Original Article

A survey on consciousness towards the proper use of metformin and medical cost in Japanese patients with type 2 diabetes

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To investigate the patients' consciousness regarding the use of metformin and medical cost in Japanese patients with type 2 diabetes taking metformin. This cross-sectional study investigated patients' general characteristics and consciousness regarding medical cost, kidney function, liver function, and metformin usage, using a self-administered, internet-based questionnaire. Among 1,000 patients, 81.0% felt unsatisfied with treatment for type 2 diabetes, with the main reason for dissatisfaction being high medical cost, with 540 patients reporting this. In addition, 16.8% of patients experienced treatment disruption and among them, 48.2% (81/168) answered that the reason was high medical cost. Over half of the patients did not understand their kidney and liver functions, respectively. Only 8.9% and 7.1% of patients knew both the words and meanings behind sick days and lactic acidosis, respectively. In conclusion, many patients with type 2 diabetes taking metformin were not satisfied with their treatments, with the main reason being high medical cost. Moreover, they did not have sufficient knowledge of sick days and/or lactic acidosis.

Key Words: awareness, health literacy, type 2 diabetes, survey, patient's care

P eople with type 2 diabetes (T2D) are now increasing in number all over the world. To prevent diabetic complications, maintaining a good blood glucose level is required.[1,2] Lifestyle management, including regular exercise and proper diet, are the main treatments;[3] however, in patients with T2D, it is difficult to achieve a good blood glucose level using these treatments. Thus, to achieve a good blood glucose level, many patients with T2D receive a pharmacologic therapy.[4,5] The medical cost for diabetes mellitus has been increasing in Japan.[6] Thus, it has been advocated to suppress medical cost.

Metformin is used in many countries as the first-line drug for the treatment of T2D because of its price, safety, and protective effects on cardiovascular disease (CVD).[5] On the other hand, dipeptidyl peptidase-4 (DPP4) inhibitors are chosen as the first choice in Japan.[7] One of the possible reasons why metformin is not chosen as the first choice is an excessive concern for lactic acidosis. In the past, the use of metformin was limited by several contraindications to avoid lactic acidosis; however, based on the latest scientific findings on the safety of metformin, the restrictions on its use have been revised. Currently, moderate renal dysfunction [estimated glomerular filtration rate (eGFR) >30 to 60 ml/min/1.73 m²] is no longer a contraindication to the use of metformin in Japan.[8] According to recommendations from the Japan Diabetes Society and the Japan Association for Diabetes Education and Care, patients with severe renal dysfunction,

severe cardiovascular and pulmonary dysfunction, scheduled surgery, recent surgical history, severe hepatic dysfunction, and conditions that require patient attention (such as dehydration, sick days, and excessive alcohol consumption), are not recommended to use metformin.[9] In order to promote the proper use of metformin, it is necessary that patients have proper knowledge about metformin and their own kidney and liver functions. Further minimizing the risk for lactic acidosis and sick day will require effective dissemination of sick day management recommendations to patients.[10] However, little is known about patients' consciousness regarding the use of metformin.

Furthermore, clinical inertia, which means treatment goals not being met and adequately reinforced,[11] is also an important problem. Many causes of clinical inertia, including medical cost, have been reported.[12] One of the ways to reduce medical cost is the use of compounding agents.[13] Many combination medications for diabetes are now available in the market. Previous studies[14,15] revealed that the use of combination medications increased patient adherence. However, little is known about patients' consciousness regarding medical cost and the combination medication.[16]

Thus, the purpose of this cross-sectional study was to investigate patient consciousness regarding the use of metformin and medical cost in Japanese T2D patients taking metformin by using an internet survey.

