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# Relationship between medication adherence and glycemic control in Japanese patients with type 2 diabetes

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A cross-sectional survey of 358 patients was conducted among type 2 diabetes patients recruited at medical institutions or via an online research company. Medication adherence was measured using the 8-item Morisky Medication Adherence Scale (MMAS-8). Univariate and multivariate regression analyses of glycosylated hemoglobin ($HbA_{1c}$) were performed in addition to assessing demographic and disease characteristics and MMAS-8. In conclusion, medication adherence as measured by the MMAS-8 score independently contributes to altering the $HbA_{1c}$ level in the range of 1.12 %. The number of medications prescribed and insulin use are also related to $HbA_{1c}$.

## 1. Introduction

The increasing population of diabetic patients, with approximately 415 million in 2015 and 642 million expected in 2030 worldwide, is a global burden (http://who.int/diabetes/global-report/en/). The prevalence of diabetes in Japan among those aged 20 to 79 years is 10.1 %, which is higher than in many other countries: Korea, 9.5 %; China, 9.4 %; U.S.A., 9.1 %; France, 8.0 %; U.K., 7.7 %; and Germany, 7.4% (http://www.who.int/diabetes/country-profiles/en/). Those receiving treatment for diabetes in Japan total 3.16 million patients, which is only one-third of potential patients but among the highest in the periodic national surveys performed every three years (http://www.mhlw.go.jp/toukei/saikin/hw/kanja/14/index.html).

From around 2010, various new classes of medications, i.e., dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 agonists, sodium-glucose co-transporter 2 inhibitors, and their combinations, became available and contributed to better control of glycemic levels. According to a large-scale nationwide consecutive survey conducted by the Japan Diabetes Clinical Data Management Study Group (JDDM) (http://jddm.jp/), the mean glycosylated hemoglobin ($HbA_{1c}$) level has gradually decreased. However, that of patients with type 2 diabetes increased slightly after the lowest value of 6.9 % had been recorded in 2013. The proportion of patients who do not achieve the glycemic target is 43.8 % (http://jddm.jp/). Similarly, insufficient $HbA_{1c}$ levels in 9 European countries average 46.4 % (Stone et al. 2013). Considering that the average compliance with treatment guidelines was reported to be 42.8 % (Khunti et al. 2018), the availability of effective medications alone cannot resolve the problems in diabetic patient care.

Patient-related factors should therefore be addressed, particularly medication adherence because "medication adherence is the primary reason for suboptimal clinical benefit of therapy" (http://www.who.int/chp/knowledge/publications/adherence_report/en/). The adherence rate was reported to vary from 38.5 to 93.1 %, and only 6 of 27 studies (22.2 %) reported 80 % or higher rates of adherence (Krass et al. 2015). Some studies in diabetic patients revealed that male gender, younger age, medication complexity, depression, and medication expenditure are associated with insufficient adherence to given medication regimens (Chao et al. 2005; Cohen et al. 2010; Kreyenbühl et al. 2010; Wong et al. 2011; Bailey et al. 2012; Raum et al. 2012). There is no doubt that improving adherence to medication is imperative to achieve the expected clinical benefits of pharmacotherapy. However, knowledge of the effect of medication adherence on $HbA_{1c}$ levels is limited.

In this study, we attempted to identify the extent to which medication adherence independently contributes to altering glycemic control using a validated self-administered questionnaire based on psychometric properties.

## 2. Investigations and results

### 2.1. Study population

A total of 358 patients were included in the analysis. The demographic and disease characteristics of the participants analyzed, in addition to the 8-item Morisky Medication Adherence Scale (MMAS-8) scores, are shown in Table 1. Two hundred and eighteen (60.9 %) were men, and the mean (±SD) of age, diabetes duration, number of medications (for diabetes), MMAS-8 scores, and $HbA_{1c}$ levels were 60.3±11.7 years, 12.2±8.9 years, 2.1±1.1 medications, MMAS-8 6.5±1.6, and 7.2±1.0 %, respectively. By type of channel, 212 participants (59.2%) were enrolled directly and 146 (40.8 %) indirectly. Those who enrolled *via* the indirect channel included more men, were younger, used insulin less often, and were less likely to have family members with diabetes than those enrolled *via* the direct channel.

