Predictors of treatment failure during the first year in newly diagnosed type 2 diabetes patients: an observational study

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Background. Diabetic patients who fail to achieve early glycemic control may increase the future risk of complications and mortality. The aim of the study was to identify factors that predict treatment failure during the first year in adults with newly diagnosed type 2 diabetes mellitus (T2DM). **Methods.** This retrospective cohort study conducted at the Changhua Christian Hospital in Taiwan enrolled 5759 eligible patients with newly diagnosed T2DM between 2002 and 2017. Data were collected from electronic medical records. A subgroup analysis of 3059 patients with baseline HbA1c ≥8% was performed. Multivariable logistic regression analysis using backward elimination was performed to establish prediction models. **Results.** Of all study participants, 335 (5.8%) were classified as treatment failure (TF) during the first year. For every 1% increase in baseline HbA1c, the risk of TF was 1.25 times higher. Patients with baseline HbA1c ≥8% had a higher rate of TF than those with HbA1c <8% (9.5% vs 1.6%). Older age, medication adherence, self-monitoring of blood glucose (SMBG), and higher level of education predicted a lower risk of TF. Regular exercise may prevent TF only in patients with baseline HbA1c ≥8%. **Conclusions.** Age, education level, performing SMBG, medication adherence, regular exercise, and insulin use were the major predictors of TF during the first year in newly diagnosed diabetes patients with baseline HbA1c ≥8%.

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Abstract

Background. Diabetic patients who fail to achieve early glycemic control may increase the future risk of complications and mortality. The aim of the study was to identify factors that predict treatment failure during the first year in adults with newly diagnosed type 2 diabetes mellitus (T2DM).

Methods. This retrospective cohort study conducted at the Changhua Christian Hospital in

Taiwan enrolled 5759 eligible patients with newly diagnosed T2DM between 2002 and 2017. Data were collected from electronic medical records. A subgroup analysis of 3059 patients with baseline HbA1c ≥8% was performed. Multivariable logistic regression analysis using backward elimination was performed to establish prediction models.

Results. Of all study participants, 335 (5.8%) were classified as treatment failure (TF) during the first year. For every 1% increase in baseline HbA1c, the risk of TF was 1.25 times higher. Patients with baseline HbA1c ≥8% had a higher rate of TF than those with HbA1c <8% (9.5% vs 1.6%). Older age, medication adherence, self-monitoring of blood glucose (SMBG), and higher level of education predicted a lower risk of TF. Regular exercise may prevent TF only in patients with baseline HbA1c ≥8%.

Conclusions. Age, education level, performing SMBG, medication adherence, regular exercise, and insulin use were the major predictors of TF during the first year in newly diagnosed diabetes patients with baseline HbA1c ≥8%.

Introduction

Diabetes mellitus (DM) is among the most serious chronic diseases worldwide. The prevention and treatment of diabetes is a major health care issue due to its high prevalence, related comorbidities, complications, and high related medical cost. Early glycemic control may have long-lasting (at least 10 years) effects in reducing the risk of severe microvascular and macrovascular complications, known as the legacy effect (metabolic memory) [1, 2]. Walraven - et al. reported that patients who responded quickly to glycemic control showed a lower prevalence of retinopathy and microalbuminuria [3]. A large cohort study of newly diagnosed diabetes patients with at least 10-year survival showed that poor control (mean HbA1c ≥8.0%)

during the first year was associated with increased future risk of microvascular events and mortality [4]. These findings highlight the urgency of improving glycemic control in newly diagnosed diabetes patients.

Despite a tendency for better islet function in newly diagnosed patients with type 2 DM (T2DM), many still fail to achieve early glycemic control. A nationwide prospective cohort study reported that 31.5% of newly diagnosed Chinese diabetes patients failed to achieve HbA1c target levels (<7.0%) after 12 months of treatment [5]. Early detection of the factors that predispose to treatment failure could help identify those at risk of not achieving glycemic control and enable tailoring of treatment measures.

Previous studies investigating predictors of poor glycemic control rarely focused on newly diagnosed T2DM patients [5, 6]. There exist characteristic differences between newly diagnosed patients and those who had been on long-term treatment; thus, their predictors may also differ. Ren et al. reported that predictors of the response to anti-diabetic therapy differed between early- and advanced-stage T2DM [7]. The findings of interventional studies may not reflect the situation in clinical practice, particularly medication adherence [8, 9]. Therefore, further studies focusing on newly diagnosed patients using real-world data are required to fill this information gap. The aim of the present study was to determine the major factors predicting treatment failure during the first year in adults with newly diagnosed T2DM.