Materials and Methods

Study design and participants. This cross-sectional study is based on data from a self-administered, internet-based questionnaire for Japanese T2D patients taking metformin. The internet-based questionnaire was conducted by Asmarq Co., Ltd. (Tokyo, Japan). The questionnaire was distributed to registered members of Asmarq's survey panel (D-style web). Informed consent was always obtained from all the registered members at the time of registration. The selection criteria were patients aged 16 years or older who were currently diagnosed and treated for T2D with metformin-containing medications (Metgluco tablets, Glycoran tablets, metformin hydrochloride tablets MT, Metact combination tablets, Equmet combination tablets, Inisync combination tablets, and Metoana combination tablets). The patients were enrolled by region (Hokkaido/Tohoku, Kanto, Chubu, Kinki, Chugoku/Shikoku, and Kyushu/Okinawa) according to the proportion of the population in the region. The survey was conducted from December 20, 2019 and finished December 26,

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2019, since responses from one thousand participants, the target sample size, were gathered. This study was approved by the ethics committee of the Kyoto Prefectural University of Medicine (ERB-C-1760).

Questionnaire for general characteristics. Using the questionnaire, the data of age, sex, place of residence, height, body weight, household income (<2,000,000 JPY, 2,000,000 to <4,000,000 JPY, 4,000,000 to <6,000,000 JPY, 6,000,000 to <8,000,000 JPY, 8,000,000 to <10,000,000 JPY, 10,000,000 JPY or more, or Decline to answer), living conditions (Living alone, With partner only, With families, or Others), job conditions (Employed, Self-employed, Part-time job, or Others), duration of diabetes, number of medications taken for T2D, usage of injections for diabetes (insulin and/or Glucagon-like Peptide 1), type of hospital (Clinic, university hospital, or hospital other than university hospital), type of doctor (Diabetologist, Non-diabetologist, or Unknown), and frequency of forgetting to take medicine [Almost none, Sometimes forget (2–3 days a week), Often forget (more than 4 days a week)] were gathered.

Questionnaire for consciousness for medical cost for diabetes. Using the following questionnaire, data on patient awareness of medical costs for diabetes were gathered: 1) Satisfaction with treatment for T2D (Satisfied or Not satisfied); if they answered that they were not satisfied, the reason (high medical cost, need for long-term treatment, not good glycemic control, too much medications, medication side effects, lack of doctor's explanation, and/or others); 2) percentage co-payment of medical cost (None, 10%, 20%, 30%, or others); 3) monthly medical cost of treatment for T2D divided into four groups (<3,000 JPY, 3,000 to <6,000 JPY, 6,000 to <10,000 JPY, or 10,000 JPY or more); 4) Have you received an explanation from your doctor or pharmacist about the price difference between different medicines (Always received at medication initiation and/or change, received, not received, or Do not remember)? Among the patients other than those who answered that they always received at medication initiation and/or change, would you want to receive an explanation from your doctor or pharmacist about the price difference between different medicines at medication initiation and/or change? (Hope, Not hope, or Either way); 5) Would you like to change to a cheaper medication that has about the same effect? (Yes or No); 6) Experience of treatment disruption? (Yes or No) If they answered yes, the reason was asked to be indicated (high medical cost, burden to visit hospital, not good glycemic control, long waiting times, not seeing the necessity for treatment, not a good fit with the medical staff, and/or others); 7) Are you currently taking a combination medication for the treatment of T2D (Yes, No, or Unknown)? If they answered No or Unknown, do you know combination medications (Yes, or No)? Would you like to change to a combination medication, if recommended by your doctor (Strongly hope, hope, not hope, or either way)?

Questionnaire for consciousness for kidney functions, liver functions and metformin usage. A questionnaire was used to ask the participants if they understood their kidney function [Level of kidney function (mild/moderate/severe), eGFR, serum creatinine level, and/or others] and/or liver function [Level of liver function (mild/moderate/severe), Aspartate aminotransferase (AST) level, Alanine aminotransferase (ALT) level, and/or others]. In addition, we asked them if they understood the sick day, using the question "Do you know of sick days, which are days wherein a diabetic patient has a fever, diarrhea, vomiting, or is unable to eat due to loss of appetite during treatment (Known both words and meanings, Known words, Known meanings, or Not known)?" We also asked them if they understood lactic acidosis, using the question "Are you aware of lactic acidosis, which is a rare side effect of metformin that increases lactic acid in the blood and causes the blood to become more acidic (Known words and meanings, Known words, Known meanings, or Not

known)?"

