ORIGINAL ARTICLE

Understanding of antidiabetic medication is associated with blood glucose in patients with type 2 diabetes: At baseline date of the KAMOGAWA-DM cohort study

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ABSTRACT

Aims/Introduction: Medication adherence, which is decreased by a poor understanding of medications, has a close association with blood glucose level in patients with type 2 diabetes. However, a relationship between the understanding of antidiabetic medication and blood glucose level in patients with type 2 diabetes is unclear. Here, we aimed to investigate the relationship between the understanding of antidiabetic medication and blood glucose level in patients with type 2 diabetes.

Materials and Methods: Lifestyle factors were evaluated by a questionnaire method, in the present cross-sectional study. Poor understanding of antidiabetic medication (PUAD) was defined as a discrepancy between the answer and the actual use of oral antidiabetic medication on the questionnaire. Poor blood glucose level was defined as hemoglobin A1c ≥8%. To investigate the impact of PUAD on poor blood glucose level, propensity-score matching analysis was used to remove the bias of confounding variables, including sex, age, log (duration of diabetes +1), body mass index, number of oral antidiabetic medications, smoking status, alcohol drinking, exercise, nephropathy, neuropathy, oral antidiabetic medications and insulin.

Results: Among 479 patients, 40 patients (8.4%) were categorized into the PUAD group. The hemoglobin A1c of patients with PUAD was higher than that of patients without (7.5 [1.3] vs 7.2 [0.9]%, $P = 0.041$). In the propensity-matched 74 patients, PUAD was associated with poor blood glucose level (odds ratio 5.45, 95% confidence interval 1.54–25.8, $P = 0.007$) by logistic regression analysis.

Conclusion: A poor understanding of antidiabetic medication is associated with poor blood glucose level in patients with type 2 diabetes.

INTRODUCTION

Currently, the number of patients with diabetes is increasing worldwide, and it is well known that diabetes give rise to various complications[1]. To prevent these complications, maintaining a good blood glucose level is required[2,3]. Both exercise and diet therapies are the main therapies; however, it is difficult to achieve a good blood glucose level with these therapies only in patients with type 2 diabetes[4]. Thus, to achieve a good blood glucose level, many patients with type 2 diabetes receive a medication therapy[4]. Regardless of these various approaches, many patients cannot achieve a good blood glucose level[5].

One of the reasons why many patients cannot achieve a good blood glucose level is poor medication adherence[6]. The risk of diabetic complications was reduced by proper use of antidiabetic medications, and medication adherence reinforces the effect of medications[7]. In fact, medication adherence affects the blood glucose level[4,8–10].

In contrast, it is reported that an understanding of medications prescribed for patients is associated with their medication

adherence[11]. Although some previous studies reported the relationship between medication adherence and blood glucose level, no previous studies reported the relationship between the understanding of antidiabetic medications and blood glucose level in patients with type 2 diabetes[12]. Thus, we examined the relationship between the understanding of antidiabetic medications and blood glucose level in patients with type 2 diabetes at the baseline date of the KAMOGAWA-DM cohort study.

METHODS

Patients and study design

The KAMOGAWA-DM cohort study, which was started to elucidate the natural history of patients with diabetes from 2014, is an ongoing cohort study of patients with diabetes[12]. We gave informed consent to all patients for this cohort study, and we recorded patients' medical data into a database after eliminating personal identification information. In this cross-sectional study, we enrolled the outpatients at the Kyoto Prefectural University of Medicine (Kyoto, Japan), from January 2014 to January 2016. Patients who used steroid treatment, with active malignancy, with severe renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2)[13], after a renal transplantation, after a liver transplantation and with missing data of covariates were excluded from the present study. We also excluded patients who attended a hospital for psychosis, because they could not take medication regularly; and patients whose answer for insulin use showed a discrepancy to actual use in the questionnaire, because their answer was not credible. In addition, we excluded the patients with anemia whose hemoglobin concentration was <11 g/dL[14], because anemia affects hemoglobin A1c (HbA1c) levels. Approval for this study was obtained from the Ethics Committee of Kyoto Prefectural University of Medicine (No. RBMR-E-466-1).

Questionnaire and measurements

Lifestyle factors were assessed by a questionnaire survey, including "Do you take antidiabetic medications?". Current treatments data, including medications for diabetes and total number of oral medications, were gathered from medical records. In regard to the exercise status, we defined the patients who did any sports once a week regularly as regular exercisers[15]. In regard to alcohol, we defined patients who drank alcohol daily as alcohol drinkers. In regard to smoking, patients were categorized into three groups; never-smoker, ex-smoker or current smoker[16]. We defined a poor understanding of antidiabetic medication (PUAD) as the answer to the question "Do you take antidiabetic medications?" being inconsistent with the actual prescriptions on the questionnaire (Figure S1).