Materials & Methods

Subjects

This retrospective cohort study was conducted at the Changhua Christian Hospital (CCH), Taiwan. A total of 24473 patients with T2DM were enrolled in the diabetes case management

program (DCMP) at the CCH Diabetes Care Centre between January 2002 and December 2017. Patients were screened for eligibility using data from the hospital's electronic medical record system.

Patients diagnosed with T2DM, according to the criteria established by the American Diabetes Association, were included [10]. Those in whom the onset of diabetes occurred over 12 months prior to enrolment or at an age <30 years were excluded. The latter was to reduce the likelihood of type 1 diabetes. Patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 were also excluded as this may have affected the HbA1c level and not accurately reflect the true glycemic status [11]. In the end, 5759 eligible patients with >1 year of analytical data were included (Figure 1).

Data collection

Data collected from the hospital's electronic medical record system included the DCMP diabetes registry, prescriptions, laboratory data, and CCH research database. Diabetes specialists referred patients with T2DM to the Diabetes Care Center to participate in the DCMP, usually 2 to 6 weeks after the first outpatient clinic visit. All patients received basic data registry, underwent health-related behavior survey, physical examination, and laboratory testing. They attended standardized one-to-one diabetes self-management (DSM) education classes upon enrolment into the DCMP. After completing the course, a certified diabetes educator conducted face-to-face interviews and evaluated and recorded each patient's frequency of performing Self-monitoring of blood glucose (SMBG), knowledge regarding glycemic control, willingness toward DSM, and medication adherence.

Outcome measurement

Treatment failure (TF) was defined as never achieving post-treatment HbA1c <8% at 3, 6, 9, or 12 months after initiating treatment during the first year. Participants with at least one of the four post-treatment HbA1c levels <8% were categorized as non-TF (reference group). Serum HbA1c was measured through ion-exchange high-performance liquid chromatography using the VARIANTTM II Turbo system.

Other Variables

Basic data included age at onset of diabetes, gender, level of education, and family history of diabetes. Health-related behaviors included current smoking (tobacco use within the preceding year), drinking (alcohol consumption more than once per week within the preceding year), and physical activity [regular (≥30 min/day, ≥3 days/week), occasional (low level of exercise less than the regular exercise criteria) or no exercise]. SMBG was defined as self-assessment of blood glucose levels using a glucometer more than once per week. Knowledge regarding glycemic control was defined as an understanding of the need for and methods of controlling blood glucose. Willingness toward DSM was defined as the motivation to learn self-management techniques. Medication adherence was defined as taking medication regularly at the dose recommended by the physician over the past week. Four-point scales were used to assess the three aforementioned variables. Data were merged into simple dichotomies (i.e., top-two-box vs. bottom-two-box) and categorized as adequate (yes) or inadequate (no) for analysis.

Physical examination included measurement of blood pressure (BP), height, and body weight. Systolic BP and diastolic BP were measured with patients in a seated position after a 10-min rest. The mean BP was calculated as (1/3 SBP + 2/3 DBP). Body mass index (BMI) was calculated as

116 body weight (kg)/height (m^2). Baseline laboratory data, including total cholesterol (TC), high-
117 density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol
118 (LDL-C), creatinine, and glutamic pyruvic transaminase (GPT) levels were measured using a
119 UniCel DxC 800 Synchron Clinical System (Beckman Coulter, Brea, CA, USA). The eGFR was
120 calculated using the equation recommended by the National Kidney Foundation [12].
121 Individual anti-diabetic medication use during the first six months was categorized as oral
122 anti-diabetic drugs (OAD) alone, insulin alone, both, or none. Only medication used for >1
123 month was included. Data on the 19 major non-psychiatric comorbidities in the Charlson
124 comorbidity index during the year preceding enrolment were collected for each patient from the
125 CCH research database [13]. Major comorbidities including congestive heart failure, coronary
126 artery disease, and cerebrovascular accident were analyzed as independent variables.
127
128 **Statistical analysis**
129 Data were expressed as frequency with percentage and mean ± standard deviation for
130 categorical and continuous covariates respectively. Univariable logistic regression analysis was
131 performed to calculate odds ratios (ORs) of TF vs non-TF for all variables. Subsequently,
132 multivariable logistic regression analysis using backward elimination was performed to establish
133 prediction models adjusted for significant covariates as shown in Table 1. Area under the
134 receiver operating characteristic curve (AUC) and R-square were used to assess the predictive
135 ability of the models for predicting TF. We performed a subgroup analysis of patients with
136 baseline HbA1c ≥8% to demonstrate the effect of initial poor glycemic status on TF. All tests
137 were two-tailed with a significance level of 0.05. IBM SPSS version 22 software (IBM Corp.,
138 Armonk, NY, USA) was used for the analyses.

