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Assessing the Association between Anti-Diabetic Medication Adherence and Glycemic Control in Type 2 Diabetes

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Abstract

Objective: Adherence to anti-diabetic medications in diabetic patients plays a considerable role in glycemic control, prevention of short-term and long-term morbidities, and diabetes-related mortality. The current study aims to evaluate the factors associated with adherence to medications among patients with type 2 diabetes.

Materials and Methods: The current study was conducted on 366 diabetic patients who were referred to the Institute of Endocrinology and Metabolism. The HbA1C was measured at baseline and then after six months. The validated questionnaire on adherence to refills and medication scale (ARMS) was filled, and factors associated with medication adherence were assessed. The higher ARMS scores represented poorer adherence to the medication.

Results: Diabetic patients with adherence to anti-diabetic agents represented significantly lower levels of HbA1C both at baseline ($P< 0.001$) and the six-month follow-up ($P< 0.001$) compared to the non-adherent group. In the correlation analyses, the ARMS score was significantly correlated with the A1C levels measured at the baseline (rs= 0.37, $P< 0.001$) and after 6 months (rs= 0.40, $P< 0.001$) as well as the duration of diabetes (rs= 0.16, $P= 0.003$). The subsequent logistic regression analysis highlighted the use of insulin as the main determinant of adherence to medications (OR: 0.59; 95%CI: 0.35-0.99), after controlling for age, gender, diabetes duration and number of medications.

Conclusion: The current study revealed that adherence to the anti-diabetic medication is associated with remarkably improved glycemic control. Diabetes duration and insulin use were inversely correlated with adherence to medication, while there was no association with age, gender, numbers of drugs.

Keywords: Type 2 diabetes, Medication adherence, Glycemic control

QR Code

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Introduction

The progressive trend in the prevalence and related complications of type 2 diabetes mellitus (DM) has made this metabolic disorder among the most critical health concerns of the 21st century. Because of the ongoing increase in the number of patients with the DM diagnosis, plus the more novel issues of aging and obesity, the world will face 693 million diabetic cases by 2045, among who most are living in low-to-middle-income communities (1,2).

The chronic nature of DM leads to several micro- and macro-vascular related morbidities, and mortality (3-6) that are directly associated with improper blood sugar control; an issue that poses a considerable burden on individuals, families, healthcare systems and eventually, communities (7).

The current recommendations for glycemic control indicate HbA1C as the hallmark for blood sugar management, while age and duration of illness are considered, as well (8); however, HbA1C levels of greater than 9% are universally well-known for poor glycemic control (9). In a previous study conducted in our center, only 42% of patients had HbA1c< 7(10).

Although all the evidence supports the significance of hypoglycemic medication use for glycemic control, prevention of long-term complications and the improvement of quality of life, the patients' inappropriate adherence to medications has remained a notifying concern worldwide as far as most of the reports in the literature have represented poor-to-low levels of adherence (11-15). Further evaluations have revealed that young age in diabetic patients and long-term diabetes are the factors related to increased risk of poor glycemic control, although the associated factors are not well understood (5,16-18).

It is known that the factors associated with poor medication adherence may be affected by culture and ethnicity. Accordingly, the current study aimed to assess the patients' adherence to anti-diabetic treatments, and the associated risk factors for poor medication adherence.

Material and methods

Participants

The current cohort study was conducted on 366 diabetic patients who were referred to the Institute of Endocrinology and Metabolism, Iran University of Medical Sciences from April 2018 to July 2019.

The study population consisted of patients with type 2 diabetes, aged 30-80 years-old who were under either oral anti-hyperglycemic agents, insulin or both. The diagnostic criteria for diabetes mellitus were based on the American Diabetes Association definitions. Patients with type 1 diabetes were excluded.

Measures

The patients' serum levels of HbA1C were measured before study initiation in order to assess the basal status of the glycemic state, and then the laboratory test was performed after 6 months. All the tests were sent to a reference laboratory to minimize the probability of bias. Enzymatic assays were performed to measure the serum levels of HbA1C by pishtazteb kits (pishtazteb. Co., Iran). Moreover, the study population adherence to anti-diabetic medications was evaluated using the Persian validated questionnaire of adherence to refills and medications scale (ARMS). Patients' responses to the questionnaire were collected using both methods: direct self-completion by the patient or interviews, depending on their level of literacy and understanding of the questions.