Body mass index was calculated as weight in kilograms divided by height in meters squared. We collect the venous blood after an overnight fast, and we checked the levels of several factors, including total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting plasma glucose, gamma-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, uric acid

and creatinine. Glomerular filtration rate was approximated by the Japanese Society of Nephrology equation: estimated glomerular filtration rate (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (×0.739 for women)[17]. The National Glycohemoglobin Standardization Program unit was used for HbA1c, and we defined HbA1c ≥8% (63 mmol/mol) as a poor blood glucose level[18].

We assessed the relationship between the poor understanding of antidiabetic medication and the prevalence of microvascular complications, which included diabetic nephropathy and diabetic neuropathy. As for diabetic nephropathy, we divided patients into three groups according to the urinary albumin excretion level: <30 mg/g, 30–300 mg/g and <300 mg/g creatinine[19]. In regard to diabetic neuropathy, we judged the presence of diabetic nephropathy by assessing whether the attending physician had diagnosed neuropathy in medical record (Figure 1).

We also examined the diabetic medications and categorized them as follows: insulin secretagogues, incretin-based therapy, insulin sensitizers, nutrient load reducers and insulin. We categorized sulfonylureas and glinides into insulin secretagogues, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonist into incretin-based therapy, pioglitazone and metformin into insulin sensitizers, and α-glucosidase inhibitors and sodium-glucose cotransporter inhibitors into nutrient load reducers.

Statistical analysis

Statistical analyses were carried out using JMP version 12.0 software (SAS Institute, Cary, NC, USA), and $P < 0.05$ was defined as significant statistically. We calculated the mean, median and frequencies of variables. Continuous variables were shown as the mean (standard deviation [SD]), and if the variables were skewed, as the median (interquartile range). Student's t-test or the Mann–Whitney U-test were used to evaluate statistical significance of differences between groups. Category variables were shown as the number. The χ^2-test was used to evaluate statistical significance of differences between groups.

Univariate logistic regression analyses were carried out to evaluate the effect of various factors, including PUAD, on poor blood glucose level.

In the present study, 94 (19.6%) patients had a poor blood glucose level. Because this number of patients might be small for statistical analysis, we used propensity scores, which preserved statistical power by reducing the covariates into a single variable. For the assessment of the propensity score, the dependent variable was the PUAD. The propensity score was evaluated using multivariable logistic regression models that included the following parameters: sex, age, log (duration of diabetes +1), body mass index, number of oral antidiabetic medications, smoking status, alcohol drinking, exercise, nephropathy, neuropathy, insulin secretagogues, incretin-based therapy, insulin sensitizers, nutrient load reducers and insulin.
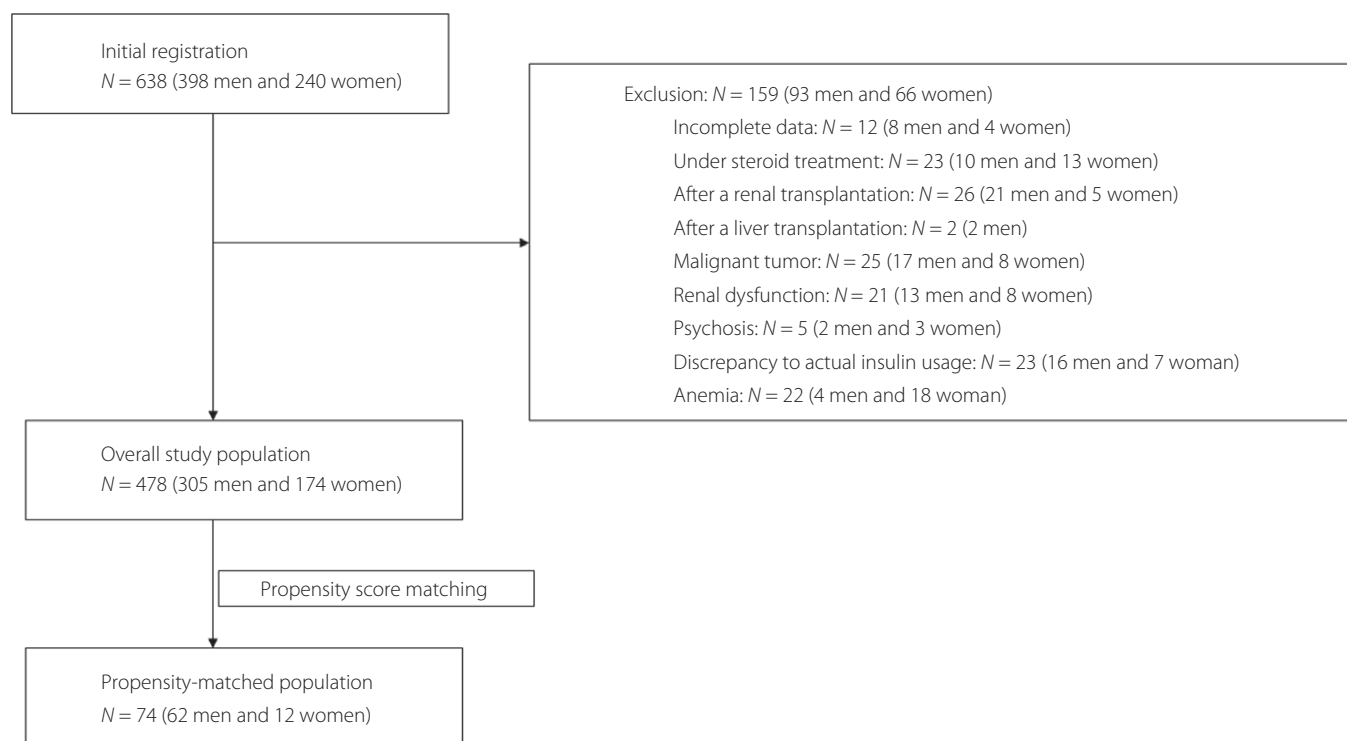
Figure 1 | Inclusion and exclusion flow.