139

140 **Ethics statement**

141 The study was approved by the Institutional Review Board of Changhua Christian Hospital

142 (CCH IRB No: 191212). Informed consent was waived.

143

144 Results

145 We identified 5759 eligible patients (mean age, 55.9 ±11.9 years; 53.3% males) between 2002

146 and 2017. Among these patients, 335 (5.8%) were categorized as the TF group. Compared with

147 the non-TF group, the TF group was younger (51.9 vs 56.2 years, p <0.01) and included more

148 current smokers (21.5% vs 15.9%, p=0.01), whereas the distribution of gender, BMI, alcohol

149 drinking, and family history of diabetes were similar. Patients in the non-TF group had higher

150 levels of education (Table 1). Higher baseline HbA1c level, lipid levels (TC, HDL-C, LDL-C

151 and TG), mean BP, eGFR, and GPT indicated higher risk of TF. For every 1% the increase in

152 baseline HbA1c, the risk of TF was 1.25 times higher. Use of fibrates and insulin (alone or

153 combined with OAD) during the first 6 months predicted greater TF. Higher Charlson

154 comorbidity index, regular exercise, good medication adherence, performing SMBG, good

155 knowledge regarding glycemic control, and adequate willingness toward DSM reduced risk of

156 TF.

157 According to baseline HbA1c level, the study subjects were divided into two subgroups. The

158 higher HbA1c subgroup was composed of 3059 patients with HbA1c ≥8%, including 292 (9.5%)

159 with TF. In contrast, only 43 (1.6%) of the 2700 patients with HbA1c <8% had TF during the

160 first year. Therefore, two prediction models were established: model 1, which consisted of all

161 study subjects, and model 2, which consisted of a subgroup of patients with baseline HbA1c

≥8.0%, using multivariable backward stepwise logistic regression analysis (Table 2). Older age, higher education level, performing SMBG, and medication adherence predicted a lower risk of TF in both models. Higher baseline HbA1c and inadequate knowledge regarding glycemic control increased the risk of TF in model 1, but the increase was not statistically significant in model 2. Conversely, regular exercise contributed to risk reduction in model 2 rather than model 1. Using insulin within the first 6 months was predictive of TF. Although high TC indicated a higher risk of TF in model 1, it was replaced by high TG in model 2.

Discussion

Previous studies on predictive factors or model of newly diagnosed T2DM were predominantly based on baseline HbA1c, which is a strong major predictor [3, 5, 6, 14, 15]. Higher baseline HbA1c may reflect poor beta cell function or prolonged hyperglycemia due to delayed diagnosis of DM [6, 14]. Consistent with aforementioned studies, patients with baseline HbA1c ≥8% had a higher rate of TF than those with HbA1c <8% (9.5 vs 1.6%). However, it is worth noting that baseline HbA1c became an insignificant predictor in the subgroup model after adjusting for other factors. In other words, further increase in baseline HbA1c ≥8% may raise a limited risk of TF. Other factors, including SMBG, medication adherence, and regular exercise may be more predictive in newly diagnosed patients with baseline HbA1c ≥8%.

SMBG had a greater protective effect than other modifiable variables, especially in model 2, indicating it may be more influential in reducing the risk of TF in patients with baseline HbA1c ≥8%. It supports clinicians to encourage patients with high baseline HbA1c to engage in SMBG. Medication adherence and education level predicted lower risk of TF in both models. Medication non-adherence is common and may account for up to 75% of the gap in clinical efficacy between

randomized controlled trial and real-world results in HbA1c reduction [16, 17]. The present study highlights the importance of monitoring medication adherence in clinical practice to reduce risk of TF.

Higher level of education was positively correlated with good medication adherence, SMBG, adequate knowledge regarding glycemic control, willingness toward DSM, and regular exercise (Table 3). Our findings are consistent with those of a previous study in Taiwan that showed that higher educational attainment was significantly associated with better understanding of health education and instructions, adequate health literacy, and better glycemic control [18]. Knowledge regarding glycemic control was not a significant predictor in the subgroup analysis, possibly due to its higher correlation with SMBG (R = 0.31), level of education (R = 0.21), and physical activity (R = 0.21) (Table 3); indicating that self-care behaviors are more predictive of TF than knowledge in patients with baseline HbA1c ≥8%.