The patients were also asked whether they had received the following instructions from their doctor or pharmacist: 1) On a sick day, stop taking the medication that contains metformin and talk to your doctor; 2) if symptoms of lactic acidosis appear, visit the hospital; 3) Do not drink too much alcohol; 4) Drink a proper amount of water, and 5) Inform your doctor before undergoing of any tests that use iodine contrast agents, such as angiography, urography, or CT scans. Questions about sick days 1) and lactic

Table 1. Clinical characteristics of study participants

Total n = 1,000	Mean ± SD, n (%)
Age, years	60.7 ± 10.6
Age group	
≤50	162 (16.2%)
51–64	440 (44.0%)
≥65	398 (39.8%)
Sex	
Men	868 (86.8%)
Women	132 (13.2%)
Height, cm	167.6 ± 7.5
Weight, kg	70.3 ± 14.1
Body mass index, kg/m²	25.0 ± 4.4
Household income	
<2,000,000 JPY	113 (11.3%)
2,000,000 to <4,000,000 JPY	249 (24.9%)
4,000,000 to <6,000,000 JPY	195 (19.5%)
6,000,000 to <8,000,000 JPY	151 (15.1%)
8,000,000 to <10,000,000 JPY	77 (7.7%)
10,000,000 JPY or more	108 (10.8%)
Decline to answer	107 (10.7%)
Living conditions	
Living alone	176 (17.6%)
With partner only	355 (35.5%)
With families	454 (45.4%)
Others	15 (1.5%)
Job conditions	
Employed	402 (40.2%)
Self-employed	111 (11.1%)
Part-time job	74 (7.4%)
Others	413 (41.3%)
Duration of diabetes, years	12.5 ± 8.6
Number of medications taken for T2D	3.0 ± 2.0
Usage of injections (insulin and/or GLP-1)	
Yes	232 (23.2%)
No	768 (76.8%)
Hospital types	
Clinic	703 (70.3%)
University hospital	72 (7.2%)
Hospital other than university hospital	225 (22.5%)
Type of doctor	
Diabetologist	525 (52.5%)
Non-diabetologist	429 (42.9%)
Unknown	46 (4.6%)
Frequency of forgetting to take medicine	
Almost none	874 (87.4%)
Sometimes forget (2–3 days a week)	118 (11.8%)
Often forget (more than 4 days a week)	8 (0.8%)

GLP-1, glucagon-like Peptide 1; T2D, type 2 diabetes.

acidosis 2) were asked to the patients other than those who were unaware about sick days and lactic acidosis, respectively.

Statistical analysis. Statistical analysis was conducted by Sugimoto Data Analysis Service. The mean (SD) or frequencies of potential confounding variables were expressed.

To clarify the differences among age groups, we divided the patients into three groups according to age (≤50, 51–64, and ≥65 years). The differences among groups were evaluated using the chi-squared test or one-way ANOVA. In addition, the Tukey-Kramer method or Bonferroni's multiple comparison test was used for multiple comparisons. Statistical significance was set at $p<0.05$.

Results

This study included 1,000 Japanese T2D patients taking metformin. The general characteristics of the study participants are described in Table 1. The mean (SD) age, duration of diabetes, and body mass index were 60.7 (10.6) years, 12.5 (8.6) years, and 25.0 (4.4) kg/m², respectively. The mean number of medications used for T2D was 3.0 (2.0), while 23.2% of patients used injection. A total of 70.3% of patients were treated in clinics, while 29.7% of patients were treated in hospitals (including university hospitals). Moreover, 52.5% of patients received treatment by a diabetologist. In total, 87.4% of patients took all medications daily, with high medication adherence.

