7%) cases had stroke. We analyzed the association between glycemic control and the prevalence of comorbidity (Table 3). The results indicated that hypertension was more common in patients with good glycemic control compared to those with poor glycemic control (P = 0.013).

Table 3: The association between glycemic control and comorbidity

Characteristics	Poor glycemic control (n = 351)	Good glycemic control (n = 218)	P value
CHD			
Yes	122 (34.8%)	88 (40.4%)	0.178
No	229 (65.2%)	130 (59.6%)	
Hypertension			
Yes	185 (52.7%)	138 (63.3%)	0.013
No	166 (47.3%)	80 (36.7%)	
Stroke			
Yes	126 (35.9%)	94 (43.1%)	0.085
No	225 (64.1%)	124 (56.9%)	

*CHD: coronary heart disease

Blood pressure differences in glycemic control

In view of the association between hypertension and glycemic control, we classified the patients into two groups based on whether they had hypertension. The factors related to poor glycemic control were analyzed in both groups. In patients with hypertension, the status of glycemic control was associated with gender, diabetes duration, weight, BMI, ALT, and TB. Contrastingly, DBP and ALT were related in patients without hypertension (Table 4).

Table 4: The factors related to glycemic control in patients with and without hypertension

Characteristics	With hypertension		P value	Without hypertension		P value
	Poor (n = 185)	Good (n = 138)		Poor (n = 166)	Good (n = 80)	
Age (years)	67.00 (63.00-73.00)	66.00 (62.75-72.25)	0.768	64.00 (60.00-69.00)	65.00 (62.00-71.75)	0.065
Gender (male/female)	89/96	51/87	0.045	74/92	32/48	0.497
Diabetes Duration (years)	10.00 (5.00-16.00)	6.00 (1.00-12.00)	<0.001	6.00 (3.75-12.00)	4.50 (2.00-13.00)	0.099
SBP (mmHg)	144.00 (130.00-156.00)	138.00 (128.00-154.00)	0.052	124.00 (116.00-136.00)	123.00 (112.00-134.00)	0.236
DBP (mmHg)	80.00 (76.00-88.00)	80.00 (74.00-88.00)	0.595	78.00 (70.00-82.00)	76.00 (68.00-80.00)	0.023
Weight (kg)	71.20 (64.75-81.35)	68.55 (60.08-77.05)	0.030	67.05 (59.48-74.13)	65.75 (60.20-71.98)	0.706
Waist (cm)	90.00 (84.50-98.00)	90.00 (83.40-95.00)	0.124	86.75 (80.00-92.63)	85.60 (80.00-92.00)	0.583
BMI (kg/m2)	26.67 (24.95-29.30)	26.19 (23.92-28.11)	0.014	25.30 (23.19-27.00)	24.64 (23.29-27.44)	0.457
MET Value (MET/wk)	840.00 (0.00-1386.00)	693.00 (0.00-1386.00)	0.407	882.00 (17.33-1680.00)	924.00 (49.50-1386.00)	0.851
FPG (mg/dl)	161.44 (141.80-182.52)	114.95 (99.01-122.75)	<0.001	165.50 (143.56-192.93)	113.06 (97.03-120.50)	<0.001
ALT (U/L)	23.00 (16.00-33.00)	20.00 (14.00-26.00)	0.002	23.00 (16.00-33.00)	18.00 (14.25-24.00)	0.001
AST (U/L)	18.00 (14.00-24.50)	19.00 (15.00-23.00)	0.570	17.00 (14.75-20.00)	17.00 (15.00-21.00)	0.546
TB (U/L)	12.20 (9.15-15.80)	10.80 (8.08-14.85)	0.017	12.40 (9.88-16.10)	11.63 (9.30-13.90)	0.127
Cr (umol/L)	78.20 (65.25-94.90)	75.00 (66.53-93.15)	0.575	70.40 (61.73-82.58)	72.00 (62.15-84.83)	0.661
BUN (mmol/L)	5.76 (4.67-7.30)	5.58 (4.50-6.69)	0.079	5.34 (4.57-6.26)	5.65 (4.72-6.64)	0.158
TC (mmol/L)	5.30 (4.60-5.85)	5.11 (4.46-5.90)	0.224	5.40 (4.70-6.00)	5.20 (4.40-5.79)	0.069
TG (mmol/L)	1.60 (1.15-2.20)	1.50 (1.10-2.00)	0.232	1.40 (1.00-2.20)	1.30 (0.90-1.89)	0.114
LDL (mmol/L)	2.87 (2.26-3.50)	3.00 (2.29-3.76)	0.214	2.78 (2.19-3.36)	2.90 (2.27-3.65)	0.131
HDL (mmol/L)	1.33 (1.15-1.54)	1.37 (1.13-1.51)	0.723	1.40 (1.25-1.60)	1.45 (1.19-1.65)	0.928
Education						
Low	90 (48.65%)	79 (57.25%)	0.353	94 (56.63%)	45 (56.25%)	0.654
Mid-low	63 (34.05%)	38 (27.54%)		49 (29.52%)	27 (33.75%)	
Mid-high	24 (12.97%)	18 (13.04%)		18 (10.84%)	5 (6.25%)	
High	8 (4.33%)	3 (2.17%)		5 (3.01%)	3 (3.75%)	
Marital Status						
Married/Remarried	144 (77.84%)	104 (75.36%)	0.602	135 (81.33%)	62 (77.5%)	0.482
Divorced/Widowed/ Single	41 (22.16%)	34 (24.64%)		31 (18.67%)	18 (22.5%)	