The present study showed that older age reduced the risk of TF in newly diagnosed T2DM patients, which was consistent with most previous studies [3, 14, 16, 19]. While older patients tended to have more unfavourable factors, such as less knowledge regarding glycemic control, less likely to perform SMBG and lower level of education, they had a lower risk of TF in the first year (Table 3). The opposite effect could be explained by age-associated differences in the pathogenesis of T2DM proposed previously [20, 21]. Martono et al. reported that younger patients are predisposed to insulin deficiency, while older patients are more inclined to be insulin-resistant [19]. Previous studies showed insulin therapy, either alone or combined with OAD, was associated with a higher risk of TF [5, 22]. A common explanation is that insulin users have more severe beta cell loss and are therefore prone to treatment failure.

The strengths of this study include its large sample size, the focus on newly diagnosed

T2DM and further identification of predictors in patients with baseline HbA1c ≥8%. The National Health Insurance in Taiwan covers more than 99% of the country's 23 million people and provides easy access to medical services [23]. Therefore, the treatment and outcome in the study were less affected by insurance factors.

Our study had several limitations. First, patients attending a medical centre may have higher disease severity. Therefore, we adjusted relevant variables for comorbidity and performed subgroup analysis of patients with HbA1c ≥8% to reduce the selection bias. Second, our models were limited by the absence of income, dietary habits and occupation information, which may contribute to glycemic control. Third, selection bias may exist since our study population did not include those patients with missing data or <1-year follow-up. Fourth, some of the data were self-reported, such as medication adherence and SMBG frequency, and social desirability bias could be a problem. Finally, the generalizability of the real-world study findings may be limited to settings with similar medical and sociocultural environment.

Conclusions

Baseline HbA1c has been an important indicator in clinical treatment guidelines to assess the severity of glycemic control and guide clinicians to use initial OAD combination therapy or even insulin therapy [24]. The current study showed that patients with baseline HbA1c ≥8% did have a much higher rate of TF. However, subgroup analysis for them demonstrated that when baseline HbA1c above 8%, the increase in HbA1c did not further raise the risk of TF. Other factors, including age, education level, performing SMBG, medication adherence, regular exercise and using insulin, became more predictive. This reminds clinical staffs to aggressively promote

patients' medication adherence, performing SMBG and regular exercise to reduce their risk of TF during the first year among newly diagnosed patients with baseline HbA1c ≥8%.

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Figure 1

Figure 1 Flowchart of the study population. Abbreviations: CCH, Changhua Christian Hospital; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate

Abbreviations: CCH, Changhua Christian Hospital; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

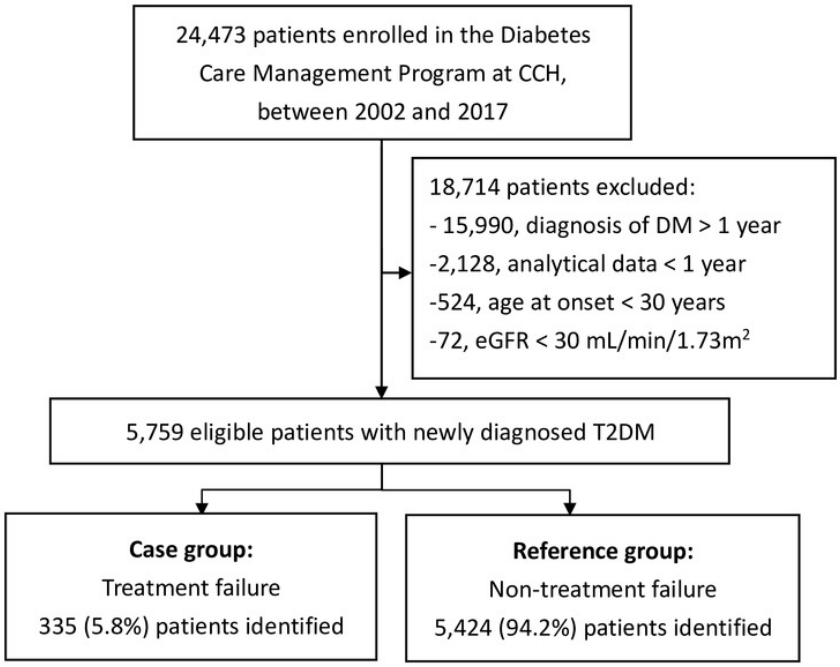
24,473 patients enrolled in the Diabetes Care Management Program at CCH, between 2002 and 2017
18,714 patients excluded:
- 15,990, diagnosis of DM > 1 year
-2,128, analytical data < 1 year
-524, age at onset < 30 years
-72, eGFR < 30 mL/min/1.73m2
5,759 eligible patients with newly diagnosed T2DM
Case group:
Treatment failure
335 (5.8%) patients identified
Reference group:
Non-treatment failure
5,424 (94.2%) patients identified