Figure 1 and Table 2 show the results of consciousness about medical cost. Surprisingly, 81.0% of them felt unsatisfied with their current treatment for T2D, with the main reason for dissatisfaction being high medical cost, which accounted for 54.0% ($n =$ 540) (Fig. 1). In addition, 72.4% ($n = 168$) of patients who received an injection for diabetes ($n = 232$) were unsatisfied with treatment for T2D due to high medical costs. In contrast, 48.4% ($n = 372$) of patients who did not receive an injection ($n = 768$) were unsatisfied for the same reason (Fig. 2). The monthly medical cost of treatment for T2D showed that 49.9% of them used over 6,000 JPY per month for medical costs (Table 2). Among patients with a monthly medical cost of 6,000 JPY or more ($n = 499$), 70.3% ($n = 351$) were unsatisfied with treatment for T2D due to high medical costs. In contrast, 37.7% ($n = 189$) of patients with a monthly medical cost of less than 6,000 JPY ($n = 501$) were unsatisfied for the same reason (Fig. 2). On the other hand, only 26.8% of patients always received an explana-

tion for differences in drug prices at medication initiation and/or change, and 76.8% of patients wanted to change to a cheaper medication. In addition, 16.8% of patients experienced treatment disruption. Among these patients ($n = 168$), 48.2% ($n = 81$) answered that the reason for treatment disruption was high medical cost, 17.3% ($n = 29$) did not feel the necessity for treatment, and 15.5% ($n = 26$) did not fit well with the medical staff. Moreover, 41.2% of patients were currently taking combination medication for the treatment of T2D, while 48.9% of them did not know what a combination medication is. Among patients who received treatment by a diabetologist ($n = 525$), 42.3% ($n = 222$) were taking combination medications for the treatment of T2D, while 41.3% ($n = 177$) of patients who received treatment by a non-diabetologist ($n = 429$) were taking combination medications as well. Among patients who were not taking combination medications ($n = 588$), 59.5% ($n = 350$) wanted to change to combination medications.

Table 3 shows the results of consciousness regarding kidney function, liver function, and metformin usage. Only 45.7% and 47.4% of patients understood their kidney and liver functions, respectively. Surprisingly, only 8.9% of them knew both the words and meanings behind sick days, and only 7.1% knew those of lactic acidosis. Only 9.7% of patients were told to stop taking the medication that contains metformin on a sick day and to talk to their doctor. Only 8.7% of patients were told to visit the hospital if symptoms of lactic acidosis appeared. Figure 3 shows the knowledge of sick days and lactic acidosis stratified by the duration of diabetes or injection usage. Among patients with a duration of diabetes equal to 11 years or more ($n = 486$), 84.0% ($n = 408$) did not know about sick days and 88.3% ($n = 429$) did not know of lactic acidosis. In contrast, 73.5% ($n = 378$) of patients with a duration of diabetes of less than 11 years ($n = 514$) did not know about sick days and lactic acidosis, respectively. Moreover, among patients with injection usage ($n = 232$), 53.4% ($n = 124$) did not know about sick days and 62.9% ($n = 146$) did not know of lactic acidosis; among patients without injection usage ($n = 768$), 86.2% ($n = 662$) did not know about sick days and 86.1% ($n = 661$) did not know about lactic acidosis.