The ARMS consists of 12 items divided into two subscales of adherence to refilling prescriptions and adherence to taking medications. These 12 items are assessed through 12 questions with Likert scale responses, including "none," "some," "most," and "all" of the time. The values are given from 1 to 4, thus the final scores range from 12 to 48

(19). The score of 12 was considered as adherent; otherwise, the patients were defined as non-adherent to medication. The higher scores represented poorer adherence to the medication; therefore, the correlations have been measured inversely.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: IBM Corp; 2015). The descriptive data were presented as mean±SD, median (IQR) for skewed data, or n (% within group) for categorical variables. Within-group comparisons were performed using Wilcoxon-rank test. Between-group comparisons were performed using independent sample T-test and non-parametric Mann-Whitney U test, as appropriate. Categorical data were compared using χ^2 test or Fisher Exact test. A Spearman's correlation analysis was undertaken to examine the correlations of the adherence to medications with various variables of interest. The main predictors of medication adherence were then explored using logistic regression analyses. For performing these analyses, adherence to medication was entered in the models as the dependent (binary) variable, with use of insulin, duration of diabetes, age, gender and the number of medications taken per day as covariates. All tests were 2-tailed, and P-value of less than 0.05 was considered as the significant level.

Ethical considerations

The study was ethically approved by the Ethics Committee (EC) of the Institutional Review Board (IRB) of the Iran University of Medical Science; with a reference number of IR.IUMS.FMD.REC.1402.483.

Participants were asked for both written and verbal consent forms, and after the objectives of the study were briefed, consent was accessed to interview them. Confidentiality was kept and sufficiently anonymized, and the study was conducted according to the Helsinki legislation

Results

In the present study, the adherence to anti-diabetic medications was evaluated in 366 diabetic patients who started the study; among which 201 patients (54.9%) were female and the remaining 165 ones (45.1%) were male (Table 1). The mean (±SD) age of the study population was 60.11(±9.48) years old (range: 34-86 years old), with the median (IQR) diabetes mellitus duration of 10 (6.0-19.5) years. All 366 participants completed the study, with 239 (65.3%) of being adherent to the medications; whereas, the other 127 ones (34.7%) were not adherent.

As presented in Table 2, participants in the adherent and non-adherent groups were comparable in terms of age (P= 0.88) and gender (P= 0.42). However, diabetic cases who were adherent to the medications had a significantly shorter duration of diabetes compared to those in the non-adherent group [10.0 (5.0-18.0) vs.14.0 (8.0-20.0) years, P= 0.004]

In addition, there was a significant difference between the adherent and non-adherent groups in terms of taking anti-hyperglycemic medications. Namely, while 47.2% of participants in the non-adherent group were on insulin therapy (with or without oral anti-diabetic medications); this rate was only 32.2% among the patients with adherence to medications (P= 0.006). Moreover, the levels of HbA1C were remarkably higher among the non-adherent to the medication cases, than those in the adherent group, both at the baseline [6.8% (6.2-7.5) vs. 7.8% (7.0-8.8), P< 0.001] and by the end of the study [6.7% (6.2-7.5) vs. 8.0% (7.0-8.9), P< 0.001]. However, the comparison of baseline HbA1C levels with the end of the study revealed no significant change neither in the diabetic patients who were adherent to the medications nor among the non-adherent ones (Figure 1).

Among the parameters evaluated in the correlation analyses, the ARMS score was significantly correlated with the A1C levels measured at the baseline (rs= 0.37, P< 0.001) and after 6 months (rs= 0.40, P< 0.001) as well

as the duration of diabetes mellitus (rs= 0.16, *P*= 0.003).

The subsequent logistic regression analysis highlighted both the use of insulin (OR: 0.49; 95% CI: 0.30-0.79) and duration of diabetes (OR: 0.96; 95% CI: 0.94-0.99) as the main determinants of adherence to medications, after adjusting for age, gender and number of medications per day (Table 2, Model 1&2). Although only the use of insulin remained as the significant predictor, when both these variables were included in the multivariate model (Table 2, Model 3). Accordingly, diabetic patients taking insulin had a 41% reduction in the odds of adherence to the anti-hyperglycemic medications compared to those who were not on insulin therapy (OR: 0.59; 95% CI: 0.35-0.99).