The c-statistic for the propensity score model was 0.80, which shows an acceptable discrimination. Then, 1:1 matching on the propensity score was carried out using nearest neighbor matching with a maximum caliper of 0.05 of the propensity score. Finally, 74 patients were selected for the propensity-matched population, and we calculated the odds ratio for poor blood glucose level by logistic regression analysis.

RESULTS

A total of 638 patients (398 men and 240 women) were enrolled into the present cross-sectional study. Then, 159 patients (93 men and 66 women) were excluded. Thus, 479 patients (305 men and 174 women) were selected for this study.

Table 1 shows the clinical characteristics of the overall study patients according to the presence of PUAD. The mean age and median of duration of diabetes (interquartile range) were 68.4 years (SD 10.4 years) and 12 years (SD 7–20 years), respectively. The mean HbA1c was 7.2% (SD 1.0%; 55.3 mmol/mol [SD 10.6 mmol/mol]), and 94 patients (20%) were categorized as having a poor blood glucose level. A total of 281 patients (59%) had hypertension, and 425 patients (89%) use medication for diabetes. The mean total number of oral medications and the number of oral antidiabetic medications were 5.4 (SD 3.3) and 1.7 (SD 1.2), respectively. In addition, 40 patients (8.4%) were categorized into the PUAD group. The HbA1c of patients with PUAD was higher than that of patients

without (7.5% [SD 1.3%] vs 7.2% [SD 0.9%], $P = 0.041$ [58.5 mmol/mol (SD 14.0 mmol/mol) vs 55.0 mmol/mol (SD 10.2 mmol/mol)]). The number of antidiabetic medications of patients with PUAD was lower than that of patients without (1.1 [SD 1.0] vs 1.7 [SD 1.2], $P = 0.001$).

Table 2 shows the unadjusted odds ratios of various factors for poor blood glucose levels for the overall patient cohort. PUAD (odds ratio 2.13, 95% confidence interval 1.02–4.23, $P = 0.044$) was associated with poor blood glucose level.

Table 3 shows clinical characteristics of propensity-matched 74 patients (62 men and 12 women) according to the presence of PUAD. The mean age (SD) and median of duration of diabetes (interquartile range) were 66.3 (13.1) years and 15 (7–23) years, respectively. Clinical characteristics were not different between groups without the ratio of poor blood glucose level (32% (case/n = 12/37) in patients with PUAD vs 8% (case/n = 3/37) in patients without, $P = 0.009$). In addition, PUAD was associated with poor blood glucose level (odds ratio: 5.45, 95% confidence interval 1.54–25.8, $P = 0.007$) by logistic regression analysis.