Smoke						
Never	138 (74.60%)	106 (76.81%)	0.738	128 (77.11%)	59 (73.75%)	0.487
Former	21 (11.35%)	12 (8.70%)		16 (12.03%)	6 (7.5%)	
Current	26 (14.05%)	20 (14.39%)		22 (10.86%)	15 (18.75%)	
Drinking						
Non-drinkers	144 (77.84%)	110 (79.70%)	0.723	119 (71.69%)	63 (78.75%)	0.052
Moderate-drinkers	24 (12.97%)	14 (10.15%)		26 (15.66%)	4 (5%)	
Heavy-drinkers	17 (9.19%)	14 (10.15%)		21 (12.65%)	13 (16.25%)	

* SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; MET: metabolic equivalents; FPG: fasting plasma glucose; ALT: alanine transaminase; AST: aspartate aminotransferase; TB: total bilirubin; Cr: creatinine; BUN: blood urea nitrogen; TC: total cholesterol; TG: total triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein

Multivariate analysis showed that gender (OR: 0.431, 95% CI: 0.213-0.872, P = 0.019), diabetes duration (OR: 1.073, 95% CI: 1.039-1.109, P < 0.001), BMI (OR: 1.185, 95% CI: 1.039-1.352, P = 0.011), and ALT (OR: 1.034, 95% CI: 1.015-1.055, P = 0.001) were significantly associated with poor glycemic control in patients with hypertension (Table 5). However, DBP (OR: 1.039, 95% CI: 1.005-1.073, P = 0.023) was the only risk factor for poor glycemic control in diabetes patients without hypertension (Table 6).

Table 5: Multivariate analysis of the factors related to poor glycemic control in patients with hypertension

Characteristics	OR	95% CI	*P* value
Gender	0.431	0.213-0.872	0.019
Diabetes duration	1.073	1.039-1.109	<0.001
Weight	0.969	0.929-1.011	0.146
BMI	1.185	1.039-1.352	0.011
ALT	1.034	1.015-1.055	0.001
TB	1.037	0.997-1.078	0.067

* BMI: body mass index; ALT: alanine transaminase: TB: total bilirubin

Table 6: Multivariate analysis of the factors related to poor glycemic control in patients without hypertension

Characteristics	OR	95% CI	P value
DBP	1.039	1.005-1.073	0.023
ALT	1.008	0.990-1.026	0.409

*DBP: diastolic blood pressure; ALT: alanine transaminase

Discussion

The prevalence of diabetes has been increasing over recent decades, and the number of diabetes patients was expected to increase to 693 million by 2045 [16]. Different medications targeting different pathogenesis are available for diabetes patients; however, the overall status of glycemic control is unsatisfactory. In this study, only 38.3% of T2DM patients obtained good glycemic control, although with higher adherence to prescription. This percentage is lower than that reported by Peng et al, who found that about 44% of T2DM patients achieved the target of glycemic control (HbA1c ≥7.0%) based on their nationwide prospective cohort study in China1. Glycemic control is far from optimal17. It is a challenge to improve the management of diabetes.

