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Present status of sulfonylurea treatment for type 2 diabetes in Japan: second report of a cross-sectional survey of 15,652 patients

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Abstract. Sulfonylureas are commonly used for the treatment of patients with type 2 diabetes mellitus (T2DM). However, some clinical concerns regarding their use have grown over the past decade. Thus, results of a previous Japan-wide cross-sectional survey of patients with type 2 diabetes mellitus (T2DM) were analyzed to determine the present status and problems associated with the use of sulfonylureas in the treatment of T2DM by general practitioners (GPs) and diabetes specialists. Of 15,652 patients across 721 clinics and hospitals from the previous survey, 15,350 were diagnosed as T2DM (14,312 by GPs and 1,038 by specialists). For each patient, data were collected for HbA1c levels, age, height, body weight, and treatment modality. Of T2DM patients being treated by GPs, 35.4% and 60.0% received sulfonylureas in entire oral drugs or as monotherapy, respectively, compared with 29.2% and 61.2% of patients, respectively, treated by specialists. Of the patients treated with sulfonylurea monotherapy, 1335 patients (35.2%) achieved HbA1c <6.5%, whereas HbA1c was ≥8.0% in 531 patients (14.0%). Patients with HbA1c levels ≥8.0% had a higher body mass index, used glibenclamide more frequently, and used higher doses of sulfonylureas than patients in whom HbA1c levels were <6.5%. In conclusion, the present study shows that sulfonylureas are central in the treatment of T2DM in Japan. However, careful consideration of suitable patients, agents, and doses is necessary to achieve appropriate glycemic control.

Key words: Sulfonylurea, T2DM, Cross-sectional survey, HbA1c, General practitioner

SULFONYLUREAS are commonly used for the treatment of patients with type 2 diabetes mellitus (T2DM). The central position of sulfonylureas in the treatment of T2DM has been maintained over the years by many international guidelines, including the 1999 guidelines of the International Diabetes Federation (IDF) [1], the 2002 guidelines of the National Institute of Clinical Excellence [2], the 2004 guidelines of the American Diabetes Association [3], and even in the most recent 2005 IDF Global Guidelines for T2DM [4]. Despite the extensive use of sulfonylureas, clinical concerns regarding their use have grown over the past decade. Desensitization of insulin secretion with sulfonylurea is known as secondary sulfonylurea failure [5]. It is assumed that the secondary sulfonylurea failure is a state of loss of β-cell mass and function which may be induced by long-time over-stimulation of the β-cell with sulfonylurea and glucose toxicity [6,7]. Besides the development of hypoglycemia, bodyweight gain and limited specificity for β-cell K_{ATP} channels are the other concerns.

A survey of diabetes care specialists in Japan in 2002 found that approximately 40% of the entire patients with T2DM, that is 78% of patients on oral hypoglycemic agents (OHAs) were being treated with sulfonylureas alone or in combination with other OHAs [8]. In contrast, 26.1% and 20.6% of the entire patients with T2DM were being treated with sulfonylureas alone and or in combination with other OHAs in USA in 2000 [9]. It was reported that 29.4% of the entire patients with T2DM received monotherapy with

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sulfonylurea in France in 2003 [10] and 11.7% of the entire patients with T2DM did in Germany in 2004 [11]. Compared with other countries, the high proportion of T2DM patients being treated with sulfonylureas in Japan may be due to the fact that the insulin secretory capacity of most Japanese patients with T2DM is less than that of Caucasian T2DM patients [12]. However, the percentage of patients in Japan being treated with sulfonylureas alone decreased over the period 2000–2002 from 42.9% to 37.1%, respectively [8]. A combination of factors, such as reports on the adverse effects of sulfonylureas, the recent development of new drugs (e.g. nateglinide and thiazolidinedione (TZD) derivatives), and the results of clinical trials of combined drug therapy (e.g. the UKPDS [13, 14] and STOP NIDDM [15] studies), are likely to account for this trend. Therefore, we focused on the present status of OHA therapy, especially with sulfonylurea, excluding insulin therapy in this analysis of our previous cross-sectional survey in Japan.

In a previous study, using results from a cross-sectional survey of 15,652 patients with diabetes mellitus (DM) in Japan, we found that there was no significant difference in mean glycosylated hemoglobin (HbA1c) levels in patients being treated by general practitioners (GPs) or diabetes specialists, regardless of treatment modality [16]. Thus, the aim of the present study was to clarify the current status of and problems associated with the use of sulfonylureas in T2DM patients who were being treated by either a GP or a diabetes specialist so that the further appropriate use of sulfonylureas could be directed.