DISCUSSION

The present study shows that PUAD was associated with poor blood glucose levels in patients with type 2 diabetes. The proportion of patients with PUAD was 8.4% in this study. It was reported that half of the patients, who suffered chronic disease, had low adherence[20]. In addition, it was reported that 15–33%

Table 1 | Clinical characteristics of overall study patients according to the presence of a poor understanding of antidiabetic medication

	Total	Poor understanding of antidiabetic medication (−)	Poor understanding of antidiabetic medication (+)	P
n	479	439	40	−
Men/women (n)	305/174	271/168	34/6	0.003
Age (years)	68.4 (10.4)	68.7 (10.1)	65.5 (13.1)	0.063
Duration of diabetes (years)	12 (7–20)	12 (7–20)	15 (6–20)	0.282
Body mass index (kg/m^2)	23.6 (3.7)	23.6 (3.7)	23.9 (3.3)	0.579
Hypertension (−/+)	198/281	183/256	15/25	0.607
Hemoglobin A1c (%)	7.2 (1.0)	7.2 (0.9)	7.5 (1.3)	0.041
Hemoglobin A1c (mmol/mol)	55.3 (10.6)	55.0 (10.2)	58.5 (14.0)	0.041
Poor blood glucose level (−/+)	385/94	358/81	27/13	0.032
Fasting plasma glucose (mmol/L)	8.0 (2.3)	7.9 (2.2)	8.3 (3.8)	0.278
Total cholesterol (mmol/L)	4.7 (0.9)	4.8 (0.9)	4.4 (0.8)	0.025
Triglycerides (mmol/L)	1.2 (0.8–1.7)	1.2 (0.8–1.7)	1.3 (0.8–1.8)	0.839
HDL cholesterol (mmol/L)	1.5 (0.4)	1.6 (0.4)	1.4 (0.4)	0.049
Aspartate aminotransferase (IU/L)	25.4 (12.7)	25.5 (13.0)	24.2 (10.0)	0.521
Alanine aminotransferase (IU/L)	24.0 (17.4)	24.0 (17.7)	23.4 (14.4)	0.829
Gamma-glutamyltransferase (IU/L)	26 (18–41)	25 (18–41)	30 (21–37)	0.408
Creatinine (μmol/L)	70.4 (20.9)	70.0 (20.9)	73.8 (21.0)	0.279
eGFR (mL/min/1.73 m^2)	72.3 (18.6)	72.1 (18.5)	74.1 (19.1)	0.514
Uric acid (μmol/L)	315 (77)	316 (77)	306 (79)	0.460
Exercise (−/+)	221/258	203/236	18/22	0.880
Never-/ex-/current-smoker (n)	187/225/67	172/208/59	15/17/8	0.512
Alcohol drinking (−/+)	360/119	333/106	27/13	0.242
Nephropathy (UAE <30/30–300/<300 mg/g creatinine)	300/123/56	275/116/48	25/7/8	0.156
Neuropathy (−/+)	343/136	319/120	24/16	0.089
Medication usage for diabetes (−/+)	54/425	47/392	7/33	0.193
Total no. oral medication	5.4 (3.3)	5.4 (3.3)	5.6 (4.0)	0.667
No. oral antidiabetic medication	1.7 (1.2)	1.7 (1.2)	1.1 (1.0)	0.001
No. oral medication other than antidiabetic medication	3.7 (3.1)	3.6 (3.1)	4.5 (3.7)	0.097
Insulin (−/+)	387/92	356/83	31/9	0.581
Insulin secretagogues (−/+)	230/249	202/237	28/12	0.004
Incretin-based therapy (−/+)	170/309	152/287	18/22	0.189
Insulin sensitizers (−/+)	290/189	261/178	29/11	0.106
Nutrient load reducers (−/+)	399/80	364/75	35/5	0.457

Data are expressed as mean (standard deviation), median (interquartile range) or number. Poor blood glucose level was defined as hemoglobin A1c (HbA1c) ≥8.0%. The difference between groups was analyzed by Student's t-test, Mann–Whitney U-test or the χ^2-test. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; UAE, urinary albumin excretion.

of patients with diabetes did not take prescribed antidiabetic medications, and that of the patients with poor blood glucose level, three-fifths of patients did not take prescribed antidiabetic medications[5,21]. Medication adherence consisted of many factors, such as an understanding of medications, duration of disease, age, polypharmacy, tolerability and cost[4,22]. Although the relationship between medication adherence and glycemic control was reported in the past[6], no previous studies clarified the relationship between an understanding of antidiabetic medications and blood glucose level. This is the first study to clarify the relationship between an understanding of antidiabetic medications and blood glucose level in patients with type 2 diabetes.