The differences among age groups are shown in Supplemental Table 1–3*. The percentage of patients not satisfied with the treatment for T2D in patients aged ≤50 years was higher than that of patients in the other age groups. The reason for their dissatis-
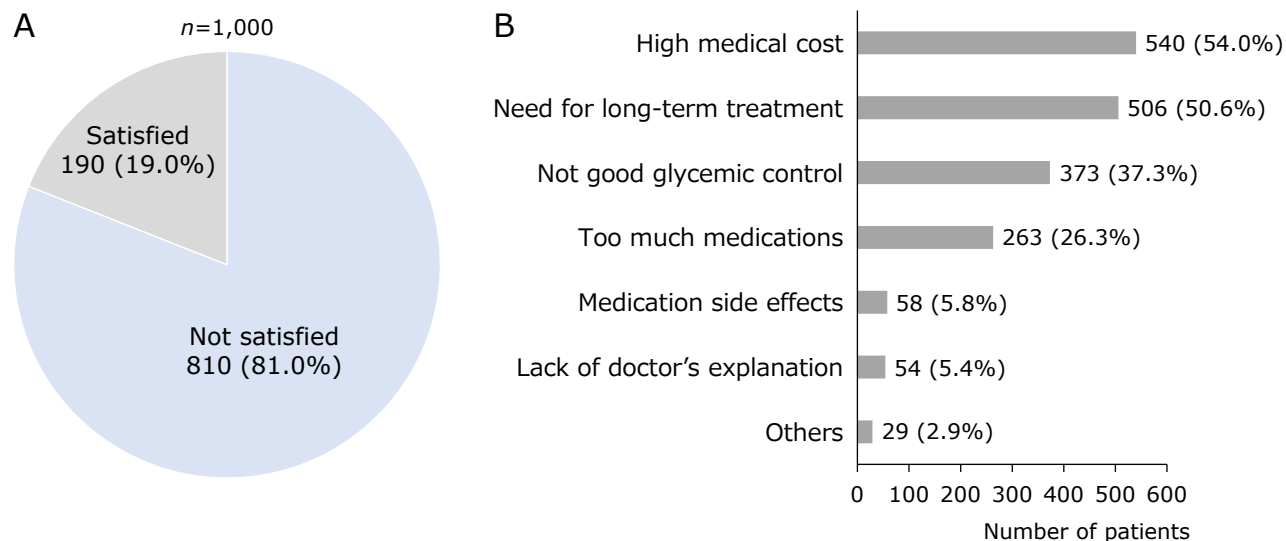
Fig. 1. Satisfaction with treatment for type 2 diabetes and the reason for not satisfied. (A) Satisfaction with treatment for type 2 diabetes. (B) The reason for not satisfied (Multiple selections possible).

Table 2. The results of consciousness for medical cost for diabetes

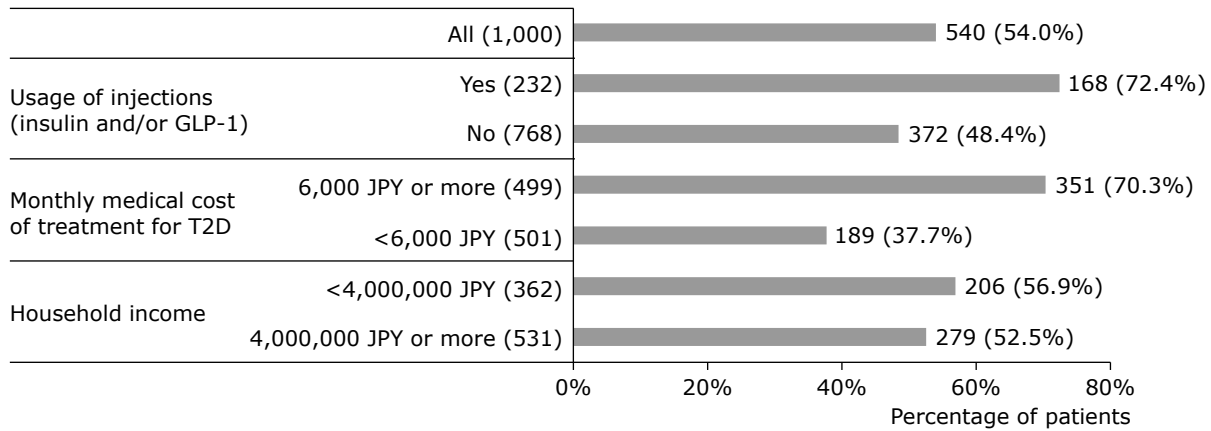| Total $n = 1{,}000$	n (%)
Satisfaction with treatment for T2D	
Satisfied	190 (19.0%)
Not satisfied	810 (81.0%)
The reason for not satisfied (Multiple selections possible)	
High medical cost	540 (54.0%)
Need for long-term treatment	506 (50.6%)
Not good glycemic control	373 (37.3%)
Too much medications	263 (26.3%)
Medication side effects	58 (5.8%)
Lack of doctor's explanation	54 (5.4%)
Others	29 (2.9%)
Percentage co-payment of medical cost	
None	29 (2.9%)
10%	86 (8.6%)
20%	151 (15.1%)
30%	726 (72.6%)
Others	8 (0.8%)
Monthly medical cost of treatment for T2D	
<3,000 JPY	166 (16.6%)
3,000 to <6,000 JPY	335 (33.5%)
6,000 to <10,000 JPY	230 (23.0%)
10,000 JPY or more	269 (26.9%)
Have you received an explanation from your doctor or pharmacist about the price difference between different medicines?	
Always received at medication initiation and/or change	268 (26.8%)
Received	305 (30.5%)
Not received	358 (35.8%)
Do not remember	69 (6.9%)
Would you want to receive an explanation from your doctor or pharmacist about the price difference between different medicines at medication initiation and/or change?	
I've already received an explanation	268 (26.8%)
Hope	405 (40.5%)
Not hope	85 (8.5%)
Either way	242 (24.2%)
Would you like to change to a cheaper medication that has about the same effect?	
Yes	768 (76.8%)
No	232 (23.2%)
Experience of treatment disruption	
No	832 (83.2%)
Yes	168 (16.8%)
Reasons for treatment disruption (Multiple selections possible)	
High medical cost	81 (8.1%)
Burden to visit hospital	63 (6.3%)
Not good glycemic control	54 (5.4%)
Long waiting times	30 (3.0%)
Not seeing the necessity for treatment	29 (2.9%)
Not a good fit with the medical staff	26 (2.6%)
Others	12 (1.2%)
Are you currently taking combination medication for the treatment of T2D?	
Yes	412 (41.2%)
No	480 (48.0%)
Unknown	108 (10.8%)
Do you know combination medications?	
I've already taken combination medication for the treatment of T2D	412 (41.2%)
Yes	99 (9.9%)
No	489 (48.9%)
Would you want to change to combination medication, if your doctor recommends?	
I've already taken combination medication for the treatment of T2D	412 (41.2%)
Strongly hope	90 (9.0%)
Hope	260 (26.0%)
Not hope	48 (4.8%)
Either way	190 (19.0%)

