Clinical backgrounds associated with discrepancy between subjective and objective assessments of medication adherence in Japanese type 2 diabetic patients

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Abstract Although medication adherence can be easily assessed by self-reports in clinical practice, accuracy is sometimes questionable. To make full use of self-reports on medication adherence in clinical practice, understanding the discrepancy between subjectively and objectively assessed adherence is important. The aim of this study was to investigate which clinical characteristics would be associated with such discrepancy regarding adherence to oral antidiabetic drugs (OADs) in type 2 diabetic patients. Our study assessed 406 Japanese type 2 diabetic outpatients treated with OADs. Medication adherence to OADs was evaluated in percentage, both subjectively by self-report and objectively by pill counts on the same day. We developed a common regression model by extending the generalized linear mixed model and statistically detected the difference in the impact of clinical characteristics between the two measures. Subjectively measured adherence was higher than objectively measured adherence, showing a 1.6-fold difference in odds ($p < 0.001$). Male gender, older age, longer diabetic duration, and taking more than two OADs daily were independently associated

with the overrating of medication adherence by self-report compared with the objectively measured adherence. On the other hand, higher glycosylated hemoglobin (HbA_{1c}) levels, taking medication before meals, and taking medication outside the home were independently associated with underrating medication adherence by self-report. In conclusion, this study demonstrated clinical characteristics associated with overrating and underrating of medication adherence by self-report in Japanese type 2 diabetic patients treated with OADs.

Keywords Medication adherence · Oral agents · Self-report · Pill counts · Discrepancy

Introduction

Most type 2 diabetic patients are treated with oral antidiabetic drugs (OADs), and adherence to the medication is a key factor in patient management. Such adherence can be evaluated either objectively or subjectively. Although objective adherence measures, including pill counts and medication event monitoring system (MEMS), provide reliable information on medication adherence, these measures are often labor-, time-, or cost-consuming [1]. It is therefore difficult in clinical practice to routinely take measures for assessing daily medication adherence. On the other hand, subjective (i.e., self-reported) measures can be easily attained. In this sense, it is clinically attractive to make full use of self-reported measures of medication adherence. However, the accuracy of these measures may be occasionally questionable; some patients will answer that they have better medication adherence than they really have, whereas others will possibly answer they have poorer adherence. It would be

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clinically useful to reveal which patient types are more likely to overrate or underrate their own medication adherence and estimate medication adherence more accurately from the self-reported measures by also considering patient characteristics.

To date, a number of studies have investigated clinical risk factors associated with poor medication adherence [2–4]. However, those studies analyzed separately the impact of risk factors regarding subjective and objective measurements and made no direct comparison between the two. Thus, which risk factors were associated with those discrepancy remained unidentified.

In this study, we developed a common regression model to determine and compare subjective and objective adherence measures by extending the generalized linear mixed model and statistically investigating whether the impact of risk factors was different between the subjectively and objectively evaluated medication adherence in Japanese type 2 diabetic patients treated with OADs.

Materials and methods

This cross-sectional observational study assessed 406 Japanese type 2 diabetic outpatients treated with OADs in Shiraiwa Medical Clinic, Osaka, Japan, whose medication adherence to OADs was evaluated with both subjective and objective measures between February and May 2015. A total of five doctors were involved in patient treatment. Patients obtained their prescriptions from the clinic and had them filled in the nearby Smile Pharmacy, Osaka, Japan. Medication adherence was measured subjectively by self-report in the clinic and objectively by pill counts in the pharmacy on the same day. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Shiraiwa Medical Clinic. Informed consent was obtained from every participant.

Measures of adherence

All patients received blister-packed OADs marked with pen to distinguish them from previously dispensed medications. Patients were asked to take the newly dispensed medications until the next visit, leaving previously prescribed prescriptions. Patients reported their self-evaluation in percentages in the clinic, and a pill count was taken by the nearby pharmacy on the same day. The number of pills they consumed was calculated as the number of dispensed minus the number of left-over pills. Medication adherence (percentage) was expressed as the ratio of the number of pills consumed to the number of pills they were expected to take between the two visits [1].

Statistical analysis

The impact of patient characteristics on subjectively and objectively assessed adherence was assessed using the generalized linear mixed model with a logit link function. The two adherence measures, described as proportion data, were treated as the dependent variable in a common model in which indication of adherence outcome (i.e., either subjective or objective assessment of medication adherence) and patient characteristics of interest were included as the fixed effects. To assess the difference in the impact of patient characteristics between the two outcomes, interaction terms between indication of the outcome and patient characteristics were also entered as fixed effects. Interpatient and interdoctor variability were treated as the random effects. The impact of a patient characteristic was considered significantly different between outcomes if the null hypothesis that the regression estimate of the interaction term equaled zero was statistically denied. The impact of patient characteristics on outcomes are represented as odds ratios (OR), equal to the exponential transformation of the regression estimate in the model. Accordingly, the discrepancies between outcomes are expressed as fold differences in odds.