Table 1(on next page)

Basic characteristics of newly-diagnosed type 2 diabetes patients: TF vs non-TF group.

Notes.

[a] Odds ratio was calculated by per 10 units increase.

Abbreviations: TF, treatment failure; Non-TF, Non-treatment failure; SD, standard deviation; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; GC, glycemic control; HbA1c, hemoglobin A1c; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; GPT, glutamic pyruvic transaminase; OAD, oral anti-diabetic drug; CCI, Charlson comorbidity index; CHF, congestive heart failure; CAD, coronary artery disease; CVA, cerebrovascular accident

	TF n = 335, n (%)	Non-TF n= 5424, n (%)	OR (95% CI)	*p*
Age at onset (years), mean ± SD	51.9 ± 10.7	56.2 ± 11.9	0.97 (0.96, 0.98)	<0.01
Gender: Male,	168 (50.2%)	2902 (53.5%)	0.87 (0.70, 1.09)	0.23
Level of education: No	59 (17.6%)	640 (11.8%)	1	
Primary school	121 (36.1%)	1806 (33.3%)	0.73 (0.53, 1.00)	0.05
High school	121 (36.1%)	2091 (38.55%)	0.63 (0.45, 0.87)	0.01
University or above	34 (10.2%)	887 (16.35%)	0.42 (0.27, 0.64)	<0.01
Family history of DM: Yes	137 (40.9%)	2347 (43.27%)	0.91 (0.72, 1.14)	0.39
Current smoking	72 (21.5%)	863 (15.91%)	1.45 (1.10, 1.90)	0.01
Alcohol drinking	15 (4.5%)	356 (6.56%)	0.67 (0.39, 1.13)	0.13
Physical activity: No exercise	220 (67.5%)	2813 (52.31%)	1	
Occasional exercise	45 (13.8%)	913 (17.0%)	0.63 (0.45, 0.88)	0.01
Regular exercise	61 (18.7%)	1652 (30.7%)	0.47 (0.35, 0.63)	<0.01
Knowledge regarding GC: Yes	133 (44.2%)	3222 (64.3%)	0.44 (0.35, 0.55)	<0.01
Willingness toward DSM: Yes	248 (79.5%)	4513 (85.7%)	0.65 (0.49, 0.86)	0.003
Perform SMBG: Yes	37 (11.0%)	1411 (26.01%)	0.35 (0.25, 0.50)	<0.01
Medication adherence: Yes	301 (89.9%)	5226 (96.35%)	0.34 (0.23, 0.49)	<0.01
Clinical variables, mean ± SD				
HbA1c at baseline (%)	10.6 ± 2.3	8.8 ± 2.6	1.25 (1.21, 1.30)	<0.01
BMI (kg/m^2)	26.3 ± 5.0	26.4 ± 4.2	0.99 (0.97, 1.02)	0.65
Mean BP (mmHg)	97.9 ± 0.7	96.5 ± 0.2	1.01 (1.00, 1.02)	0.04
Total cholesterol (mg/dL)	201.7 ± 51.4	182.8 ± 41.9	1.09 (1.07, 1.11) [a]	<0.01
Triglycerides (mg/dL)	200.6 ± 218.5	153.6 ± 140.7	1.01 (1.01, 1.02) [a]	<0.01
HDL-C (mg/dL)	49.3 ± 27.2	46.87 ± 12.4	1.01 (1.00, 1.02)	0.01
LDL-C (mg/dL)	118.64 ± 38.8	107.64 ± 33.68	1.09 (1.06, 1.12) [a]	<0.01
eGFR (mL/min/1.73m^2)	97.58 ± 61.45	91.62 ± 31.17	1.04 (1.01, 1.07) [a]	0.01
GPT (U/L)	40.16 ± 36.17	33.35 ± 31.24	1.04 (1.02, 1.07) [a]	<0.01
Anti-diabetic Medications				
None or OAD alone	247 (73.5%)	4771 (88.0%)	1	
Insulin alone	25 (7.5%)	141 (2.6%)	3.42 (2.20, 5.34)	<0.01
OAD+ insulin	63 (18.8%)	51 2(9.4%)	2.38 (1.78, 3.18)	<0.01
Anti-hypertension agent(s)	162 (48.4%)	2847 (52.5%)	0.85 (0.68, 1.06)	0.14
Use of statins	187 (55.8%)	2981 (55.0%)	1.04 (0.83, 1.29)	0.76
Use of fibrates	52 (15.5%)	623 (11.5%)	1.42 (1.04, 1.93)	0.03
Comorbidity: CCI, mean ± SD	1.7 ± 1.2	1.9 ± 1.3	0.91 (0.82, 1.00)	0.05
CHF	30 (9.0%)	663 (12.2%)	0.71 (0.48, 1.04)	0.08
CAD	24 (7.2%)	425 (7.8%)	0.91 (0.59, 1.39)	0.66
CVA	17 (5.1%)	368 (6.8%)	0.73 (0.45, 1.21)	0.23