T2D, type 2 diabetes.

Fig. 2. Dissatisfaction with treatment for type 2 diabetes due to high medical costs.

Table 3. The results of consciousness for kidney functions, liver functions and metformin usage

Total *n* = 1,000	*n* (%)
Do you know your kidney function?	
No	543 (54.3%)
Yes	457 (45.7%)
Level of kidney function (mild/moderate/severe)*	349 (34.9%)
eGFR*	219 (21.9%)
Serum creatinine level*	271 (27.1%)
Others*	4 (0.4%)
Do you know your liver function?	
No	526 (52.6%)
Yes	474 (47.4%)
Level of liver function (mild/moderate/severe)*	315 (31.5%)
AST level*	306 (30.6%)
ALT level*	303 (30.3%)
Others*	20 (2.0%)
Do you know of sick days?	
Known both words and meanings	89 (8.9%)
Known words	72 (7.2%)
Known meanings	53 (5.3%)
Not known	786 (78.6%)
Do you know of lactic acidosis?	
Known both words and meanings	71 (7.1%)
Known words	92 (9.2%)
Known meanings	30 (3.0%)
Not known	807 (80.7%)
Instruction from your doctor or pharmacist	
On a sick day, stop taking the medication	
Yes	97 (9.7%)
No	117 (11.7%)
Not known sick day	786 (78.6%)
If symptoms of lactic acidosis appear, visit hospital	
Yes	87 (8.7%)
No	106 (10.6%)
Not known lactic acidosis	807 (80.7%)
Do not drink too much alcohol	
Yes	407 (40.7%)
No	593 (59.3%)
Drink a proper amount of water	
Yes	583 (58.3%)
No	417 (41.7%)
Inform your doctor before undergoing any tests that use iodine contrast agents	
Yes	224 (22.4%)
No	776 (77.6%)