Data are given as mean $\pm$ standard deviation (SD) for continuous variables and as percentages for dichotomous variables if not otherwise mentioned. A p value <0.05 was considered to be significant, and 95 % confidence intervals (CI) are given when required. All statistical analyses were performed using R software Program (R Development Core Team).

Results

Clinical characteristics of the study population are shown in Table 1. Mean age was 65 ± 12 years and 56 % were men. Mean number of OADs and glycolated hemoglobin (HbA_{1c}) levels were 1.9 ± 1.0 and 6.8 ± 0.9 % (51 ± 10 mmol/mol), respectively. Figure 1 demonstrates the distribution of adherence, with subjectively assessed adherence being higher than objectively assessed adherence, with 1.6-(95 % CI 1.5- to 1.7-) fold difference ($p < 0.001$).

Table 2 shows crude associations of clinical characteristics with subjectively and objectively assessed adherence. Factors associated with subjectively assessed adherence were age, body mass index, HbA_{1c} levels, taking more than one type of OAD, taking medication before meals, taking medication at lunch, and taking medication outside the home. On the other hand, those associated with objectively assessed adherence were male gender, HbA_{1c} levels, taking more than one type of OAD, combination insulin therapy, taking medication at lunch, and taking medication outside the home. The impact on subjectively vs objectively

Table 1 Patient characteristics

Variables	Results
<i>n</i>	406
Male gender	227 (56 %)
Age (years)	65 ± 12
Diabetic duration (years)	10 ± 9
Body mass index (kg/m ²)	24.3 ± 4.0
Hemoglobin A1 _c	
NGSP unit (%)	6.8 ± 0.9
IFCC unit (mmol/mol)	51 ± 10
Number of OADs	1.9 ± 1.0
Combination of Insulin therapy	107 (26 %)
When is medication taken: pre- postprandial?	
After meals	267 (66 %)
Before meals	18 (4 %)
Both before and after meals	121 (30 %)
With which meal is the medication taken?	
At breakfast	167 (41 %)
At breakfast and dinner	65 (16 %)
At breakfast, lunch, and dinner	152 (37 %)
Others	22 (5 %)
Taking medication outside the home	
Seldom (less than once a month)	243 (60 %)
Sometimes (once a month ~ three times a week)	111 (27 %)
Often (more than three times a week)	52 (13 %)

Data are mean ± standard deviation for continuous variables and *n* (%) for discrete variables

NGSP National Glycohemoglobin Standardization Program, IFCC International Federation of Clinical Chemistry and Laboratory Medicine

assessed adherence was significantly different regarding all clinical risk factors except taking more than two types of OADs and taking medication at dinner.

Results of the multivariate analysis are demonstrated in Table 3. Male gender, older age, longer diabetic duration, and taking more than two different OADs were independently associated with overrating medication adherence by self-report compared with objectively measured adherence. On the other hand, higher HbA1_c levels, taking medication before meals, and taking medication outside the home were independently associated with the underrating of medication adherence by self-report compared with objectively measured adherence.

Discussion

This study revealed clinical characteristics associated with a different impact on subjectively vs objectively assessed medication adherence in type 2 diabetic patients treated

Fig. 1 Medication adherence. White and black bars represents subjectively (i.e., self-reported) and objectively (i.e., pill count) assessed medication adherence, respectively

with OADs. Male patients, those of older age, those with longer diabetic duration, and those taking more than two OADs were more likely to answer that they had higher medication adherence rate than they really had. On the other hand, patients with higher HbA1_c levels, taking medication before meals, and taking medication outside the home more likely answered that they had a lower medication adherence rate than they really had.

A number of previous studies investigated the association of clinical characteristic with either subjectively or objectively assessed medication adherence. However, it remained undetermined which clinical characteristics were associated with the discrepancy between subjectively and objectively assessed medication adherence. Understanding the factors associated with such discrepancy would help create a more accurate estimation of actual adherence from self-reported adherence in clinical practice.

Longer diabetes duration and older age were associated with overrating of medication adherence by self-report. Patients treated for many years might have been repeatedly educated about the importance of medication adherence by medical staff. They might therefore more likely recognize the importance than do those fresh from diagnosis, which would possibly drive them to make a medically “desirable” answer. Similarly, older patients, having most likely received medical treatment for chronic diseases over the long term, might have been better educated about the importance of medication adherence. The association between older age and overrating adherence might also be explained by these hypotheses.