### 2.2. Factors associated with glycemic control

Univariate and multivariate regression analyses of $HbA_{1c}$ levels are presented in Table 2. In univariate regression analysis, the number of medications (beta 0.26, 95 % CI 0.15 to 0.34, $p < 0.001$), insulin use (beta 0.23, 95 % CI 0.17 to 0.42, $p < 0.001$), and experience of hypoglycemia (beta 0.11, 95 % CI 0.01 to 0.27, $p = 0.031$) were positively and MMAS-8 score (beta –0.16, 95 % CI –0.18 to –0.04, $p = 0.002$) was negatively correlated with $HbA_{1c}$ levels. In multivariate regression analysis, the number of medications (beta 0.19, 95% CI 0.08 to 0.28, $p < 0.001$) and insulin use (beta 0.16, 95% CI 0.07 to 0.34, $p = 0.003$) were positively and MMAS-8 score (beta –0.13, 95% CI –0.15 to –0.02, $p = 0.012$) was negatively correlated with $HbA_{1c}$ levels. The direct or indirect recruiting channel was not significantly associated with $HbA_{1c}$ levels in either univariate or multivariate regression analysis.

**Table 1: Participants' background characteristics**

| | | Total ($n$ = 358) | Direct channel (n=212) | Indirect channel (n=146) |
|---|---|---|---|---|
| Male, $n$ (%) | | 218 (60.9) | 116 (54.7) | 102 (70.0) |
| Age (years, mean±SD) | | 60.3 ± 11.7 | 64.3 ± 11.7 | 54.6 ± 9.5 |
| BMI (%, mean±SD) | | 25.5 ± 5.2 | 24.7 ± 4.6 | 26.8 ± 5.8 |
| Diabetes duration (years, mean±SD) | | 12.2 ± 8.9 | 12.7 ± 9.6 | 11.4 ± 7.8 |
| Number of medications (mean±SD) | | 2.1 ± 1.1 | 2.3 ± 1.1 | 1.9 ± 1.2 |
| Oral Medications, $n$ (%)[a] | dipeptidyl peptidase 4 inhibitors | 187 (52.7) | 124 (58.5) | 63 (44.1) |
| | biguanides | 144 (40.6) | 82 (38.7) | 62 (43.4) |
| | sulfonylurea | 98 (27.6) | 67 (31.6) | 31 (21.7) |
| | α-glucosidase inhibitors | 64 (18.0) | 41 (19.3) | 23 (16.1) |
| | sodium-glucose cotransporter 2 inhibitors | 50 (14.1) | 25 (11.8) | 25 (17.5) |
| | combination drugs | 40 (11.3) | 29 (13.7) | 11 (7.7) |
| Insulin use, $n$ (%) | | 78 (22.0) | 54 (25.5) | 24 (16.8) |
| Hypoglycemia (within past year), $n$ (%) | | 85 (23.7) | 55 (25.9) | 30 (20.6) |
| Drug-related side effects, $n$ (%) | | 84 (23.4) | 50 (23.6) | 34 (23.3) |
| Diabetes patients in family, $n$ (%) | | 177 (50.0) | 115 (55.3) | 62 (42.5) |
| MMAS-8 score (mean±SD)[b] | | 6.5 ± 1.6 | 6.6 ± 1.5 | 6.4 ± 1.7 |
| $HbA_{1c}$ level, % (mean±SD) | | 7.2 ± 1.0 | 7.3 ± 1.0 | 7.2 ± 1.1 |
| | 7.0% =<, $n$ (%) | 190 (53.0) | 113 (53.3) | 77 (52.7) |

[a]Indicated only 10% or more prevalence. Excluded unknown cases (Indirect, n = 3).
[b]MMAS-8: 8-item version of Morisky Medication Adherence Scale.

**Table 2: Factors associated with glycemic control ($HbA_{1c}$ level)**

| Independent variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Beta[a] | 95% CI | $p$ value | Beta[a] | 95% CI | $p$ value |
| Gender: Male | 0.03 | (–0.07, 0.15) | 0.516 | — | — | — |
| Age (years) | 0.00 | (–0.07, 0.15) | 0.960 | — | — | — |
| BMI (%) | 0.09 | (–0.07, 0.15) | 0.098 | — | — | — |
| Diabetes duration (years) | 0.07 | (–0.00, 0.02) | 0.174 | — | — | — |
| Number of medications | 0.26 | (0.15, 0.34) | <0.001 | 0.19 | (0.08, 0.28) | <0.001 |
| Insulin use: Yes | 0.23 | (0.17, 0.42) | <0.001 | 0.16 | (0.07, 0.34) | 0.003 |
| Hypoglycemia (within past year): Yes | 0.11 | (0.01, 0.27) | 0.031 | — | — | — |
| Drug-related side effects: Yes | 0.06 | (–0.06, 0.20) | 0.274 | — | — | — |
| Diabetes patients in family: Yes | –0.00 | (–0.11, 0.11) | 0.964 | — | — | — |
| MMAS-8 score[d] | –0.16 | (–0.18, –0.04) | 0.002 | –0.13 | (–0.15, –0.02) | 0.012 |
| Recruiting channel: Indirect | –0.03 | (–0.14, 0.08) | 0.573 | — | — | — |

[a]Standardized coefficient of regression model.
[b]MMAS-8: 8-item version of Morisky Medication Adherence Scale.