eGFR, estimated glomerular filtration rate. *Multiple selections possible.
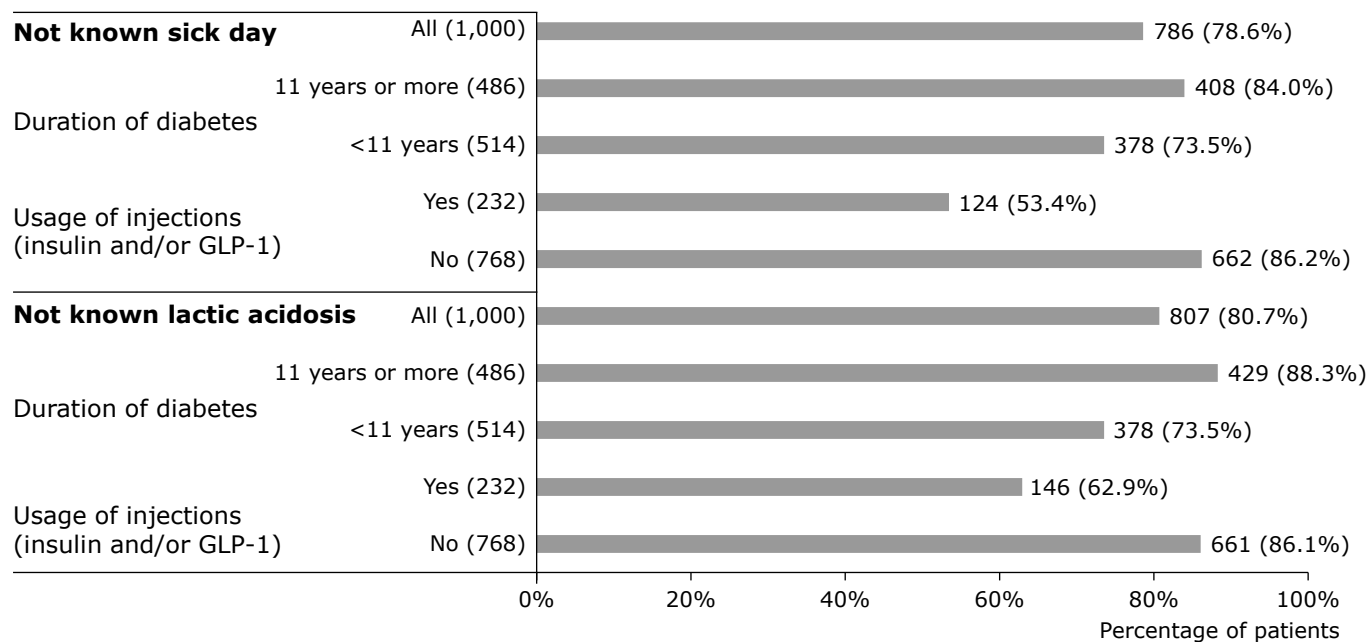
Fig. 3. Knowledge of sick days and lactic acidosis stratified by the duration of diabetes or injection usage.

faction is the higher percentage of medical cost in patients aged ≤50 years compared to other age groups. In addition, the percentage of medication side effects and lack of doctors' explanations were also higher in this specific age group (Supplemental Table 2*). Furthermore, the percentage of experience of treatment disruption in patients aged ≤50 years was higher than that in patients in the other age groups (Supplemental Table 2*). On the other hand, the percentages of patients who did not have knowledge of sick day and lactic acidosis increased with age (Supplemental Table 3*).

Discussion

This cross-sectional study of an internet survey investigated the patients' consciousness regarding the use of metformin and medical cost in Japanese T2D patients taking metformin. To avoid the side effects of metformin, knowledge of sick days and lactic acidosis is important. Surprisingly however, about 80% of patients did not have knowledge of sick days and lactic acidosis, respectively. In addition, this study showed that 80% of patients felt unsatisfied with treatment and 16.8% of patients had experience of treatment disruption, with high medical cost as the main reason for both. Moreover, only about 25% of patients always received an explanation for differences in drug prices at medication initiation and/or change, with about 75% of patients wanting to change to a cheaper medication.