Table 2 Unadjusted associations of patient characteristics with medication adherence

	Unadjusted odds ratio for subjectively measured adherence	Unadjusted odds ratio for objectively measured adherence	Fold difference
Male gender	1.1 (0.8, 1.7); ($p = 0.583$)	0.7 (0.4, 1.0); ($p = 0.033$)	1.7 (1.5, 2.0); ($p < 0.001$)
Age (in 10-year increments)	1.4 (1.1, 1.6); ($p < 0.001$)	1.1 (0.9, 1.2); ($p = 0.585$)	1.3 (1.2, 1.4); ($p < 0.001$)
Diabetic duration (in 10-year increments)	1.2 (1.0, 1.5); ($p = 0.098$)	1.0 (0.8, 1.2); ($p = 0.694$)	1.3 (1.2, 1.4); ($p < 0.001$)
Body mass index (in 5-kg/m ² increments)	0.7 (0.5, 0.8); ($p = 0.001$)	0.8 (0.6, 1.0); ($p = 0.082$)	0.8 (0.7, 0.9); ($p < 0.001$)
Hemoglobin A1c (in 1 % NGSP increments)	0.7 (0.6, 0.8); ($p < 0.001$)	0.8 (0.6, 0.9); ($p = 0.014$)	0.9 (0.8, 1.0); ($p < 0.001$)
More than one type of oral antidiabetic drug (vs 1 type)			
2 drugs	0.5 (0.3, 0.7); ($p = 0.002$)	0.6 (0.4, 1.0); ($p = 0.039$)	0.8 (0.6, 0.9); ($p = 0.003$)
>2 drugs	0.4 (0.2, 0.6); ($p < 0.001$)	0.4 (0.3, 0.7); ($p = 0.001$)	0.9 (0.8, 1.0); ($p = 0.143$)
Combination insulin therapy	0.7 (0.4, 1.0); ($p = 0.055$)	0.6 (0.4, 0.9); ($p = 0.010$)	1.2 (1.0, 1.3); ($p = 0.047$)
Taking medication before meals	0.5 (0.2, 0.9); ($p = 0.034$)	0.6 (0.3, 1.2); ($p = 0.160$)	0.8 (0.6, 1.0); ($p = 0.045$)
Taking medication (vs at breakfast)			
At lunch	0.0 (0.0, 0.1); ($p < 0.001$)	0.1 (0.0, 0.3); ($p < 0.001$)	0.5 (0.3, 0.7); ($p = 0.001$)
At dinner	0.5 (0.2, 1.1); ($p = 0.080$)	0.6 (0.3, 1.4); ($p = 0.245$)	0.8 (0.5, 1.1); ($p = 0.181$)
Taking medication outside the home (vs seldom)			
Sometimes	0.3 (0.2, 0.4); ($p < 0.001$)	0.4 (0.3, 0.6); ($p < 0.001$)	0.7 (0.6, 0.8); ($p < 0.001$)
Often	0.2 (0.1, 0.4); ($p < 0.001$)	0.5 (0.3, 0.8); ($p = 0.007$)	0.5 (0.4, 0.6); ($p < 0.001$)

Data are unadjusted odds ratio for medication adherence (95 % confidence interval); (p value). An odds ratio >1 indicates the variable of interest was positively associated with better adherence

NGSP National Glycohemoglobin Standardization Program

Another factor associated with the discrepancy between subjective and objective measures was gender. Males were more likely to overrate their medication adherence by self-report. Previous psychological studies suggest that men are more likely to overrate performance of their tasks than are women and are more reluctant to acknowledge their shortcomings [5, 6]. It might be that participants in our study assessed their own performance of medication adherence in a similar psychological manner.

Multivariate analysis (Table 3) also revealed that taking more than two types of OADs was significantly associated with overrating adherence by self-report. Although the crude analysis (Table 2) detected no significance regarding this variable, it may be the result of the influence of confounding factors. Indeed, taking more than two types of OADs was significantly positively associated with HbA_{1c} levels, frequency of taking medication before meals, and

taking medication outside the home (data not shown), all of which were negatively associated with overrating adherence. The true reason why polypharmacy was independently associated with overrating remains unknown. Patients taking many different types of OADs might incorrectly feel as if they were adherent enough, even when forgetting to take a certain medication.