## 3. Discussion

Linear regression analysis of $HbA_{1c}$ levels showed that the MMAS-8 score was an independent distinguishing modifier for glycemic control. Its beta value in multivariate regression (–0.13) indicates that a one-point MMAS-8 score difference is equivalent to a change of approximately –0.13 % in $HbA_{1c}$. This is relatively small but was confirmed to be an independent variable together with the other key variables of number of medications and insulin use. The intervariability of the entire range of MMAS-8 scores of 0 to 8 is comparable to a 1.12 % difference in $HbA_{1c}$ level, which is clinically meaningful.

This study was not longitudinal but cross-sectional and thus we cannot confirm a direct causal relationship between medication adherence and $HbA_{1c}$ level. However, many interventional studies in diabetes patients demonstrated that improved adherence was relevant to lower $HbA_{1c}$ (Odegard et al. 2005; Al Mazroui et al.

**Table 3: Question items of medication adherence (MMAS-8)[a]**

| | |
|---|---|
| Q1 | Do you sometimes forget to take your diabetic medication(s)? |
| Q2 | People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your diabetic medication(s)? |
| Q3 | Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it? |
| Q4 | When you travel or leave home, do you sometimes forget to bring along your diabetic medication(s)? |
| Q5 | Did you take your diabetic medication(s) yesterday? |
| Q6 | When you feel like your blood glucose is under control, do you sometimes stop taking your medication(s)? |
| Q7 | Taking medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your diabetic treatment plan? |
| Q8 | How often do you have difficulty remembering to take all your medication(s)? |

[a]MMAS-8: 8-item version of Morisky Medication Adherence Scale. The MMAS (8-item) content, names and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, 294 Lindura Court, Las Vegas, NV 89138-4632; USA; dmorisky@gmail.com.

2009; Maryam et al. 2010; Wolever et al. 2010; Bogner et al. 2012; Arora et al. 2014). In the two studies using the MMAS-8, the average changes in MMAS-8 score and $HbA_{1c}$ level were +0.9 point and –1.1 % (Arora et al. 2014) and +0.5 point and –0.4% (Wolever et al. 2010), respectively. Those results were interpreted to mean that changes in $HbA_{1c}$ per point in the MMAS-8 score were –1.2% and –0.8%, respectively. Possible reasons why these values were much greater than that in the current study are: (1) they represent aggregated effects of changes in medication behavior due to a lack of adjustment by co-variates; and (2) longitudinal behavioral change measured by psychometric properties like the MMAS-8 would have cascading effects on the $HbA_{1c}$ level. We assume that improving medication behavior involves actions like following a diet, exercising, or other lifestyle modifications, and such aggregated changes also contribute to significant improvement in $HbA_{1c}$ levels. Insufficient adherence jeopardizes the expected benefits from a given pharmacotherapy regimen, e.g., a 0.5–1.2 % reduction in $HbA_{1c}$ with dipeptidyl peptidase 4 inhibitors (Kaku et al. 2014a,b; Kashiwagi et al. 2014). As stated by Haynes et al. (2002), "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments", and therefore interventions to increase adherence are worthwhile.

In multivariate regression analyses, the number of medications showed evident linearity with the $HbA_{1c}$ level. In general, patients with diabetes who cannot manage their hyperglycemia with lifestyle modifications alone are started with monotherapy and, if that is not sufficient to lower $HbA_{1c}$ to a certain level, they are then prescribed combination therapy. Even though they are receiving pharmacotherapy, diabetes patients must watch their diets and exercise daily. Those who are treated with multiple medications should show cumulative pharmacological effects, but patients in this study did not exhibit such beneficial results. Medication complexity is one factor that decreases patients' adherence to medication (Kreyenbühl et al. 2010; Raum et al. 2012). In this study, those who received more medications consistently tended to be less adherent to their treatment regimens (data not shown). Possible reasons for this are that complicated regimens are troublesome or difficult to adhere to, lower adherence leads to poor glycemic control and then to the prescription of more medications; etc. It is also possible that those patients were less adherent not only to medication regimens but also to other self-care recommendations such as diet, exercise, smoking cessation, etc. and thus their $HbA_{1c}$ levels remained high, which would again cause physicians to prescribe additional medications. Conversely, if patients show enhanced medication adherence, they might also change their behavior for self-management of diet and exercise. Individual patients could have more than one reason for a lack of compliance with medication regimens and therefore should be monitored carefully by healthcare professionals in clinical practice.