Discussion

Existing evidence supports the efficacy of antihyperglycemic agents in helping diabetic patients control both their short- and long-term glycemic levels.

Table 1. Demographic, medical and clinical characteristics of participants in the study groups

Variable	Total	Adherent group (n=239)	Non-adherent group (n=127)	*P*-value
Age (years)	60.11±9.5	60.17±9.43	60.02±9.59	0.88
Less than 60 years old (%)	188 (51.4)	123 (51.5)	65 (51.2)	0.96
Gender, n (%)				
Male	165 (45.1)	111 (46.4)	54 (42.5)	0.47
Female	201 (54.9)	128 (53.6)	73 (57.5)	
Duration of diabetes (y)	10.0 (6.0-19.0)	10.0 (5.0-18.0)	14.0 (8.0-20.0)	0.004
Baseline HbA1C (%)	7.1 (6.4-8.0)	6.8 (6.2-7.5)	7.8 (7.1-8.8)	<0.001
HbA1C after 6 months (%)	7.1 (6.3-8.0)	6.7 (6.2-7.5)	8.0 (7.1-8.9)	<0.001
Medical history				
Hypertension, n (%)	228 (62.3)	157 (65.7)	71 (55.9)	0.07
Dyslipidemia, n (%)	301 (82.2)	192 (80.3)	109 (85.8)	0.19
Ischemic heart disease, n (%)	29 (7.9)	15 (6.3%)	14 (11.0)	0.11
Medications, n (%)				
Antihypertensive agents	226 (61.7)	153 (64.0)	73 (57.5)	0.22
Statins	301(82.2)	195 (81.6)	106 (83.5)	0.66
Aspirin	128 (35)	86 (36.0%)	42 (33.1)	0.57
Only oral antihyperglycemic agents	339 (92.6)	159 (66.5)	67 (52.8)	
Only insulin	137 (37.4)	10 (4.2)	14 (11.0)	0.006
Insulin+oral Antihyperglycemic agents	113 (31)	67 (28.0)	46 (36.2)	
Number of different agents taken daily, n (%)				
0	1(0.2)	1 (0.4)	0 (0)	
1	24 (6.6)	18 (7.5)	6 (4.7)	
2	76 (20.8)	52 (21.8)	24 (18.9)	0.15
3	131 (35.8)	75 (31.4)	56 (44.1)	
≥4	134 (36.6)	93 (38.9)	41 (32.2)	

Continuous variables are expressed as mean±SD or as median (IQR) for skewed data. Categorical variables are presented as n (% within group). Between-group comparisons were performed using independent sample t-test and non-parametric Mann-Whitney U test for normally distributed and skewed data, respectively. Categorical data were compared using χ^2 test or Fisher Exact test.

Table 2. The result of logistic regression analysis assessing the predictors of adherence to anti-hyperglycemic medications.

Variables		B	S.E	*P*-value	Odds Ratio	95% CI for OR	
						Lower	Upper
Model 1	The use of insulin	-0.71	0.24	0.004	0.492	0.305	0.793
Model 2	Duration of diabetes	-0.037	0.01	0.005	0.963	0.939	0.989
Model 3	The use of insulin	-0.528	0.26	0.04	0.590	0.353	0.986
	Duration of diabetes	-0.027	0.01	0.06	0.973	0.947	1.001

All multivariate models were adjusted for age, gender and the number of medication taken per day.