Low medication adherence was reported to result in poor glycemic control[6]. Medication adherence consisted of many factors, including an understanding of medications[22]. Poor understanding of medications was correlated with low knowledge of each disease[23]. As for diabetes, it was reported that an understanding of medications, through having knowledge of diabetes[24], affects medication adherence, which is associated with blood glucose level.

Table 2 | Unadjusted odds ratios for poor blood glucose level in overall patients

	Odds ratio (95% CI)	*P*
Sex	1.13 (0.71–1.84)	0.606
Age	0.98 (0.96–1.00)	0.035
Log (duration of diabetes +1)	4.58 (2.12–10.36)	<0.001
Body mass index	1.09 (1.03–1.16)	0.005
No. oral antidiabetic medication	1.54 (1.27–1.88)	<0.001
Smoking status		
Never-smoker	Ref	–
Ex-smoker	0.90 (0.55–1.47)	0.673
Current-smoker	1.04 (0.51–2.03)	0.921
Alcohol drinking	0.84 (0.48–1.42)	0.527
Exercise	0.60 (0.38–0.94)	0.026
Insulin	2.28 (1.35–3.79)	0.002
Insulin secretagogues	1.73 (1.09–2.78)	0.019
Incretin based therapy	2.19 (1.32–3.79)	0.002
Insulin sensitizers	1.81 (1.15–2.85)	0.011
Nutrient load reducers	2.17 (1.25–3.70)	0.006
Poor understanding of antidiabetic medication	2.13 (1.02–4.23)	0.044

Odds ratios given with 95% confidence intervals (CI) express the risk associated with 1-unit increase in each continuous variable. As for smoking status, never-smoker was used as reference group. Log, logarithm.

It was reported that the rate of exercise therapy of patients was affected by the understanding of the knowledge of diabetes, including diabetic medications[25]. In the present study, among patients with type 2 diabetes, there was no significant difference between the ratio of regular exercise for patients with PUAD and without (55% [case/*n* = 22/40] vs 54% [case/*n* = 236/439], *P* = 0.880). Exercise therapy was affected by environmental factors, including family support[26]. There is a possibility that these environmental factors might lead to a similarity in the habit of regular exercise between patients with a poor understanding of medication and those with a good understanding.

Generally, poor glycemic control is positively associated with microvascular complications of diabetes[1]. In the present study, there were no significant differences in the prevalence of diabetic nephropathy between patients with and without PUAD (*P* = 0.156). As for diabetic neuropathy, the ratio of diabetic neuropathy in patients with PUAD tended to be higher than that in patients without PUAD (*P* = 0.089). It was reported that microvascular complications of diabetes were associated with glycemic control, age, blood pressure and duration of diabetes[1,27]. In the present study, there were no significant differences in age, the prevalence of hypertension and the duration of diabetes between patients with and without PUAD, although glycemic control among patients with PUAD was higher than that of patients without. This might result in there being no significant difference in the prevalence of diabetic microangiopathy between patients with and without PUAD.

Furthermore, we showed the relationship between the number of oral antidiabetic medications and poor blood glucose level, which was almost same as previous studies[28,29]. In contrast, in the present study, the glucose level of patients with

PUAD was higher than that of patients without, although patients with PUAD took fewer antidiabetic medications than patients without PUAD. One of the reasons is that PUAD itself causes poor medication adherence[23].

Previous studies showed that there is a relationship between PUAD and the education of medical staff about antidiabetic medication[23]. Thus, education of medical staff might improve the blood glucose level of patients with PUAD through the improvement of PUAD[30].

There are some limitations that should be mentioned. First, because of the cross-sectional nature of the present study, the causal relationship between PUAD and poor blood glucose level was unclear. Second, we did not evaluate cognitive function. Thus, we cannot deny the possibility that an understanding of antidiabetic medication might have been affected by cognitive function. In fact, previous studies have shown that cognitive impairment and memory problems could play an important role in medication adherence[31,32]. However, in the present study, age and the duration of diabetes, which were generally associated with cognitive function in patients with type 2 diabetes[33], were not significantly different between patients with PUAD and without. Thus, the influence of cognitive function might be small. Third, we did not evaluate the number of unused medicines. Therefore, increased unused medicine led by low medication adherence might have resulted in poor blood glucose level. However, unused medicine is also related to PUAD, because medication adherence is affected by an understanding of medications[30]. Fourth, only Japanese patients were included in the present study. Therefore, whether these results can be generalized to non-Japanese patients with type 2 diabetes is uncertain. Fifth, as for the