Similarly, insulin use was also significantly associated with elevated $HbA_{1c}$ levels. According to the treatment guidelines specifically for elderly patients jointly issued by the Japan Diabetes Society and Japan Geriatrics Society (http://www.fa.kyorin.co.jp/jds/uploads/GL2016-19.pdf), 7.0 % is the general target for preventing diabetic complications but can be adjusted depending on individual patients' conditions. In practice, for patients aged 65–75 or 75 years taking insulin, sulfonylurea, or glinide agents associated with a higher risk of serious hypoglycemia, adjustment of the target $HbA_{1c}$ level to 7.5 or 8.0 %, respectively, is recommended. Due to this recommendation, physicians might have set the target $HbA_{1c}$ level higher for patients receiving such medications and/or who experienced an episode of hypoglycemia. This may be also the reason underlying the observed association between a previous episode of hypoglycemia and the $HbA_{1c}$ level in this study.

There were two limitations in this study. First, the questionnaire responses on $HbA_{1c}$ levels and medication regimens of participants recruited *via* the research company were completed by the patients themselves. Although they were requested to respond honestly to the questionnaire based on their own documented health records, it was not possible to ensure the validity of the responses by an independent source. Second, we were not able to collect information on the glycemic control target on an individual-patient basis. The general target of 7.0 % may be adjusted depending upon age, complications, risk of hypoglycemia, patients' personality, treatment motivation, etc. If a substantial number of such patients was included in this study, numerical analysis of linearity between medication adherence and $HbA_{1c}$ level would not be sufficient. Categorical analysis with nominal variables, i.e., "controlled" or "uncontrolled" based on the target determined for each patient, should be conducted.

In conclusion, medication adherence as measured by the MMAS-8 score independently contributes to altering the $HbA_{1c}$ level in the range of 1.12 %. The number of medications prescribed and insulin use are also related to $HbA_{1c}$.

## 4. Experimental

### 4.1. Participants and setting

The study participants were patients with type 2 diabetes receiving pharmacotherapy. They were recruited from among those visiting hospitals or community pharmacies (direct channel) or those registering with a Japanese online research company (indirect channel) between December 2016 and April 2017. The dual-channel recruitment method was employed because of the assumed age distribution in each, i.e., patients in the direct channel tended to be older and those in the indirect one to be younger, and thus the differences were expected to be complementary. The Ethics Committee on Human Research of the Faculty of Pharmacy, Keio University, approved this study protocol (approval nos. 161215-1 and 170120-1).

### 4.2. Measurements

Medication adherence was assessed using the validated Japanese version of the 8-item Morisky Medication Adherence Scale (MMAS-8) (Morisky et al. 1986, 2008; Morisky and DiMatteo 2011; Berlowitz et al. 2017), since it is widely used and was confirmed to be one of the most reliable self-administered questionnaires available (Clifford et al. 2014). Among the 8 questions, 7 are answered with "yes" or "no" and the 8th is answered with a 5-item Likert scale. Responses were coded by a designated rule and calculated for total scores between 0 to 8, with 8 indicating the most adherent. Glycemic control was represented by averaging at least three testing points of glycosylated hemoglobin ($HbA_{1c}$) obtained during the previous 12 months. Demographic and disease characteristics collected as background variables were age, gender, body mass index (BMI), duration of diabetes from diagnosis (diabetes duration), insulin use, number of diabetic medications, experience of hypoglycemia or drug-related side effects, and family history of diabetes.

### 4.3. Statistical analysis

We conducted both univariate and multivariate regression analyses of $HbA_{1c}$ as a continuous dependent variable. Independent variables were gender, age, BMI, diabetes duration, number of diabetic medications, insulin use (yes/no), experience of hypoglycemia (yes/no), experience of drug-related side effects (yes/no), family history of diabetes (yes/no), MMAS-8 score, and recruiting method (direct/indirect).

In multivariate regression analysis of $HbA_{1c}$ level, all the independent variables were unconditionally entered in the linear regression model, and a bidirectional stepwise algorithm was used on a threshold condition of a *p* value at 0.1
Dependent variables in regression analyses were indicated with standardized coefficients (beta), 95 % confidence intervals (CIs), and *p* values. All *p* values of less than 0.05 (2-sided test) were regarded as representing statistically significant differences. The JMP 13 statistical software package (SAS Institute Inc., Cary, NC, USA) was used for all data analyses.

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Authors' contributions: YT and MM conceived of and designed the present study and wrote the manuscript with support from TA, TH, DEM, and KT. YT performed the computations and analyses, and KT verified the analytical method. TA and TH aided in interpreting the results from the pharmaceutical practice viewpoint. DEM supervised the use of specific instruments and provided critical feedback on the results. All authors discussed the results and contributed to the final manuscript.

Conflict of interest: DEM receives an honorarium for use of the copyrighted and trademarked MMAS-8 diagnostic adherence assessment instrument. The other authors declare that they have no competing interests.

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