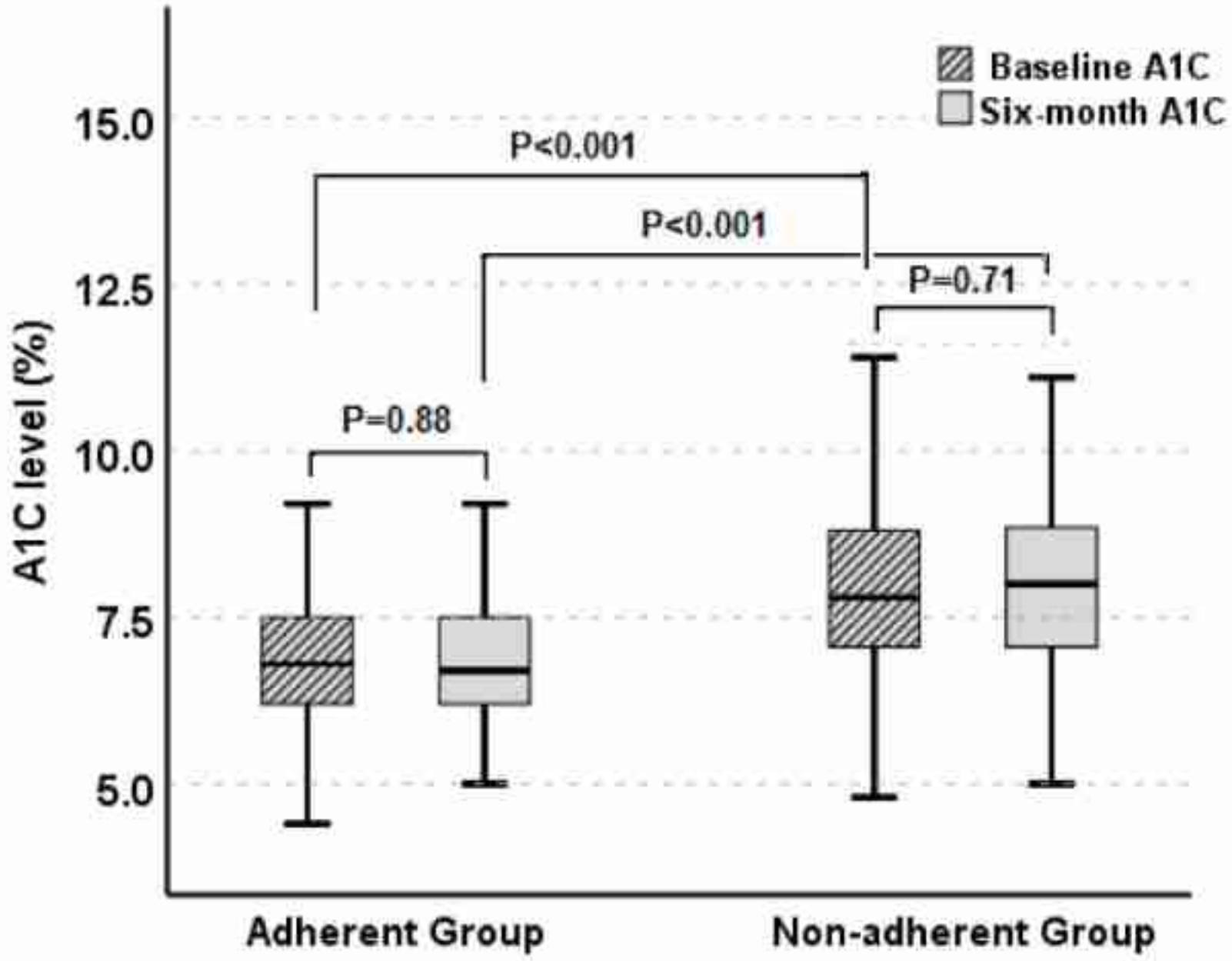

Figure 1. The comparison of hemoglobin A1C levels between the adherent and non-adherent groups

Existing evidence supports the efficacy of antihyperglycemic agents in helping diabetic patients control both their short- and long-term glycemic levels. This, in turn, delays diabetes-related complications and improves both quality of life and overall life expectancy. The definition of "good adherence" to anti-diabetic medications varies widely in the literature, ranging from 38% to 84% (8,11,12,14,20,21).

In the present study, we found that 65.3% of patients demonstrated acceptable adherence. Considering that Iran is a developing country, this adherence rate appears reasonable, particularly in comparison to studies conducted in developed countries, where diabetes management benefits from better follow-up schedules (21-23).

Consistent with most studies in the literature (6,8,24), we observed a direct association between medication adherence and HbA1c levels, a key long-term indicator of glycemic control. Our findings were further validated through a re-evaluation and comparison of HbA1c levels between adherent and non-adherent patients over the following six months.

In agreement with the current study, Osen et al. conducted a retrospective research on 19600 patients with type 2 diabetes and evaluated the role of adherence to the anti-diabetic medications in glycemic control. They defined regular drug use of more than 80% within the past 12 months prior to the HbA1C measurement, as high medication adherence and found a direct correlation between glycemic control and adherence to medications through a one-year follow-up study (25). Similar results were also reported by Holman et al. performing a 10-year follow-up study and by Sokol et al. in another 12-month follow-up study (27). Nevertheless, some of the studies have opposed a theory about the correlation of HbA1C levels with adherence to the medications (28,29); a finding that has probably occurred due to the small number of study populations or the follow-up period in which adherence to the medications was assessed.