We analyzed the factors related to poor glycemic control and found that elevated ALT and different therapy regimens were significantly associated with poor glycemic control after excluding the interference from adherence to prescription by setting inclusion criteria. The elevation of ALT is common in T2DM patients [18,19]. ALT is positively correlated with FPG and HbA1c in diabetes patients [20]. Nwosu et al found that the elevated ALT negatively impacted glycemic control in youth with T2DM [21]. Decreased ALT can predict a favorable response to treatment with GLP-1 receptor agonists [22]. Additionally, some researchers also report poor glycemic control and oral hypoglycemic agents as the causes of elevated ALT [23]. Better glycemic control can result in quickly decrease of ALT and AST in some of type 1 diabetes patients [24]. There might be a mutual influence between the impairment of liver function and poor glycemic control [25]. Therapy regimen is another factor related to glycemic control. Taking diet and exercise group as the reference, OR was successively increased in the OAD, insulin and the combined group. The possibility of good glycemic control is reduced with the increased types of oral medications or the use of insulin [7,26,27]. However, this conclusion cannot be used to illustrate that drug combination or insulin is ineffective for diabetes patients [28]. Physicians tend to prescribe drug combination or insulin for patients with uncontrolled diabetes. Therefore, complex regimens of treatment may be an indicator for more severe diabetes, but not a risk factor for poor glycemic control.

T2DM patients are often concomitant with other diseases. Our study showed that the prevalence of hypertension was higher in patients with good glycemic control. However, the previous studies indicated that the prevalence of hypertension is not associated with glycemic control or higher in diabetes patients with poor glycemic control [29-31]. We analyzed the possible

reason for our result as below. The prevalence of hypertension is 23.2% in China, and it is about 50% in the 55-74 age group [32]. This study contained 323 diabetes patients with hypertension, but only 125 of them were diagnosed simultaneously with or after suffering from diabetes. Therefore, hypertension in most of these patients should not be the outcome of poor glycemic control. Additionally, T2DM patients with hypertension can also gain better glycemic control if their hypertension is well controlled [33]. Meanwhile, several studies provided indirect support for our result [34,35]. For example, it is reported that stroke is associated with good glycemic control in T2DM patients [34]. Glycemic control impacts the outcome of heart failure in a U-shaped relationship with the optimal HbA1c of 7.5 to 8.0% [35]. More investigations are needed to clarify the association between glycemic control and hypertension.

The factors related to glycemic control were analyzed in patients with or without hypertension. In patients with hypertension, poor glycemic control was more common in these patients who were male, had a longer duration of diabetes, higher levels of BMI and ALT. However, only DBP was associated with poor glycemic control in patients without hypertension. This result indicated that blood pressure (BP) control is necessary, even in T2DM patients without hypertension. Intensive BP treatment (targeted SBP of <120 mmHg) has been found to benefit diabetes patients with HbA1c of 7.0%-7.9% by reducing cardiovascular event risk [36].

In conclusion, the status of glycemic control is unsatisfactory, although there is good adherence to prescription in the northern city of China. Liver function has an obvious influence on glycemic control. Hypertension complicates the factors of glycemic control in T2DM patients. To maintain good glycemic control, the management associated with risk factors should be different between patients with and without hypertension. Moreover, BP control should be paid more attention even in T2DM patients without hypertension.

Acknowledgment

Hao Wang was supported by the China Scholarship Council (CSC Number: 201708110200).

Author contributions

This study was conceived and designed by W.W. Data were collected by D.W, L.L and Y.L. Data were analyzed by H.W and Y.Z. The article was written by D.W, T.W, H.W, and W.W. All authors meet the ICMJE criteria for authorship.

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