Table 3 | Clinical characteristics of propensity-matched patients according to the presence of a poor understanding of antidiabetic medication

	Poor understanding of antidiabetic medication (−)	Poor understanding of antidiabetic medication (+)	P
n	37	37	−
Men/women (n)	31/6	31/6	1.0
Age (years)	67.1 (13.3)	65.5 (13.1)	0.600
Duration of diabetes (years)	14 (7–25)	15 (6–20)	0.992
Body mass index (kg/m^2)	24.3 (4.8)	24.0 (3.4)	0.732
Hypertension (−/+)	13/24	14/23	0.809
Poor blood glucose level (−/+)	34/3	25/12	0.009
Fasting plasma glucose (mmol/L)	7.9 (2.3)	8.3 (3.9)	0.576
Total cholesterol (mmol/L)	4.8 (1.2)	4.5 (0.8)	0.172
Triglycerides (mmol/L)	1.2 (0.8–1.7)	1.2 (0.8–1.8)	0.347
HDL cholesterol (mmol/L)	1.5 (0.4)	1.4 (0.4)	0.421
Aspartate aminotransferase (IU/L)	22 (20–27)	22 (18–28)	0.539
Alanine aminotransferase (IU/L)	18 (15–28)	19 (14–27)	0.916
Gamma-glutamyltransferase (IU/L)	29 (18–43)	30 (21–38)	0.864
Creatinine (μmol/L)	79.9 (28.7)	72.5 (21.0)	0.209
eGFR (mL/min/1.73 m^2)	70.6 (25.0)	75.3 (19.1)	0.366
Uric acid (μmol/L)	324 (92)	303 (80)	0.309
Exercise (−/+)	17/20	17/20	1.0
Never-/ex-/current-smoker (n)	11/16/10	13/17/7	0.696
Alcohol drinking (−/+)	26/11	25/12	0.802
Nephropathy (UAE <30/30–300/<300 mg/g)	22/9/6	25/6/6	0.673
Neuropathy (−/+)	24/13	23/14	0.809
Medication use for diabetes (−/+)	5/32	6/31	0.744
Total no. oral medication	5.1 (3.6)	5.8 (4.1)	0.401
No. oral antidiabetic medication	1.1 (0.9)	1.2 (1.0)	0.712
No. oral medication other than antidiabetic medication	4.0 (3.5)	4.6 (3.8)	0.431
Insulin (−/+)	27/10	29/8	0.588
Insulin secretagogues (−/+)	30/7	25/12	0.183
Incretin based therapy (−/+)	15/22	16/21	0.814
Insulin sensitizers (−/+)	28/9	27/10	0.790
Nutrient load reducers (−/+)	33/4	32/5	0.722

Data are expressed as mean (standard deviation), median (interquartile range) or number. The difference between groups was analyzed by Student's t-test, Mann–Whitney U-test or the χ^2-test. The propensity score was evaluated using multivariable logistic regression models that include the following parameters: sex, age, log (duration of diabetes +1), body mass index, number of oral antidiabetic medications, smoking status, alcohol drinking, exercise, nephropathy, neuropathy, insulin, insulin secretagogues, incretin-based therapy, insulin sensitizers and nutrient load reducers. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; UAE, urinary albumin excretion.

questionnaire used in the present study, there are no gold standard methods for such a questionnaire method in any languages, including Japanese.

In conclusion, the present cross-sectional study shows, for the first time, that a poor understanding of antidiabetic medication is associated with poor blood glucose levels in patients with type 2 diabetes. In clinical practice of diabetes, we should consider the understanding of antidiabetic medications.

ACKNOWLEDGMENTS

DISCLOSURE

Ltd. outside the submitted work. The sponsors were not involved in the study design; in the collection, analysis, interpretation of data; in the writing of this manuscript; or in the decision to submit the article for publication. The authors, their immediate families and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article. The authors declare that although they are affiliated with a department that is supported financially by a pharmaceutical company, the authors received no current funding for this study and this does not alter their adherence to all the journal policies on sharing data and materials. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Questionnaire used to define a poor understanding of antidiabetic medication (PUAD). The patients checked the check box according to the current treatment for diabetes. If the patients received several treatments, the patient checked several check boxes.