On the other hand, patients with higher HbA_{1c} levels were likely to underrate their adherence. In this study, measures of glycemic control, including HbA_{1c} levels, were open to the patients. Therefore, patients informed of their poor glycemic control might distinctly recall episodes of forgetting to take medications and might overestimate the frequency of those episodes. Another possible explanation might be fear of having their treatment intensified (i.e., having the number or dosage increased, or insulin therapy initiated) [7]. Because of their reluctance to have their treatment intensified, they might

Table 3 Adjusted associations of patient characteristics with medication adherence

	Adjusted odds ratio for subjectively measured adherence	Adjusted odds ratio for objectively measured adherence	Fold difference
Male gender	1.3 (0.9, 1.9); ($p = 0.249$)	0.6 (0.4, 0.9); ($p = 0.007$)	2.1 (1.8, 2.5); ($p < 0.001$)
Age (in 10-year increments)	1.1 (0.9, 1.4); ($p = 0.237$)	0.9 (0.8, 1.1); ($p = 0.382$)	1.2 (1.1, 1.3); ($p < 0.001$)
Diabetic duration (in 10-year increments)	1.4 (1.1, 1.8); ($p = 0.015$)	1.2 (0.9, 1.5); ($p = 0.188$)	1.2 (1.0, 1.3); ($p = 0.006$)
Body mass index (in 5-kg/m ² increments)	0.9 (0.7, 1.1); ($p = 0.318$)	0.9 (0.7, 1.2); ($p = 0.416$)	1.0 (0.9, 1.1); ($p = 0.639$)
Hemoglobin A1 _c (in 1 % NGSP increments)	0.8 (0.6, 1.0); ($p = 0.034$)	0.9 (0.7, 1.1); ($p = 0.238$)	0.9 (0.8, 1.0); ($p = 0.007$)
Number of oral antidiabetic drug types (vs 1 drug)			
2 drugs	0.7 (0.4, 1.2); ($p = 0.210$)	0.8 (0.5, 1.3); ($p = 0.391$)	0.9 (0.7, 1.1); ($p = 0.297$)
>2 drugs	0.9 (0.5, 1.5); ($p = 0.688$)	0.7 (0.4, 1.1); ($p = 0.132$)	1.3 (1.1, 1.6); ($p = 0.003$)
Combination insulin therapy	0.8 (0.5, 1.3); ($p = 0.316$)	0.8 (0.5, 1.3); ($p = 0.372$)	1.0 (0.8, 1.2); ($p = 0.732$)
Taking medication before meals	0.8 (0.4, 1.5); ($p = 0.461$)	1.1 (0.5, 2.2); ($p = 0.844$)	0.7 (0.6, 0.9); ($p = 0.011$)
Taking medication (vs at breakfast)			
At lunch	0.1 (0.0, 0.6); ($p = 0.009$)	0.1 (0.0, 0.5); ($p = 0.005$)	1.1 (0.7, 1.9); ($p = 0.637$)
At dinner	0.8 (0.3, 1.9); ($p = 0.607$)	0.9 (0.4, 2.3); ($p = 0.893$)	0.8 (0.6, 1.3); ($p = 0.407$)
Taking medication outside the home (vs seldom)			
Sometimes	0.4 (0.2, 0.6); ($p < 0.001$)	0.5 (0.3, 0.7); ($p = 0.001$)	0.8 (0.7, 0.9); ($p = 0.003$)
Often	0.4 (0.2, 0.7); ($p = 0.002$)	0.7 (0.4, 1.3); ($p = 0.288$)	0.5 (0.4, 0.6); ($p < 0.001$)

Data are adjusted odds ratio (95 % confidence interval); (p value). An odds ratio of more than one indicates that the variable of interest was positively associated with better adherence to medication

try to persuade their clinicians to delay the intensification by reporting their medication adherence as being so poor that they have enough room for improvement, which should precede the intensification.

In addition, patients taking medication before meals and those taking it outside the home were more likely to underrate their adherence. Although inconvenience in these situations is well recognized [8, 9], it remains unknown how it psychologically influences self-rating. It might be that these inconvenient situations more likely prompted patients to remember that they did not take their OADs, resulting in an overestimation of nonadherence. Future studies are needed to reveal the underlying psychological processes.

This study had some limitations. First, it was performed prospectively, and participants were informed of study objectives. Also, the survey itself may have become an intervention and affected medication adherence [10], although the influence was controversial [11]. Second, although there were several treating doctors, all participants were outpatients of a single institution. The patient–doctor relationship, or the characteristics of doctors in a specific clinic, might have some influence on this finding. It remains unknown whether another doctor in another institution would obtain similar responses from participants. Third, only Japanese patients were assessed. Previous studies in different countries reported different associations regarding some patient backgrounds, e.g., gender, with medication adherence [12–14], indicating that

medication insurance systems, cultures, relative socioeconomic status, and other confounding factors may influence associations. Future multicenter studies with populations of other ethnicities and regions are needed to validate our findings.

In conclusion, this study demonstrated patient characteristics associated with the discrepancy between subjective and objective measures of medication adherence in Japanese type 2 diabetic patients treated with OADs.

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Compliance with ethical standards

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no conflicts of interests associated with this manuscript.

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