Assessing the association between demographic, clinical and medical characteristics of diabetic patients with adherence to the medications revealed that insulin use and duration of diabetes were

inversely correlated with medication adherence.

These findings are in agreement with previous studies; as the chronic nature of diabetes may lead to exhaustion from drug use and, therefore, cause the patients who are struggling with diabetes for a long time to withdraw their medications (30). Capoccia et al. (15) and Juarez et al. (18) have mentioned duration of diabetes as an independent factor associated with poor medication adherence in diabetic cases, while Krass opposed (31). Furthermore, the latter finding about the inverse correlation between insulin use and medication adherence is in line with previous studies that represented better medication adherence among those under oral hypoglycemic agents treatment as compared to insulin therapy. The negative insight about the use of insulin, as well as fear of injections, embarrassment from injections in public and negative views about the lifelong use of insulin are the major causes of reluctance to insulin use (31-33). It should be noted that insulin is prescribed for those patients with poor glycemic state only, a condition that is usually a reflection of poor oral medication adherence, lifestyle and dietary habits.

Polonski and Henry ignited a thesis to investigate the scopes of poor medication adherence in different dimensions. Initially, they divided the factors into two subgroups of patient-dependent and non-patient-dependent ones. Insurance, accessibility to care centers and follow-up schedules by the healthcare system were the non-patient-related factors; while demographics, beliefs and medication-related factors were the other group. They eventually recommended evaluating the role of modifiable factors in medication non-adherence, to achieve ways in the management of them for preventing diabetes adverse effects occurring due to medication non-adherence (21).

One of the most significant factors which inversely contributed to medication adherence is medication complexity; however, we found no correlation between the number of utilized remedies per day and medication adherence; Claxton et al. found that the use of agents once a day led to adherence in 79% of the patients, while increasing the dosage to four times a day resulted in only 51% adherence (34). This finding has been confirmed by other investigations, as well (35-37). The discrepancy between our results with previous studies could be due to the fact that we just assessed the total number of agents that were prescribed and did not evaluate how often they were used per day.

Although we found no role for the age of the patients to be adherent to their medications, most of the studies in the literature have shown an inverse association (12,23), a fact that is a considerable concern for most patients with type 1 diabetes, who are mostly younger than type 2 cases (33). Most of the studies in the literature have shown that younger patients are more non-adherent to their medications, but none have assessed the probable causative role of age, a factor that should be evaluated due to the ability of younger cases to perform social chores (20,38).

Concurrent hypertension or ischemic heart disease and gender were other factors that were found irrelevant to medication adherence. Gender is one of the factors that most of the studies in the literature have not declared any correlation with medication adherence (31); however, there are a few reports representing better adherence among females (39). The correlation between types of administered agents per day and medication adherence in diabetes has not been well-investigated.

Of the limitations of the current study are its small sample population and short-term design. Besides, some confounding factors with possible effects on medication adherence or glycemic control (e.g. diet) may be missed. Further investigations are strongly recommended.

Conclusions

The current study revealed that adherence to the anti-diabetic medication is associated with remarkably improved glycemic control. Duration of diabetes and insulin use were inversely correlated with diabetic patients' medication adherence, while there was no association with age, gender, number of drugs.

This health concern of non-adherence should be a priority agenda for policy makers and researchers, who can make a great contribution to a reduction of it through collaboration with healthcare providers and patients.

Health facility is recommended to provide health education to T2DM patients, targeting patients with suboptimal adherence for intensified adherence counseling, which is essential for promoting health of patients with diabetes. More efforts are needed to increase adherence to medication by training healthcare providers about an effective communication with patients and health education to reinforce patients in knowing the full benefits of prescribed therapies.

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None.

Conflict of Interest

The authors declare that they have no competing interests.

Authors' contributions

A.VM: Conceived and designed the analysis, contributed data or analysis tools and wrote the paper.

F.ASh and F.G: Collected the data and performed the analysis.

MA.M and B.D and R.Sh: Collected the data and wrote the paper.

S.M: Conceived and designed the analysis and performed the analysis.

All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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