1

2

Table 2(on next page)

Models to predict treatment failure by multivariable logistic regression analysis using backward elimination method. Model 1: All study participants; Model 2: Subgroup analysis of patients with baseline HbA1c ≥ 8%.

Notes.

[a] Odds ratio was calculated by per 10-unit increase.

Abbreviations: OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; GC, glycemic control; SMBG, self-monitoring of blood glucose; BP, blood pressure; OAD, oral anti-diabetic drug; AUC, area under curve.

1

	Model 1 (n = 5759)		**Model 2 (n = 3059)**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
HbA1c (at baseline)	1.20 (1.15, 1.26)	<0.001	1.03 (0.96, 1.1)	0.46
Age at onset (years)	0.95 (0.94, 0.96)	<0.001	0.95 (0.93, 0.96)	<0.001
Level of education: None	1		1	
Primary school	0.59 (0.41, 0.86)	0.007	0.62 (0.41, 0.94)	0.025
High school	0.34 (0.22, 0.53)	<0.001	0.3 (0.18, 0.48)	<0.001
University or above	0.24 (0.14, 0.43)	<0.001	0.2 (0.11, 0.37)	<0.001
Physical activity: No exercise			1	
Occasional exercise			0.85 (0.58, 1.25)	0.42
Regular exercise			0.69 (0.49, 0.98)	0.038
Knowledge regarding GC: Yes	0.72 (0.55, 0.94)	0.016		
Perform SMBG: Yes	0.38 (0.25, 0.57)	<0.001	0.26 (0.17, 0.41)	<0.001
Medication adherence: Yes	0.45 (0.27, 0.75)	0.002	0.41 (0.24, 0.72)	0.002
Total cholesterol (mg/dL)	1.04 (1.01, 1.06) [a]	0.007		
Triglyceride (mg/dL)			1.01 (1.00, 1.01) [a]	0.017
Anti-diabetic medications:				
None/OAD alone	1		1	
Insulin alone	2.94 (1.76, 4.89)	<0.001	2.32 (1.32, 4.09)	0.003
OAD+ insulin	2.43(1.72, 3.43)	<0.001	2.27 (1.56, 3.29)	<0.001
AUC for model	0.781		0.739	
R-square	0.161		0.131	

Table 3(on next page)

Correlations between demographic variables and self-care factors for diabetes management.

Kendall’s tau rank correlation coefficient (r) was used.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Abbreviations: GC, glycemic control; DSM, diabetes self-management; SMBG, self-monitoring of blood glucose.

Variables	2	3	4	5	6	7	8
1. Education level	0.21***	0.07***	0.034**	0.077***	0.15***	−0.43***	0.26***
2. Knowledge regarding GC	—	0.14***	0.061***	0.21***	0.31***	−0.039**	0.04**
3. Willingness toward DSM		—	0.036**	0.053***	0.12***	−0.004	−0.01
4. Medication adherence			—	0.049***	0.047***	0.005	0.017
5. Physical activity				—	0.15***	0.087***	0.029*
6. Perform SMBG					—	−0.039***	0.053***
7. Age (years)						—	−0.09***
8. Gender (Men)							—

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