Metformin is used as the first-line drug for the treatment of T2D in many countries[5] and is considered to be a cost-effective agent. Lactic acidosis is a rare and serious side effect of metformin. To avoid this side effect, the proper use of metformin is needed.[9] In Japan, metformin is contraindicated for use in patients with severe renal dysfunction; its use in patients with moderate renal dysfunction is now possible, but dose adjustment is required. In addition, in Japan, the patient package inserts of metformin-containing products state that administration should be discontinued during sick days and consult your doctor to avoid lactic acidosis.

Thus, to safely use metformin, patients should also have an understanding of their kidney functions and knowledge of sick days[10] and lactic acidosis. However, little is known about the knowledge of sick days and lactic acidosis in Japanese T2D patients taking metformin. Surprisingly, 80% of patients did not have knowledge about sick days or lactic acidosis. In addition, more than 90% of patients did not know what to do during sick days or lactic acidosis. In particular, patients with a long duration of disease and patients who did not use injections were less likely to have knowledge of sick days or lactic acidosis. Thus, based on these facts, healthcare professionals should provide knowledge of sick days and lactic acidosis for T2D patients taking metformin. Moreover, sub-analysis showed that elderly patients were found to be more lacking in this knowledge. Since elderly patients have a higher risk of sick days and lactic acidosis,[17] healthcare professionals should take special care of elderly patients. It is unclear whether the doctor gave the patient information about sick days or lactic acidosis. In any case, the doctor needs to treat patients with the belief that they do not have an understanding of this information.

Overcoming clinical inertia is important to achieve treatment goals for diabetes.[18] Furthermore, it has been reported that treatment satisfaction was associated with improvements of adherence, compliance, and persistence.[19,20] Many patients felt unsatisfied with treatment, with the main reason being high medical cost. In fact, it needs high cost for treatment diabetes, including usage of insulin, although it has been reported that usage of inulin is effective for glycemic control.[21] Moreover, only 25% of patients always received an explanation of medical costs. One of the solutions to the medical cost might be frequent conversations between doctors and patients about treatment, including explaining medical costs. A previous study showed that many patients point out the importance of having a conversation with a doctor for treatment.[22] Another solution is the use of cheaper medications, such as combination medications. About 75% of patients wanted to change to a cheaper medication. In addition, patients that used injections and patients with monthly medical costs of treatment for T2D 6,000 JPY or more were more likely to feel unsatisfied with their medical costs. About 40% of patients were currently taking a combination medication, suggesting that their use has been widespread, but about 50% of patients still did not know about combination medications. Using these combination medications is useful not only for decreasing

medical costs, but also for enhancing medication adherence. Medication adherence is reported to be associated with glycemic control, diabetic complications, and overall costs.[23] Thus, the use of combination medications may be effective in overcoming clinical inertia. Furthermore, another solution is to enhance diet and exercise therapies. A previous study showed that these therapies are effective for glycemic control.[24]

In this study, 16.8% of patients answered that experience of treatment disruption, which is almost same as a previous report of 13% from Japan.[25] Treatment disruption is reported to be associated with risk of diabetic complications.[25] The reasons for treatment disruption in patients who experienced treatment disruption suggest that the presentation of medical cost to patients and informed choice are important to prevent treatment disruption. Moreover, sub-analysis showed that younger patients felt unsatisfied with treatment and medical costs. Since younger patients need continued treatment, healthcare professionals should take care more about medical costs and satisfaction with treatment.

We should mention the limitations of this study. First, this was a self-reported questionnaire survey. Thus, there is a possibility of false reporting. Second, many of the participants in this study were men. In addition, there is a possibility of selection bias, although participants were recruited from Asmarq's survey panel (D style web) that was registered through the general procedure. Lastly, this study included only Japanese people; thus, generalization to non-Japanese is unclear.

In conclusion, many patients with T2D taking metformin were not satisfied with their treatments, and the main reason was high medical cost. Moreover, they did not have sufficient knowledge of sick days and/or lactic acidosis.

Abbreviations

CVD	cardiovascular disease
DPP4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
T2D	type 2 diabetes

Availability of Data and Materials

Conflict of Interest

Funding

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