Materials and Methods

Ethical considerations

The protocol of the present study was approved by the Ethics Committee of the Japanese Medical and Dental Practitioners for the Improvement of Medical Care (JMDPIMC), which also included outside members such as lawyers and ethics experts. All patients provided informed consent prior to participation in the study, in accordance with the *Guidelines for Epidemiological Study in Japan*.

Patients and methods

As described previously [16], 8112 clinics and hospitals, randomly selected across Japan and comprising approximately 40% of all members of the JMDPIMC, were asked to participate in the study. In all, 721 clinics and hospitals agreed to participate in the study and 15,652 patients with type 1 DM (T1DM) or T2DM, ranging in age from 15 to 97 years, were enrolled in the study. The type of DM was determined on the basis of the criteria listed in the *Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus* [17], which are almost identical to the criteria of the World Health Organization [18]. Briefly, a diagnosis of T1DM was made in patients who were permanently insulinopenic and ketosis prone (idiopathic T1DM) or in those who were positive for autoimmune destruction markers, such as glutamic acid decarboxylase (immune-mediated T1DM). Of the 15,652 patients enrolled in the study, 15,350 were diagnosed as T2DM and, of these, 14,312 were being treated by a GP and 1038 were being treated by a specialist. The clinical characteristics of the patients treated between by a GP and a specialist, such as age (67.7 ± 11.0 *vs* 63.3 ± 12.0 yr), women/men ratio (47.9/52.1 *vs* 47.6/52.4 %) and BMI (24.4 ± 3.9 *vs* 24.1 ± 3.7 kg/m^2), were different as previously described [16]. In the present study, a 'diabetes specialist' was defined as a JDS board-certified diabetes care physician, whereas any other physicians were regarded as 'GPs'. In this study, 60 specialists and 661 GPs were participated and this ratio was almost compatible as the number of JDS board-certified diabetes care physicians / other physicians reported in each prefecture in Japan. Data were collected over the period 1–31 July 2006. To be included in the study, subjects had to visit clinics or hospitals regularly and to have their HbA1c levels determined at least once every 3 months. Each clinic or hospital was encouraged to enroll up to 30 patients in order of arrival. The most recent data for HbA1c, height, body weight, and drug therapy (including insulin), as well as the age and sex of the patients, were collected for analysis. Weight and height were measured using standard techniques and equipment. Body mass index (BMI) was calculated as the patient's weight (in kg) divided by height (in m) squared. Data were sent by fax to the central analytical facility, where the information was treated anonymously and subsequently analyzed using JMP software (SAS Institute, Cary, NC, USA).

Methods of HbA1c analysis

Almost all the GPs used the latex agglutination (LA) method to measure HbA1c, whereas almost all

the specialists used high-performance liquid chromatography (HPLC) and the number of GPs in the present study was greater than that of diabetes specialists. Furthermore, a good correlation has been confirmed for HbA1c values measured by the LA and HPLC methods [13]. Therefore, in the present study we used HbA1c levels determined by the LA method for comparisons.

Statistical analysis

Mean HbA1c levels and BMI were subjected to analysis of variance (ANOVA) followed by Tukey–Kramer's Honestly Significant Difference test. A Chi-square test was used to compare the distribution of HbA1c, patient type, and treatment modality between groups (i.e. GP treated or specialist treated). Moreover, to adjust the differences in age and sex of the patients treated between by GPs and specialists, we performed the analysis with generalized linear model (GLM). All statistical analyses were performed using JMP Version 6.0 software (SAS Institute) and $p < 0.05$ was considered significant. All results are expressed as the mean ± SD.

Results

Treatment modality for patients with T2DM

The treatment modality for T2DM differed significantly between patients being treated by GPs and those being treated by diabetes specialists ($p<0.0001$, Chi-square test). The proportion of patients being treated with an OHA was greater in the GP-treated group than in the diabetes specialist-treated group (73.2% *vs* 65.9%, respectively). However, mean HbA1c levels in patients being treated with an OHA did not differ between the GP- and diabetes specialist-treated groups, as described previously (7.0 ± 1.1% and 7.0 ± 1.2%, respectively) [16].

OHA therapy for patients with T2DM

The number of drugs used for OHA therapy differed significantly between the GP- and diabetes specialist-treated groups ($p<0.0001$, Chi-square test), even after adjusting the difference of sex and the age of the patients treated between by a GP and a specialist with GLM ($p<0.0001$; Fig. 1a). A larger proportion of patients being treated by GPs received monotherapy compared with patients being treated by a diabetes specialist (56.9% *vs*. 47.7%, respectively), and a smaller number received combined OHA therapy

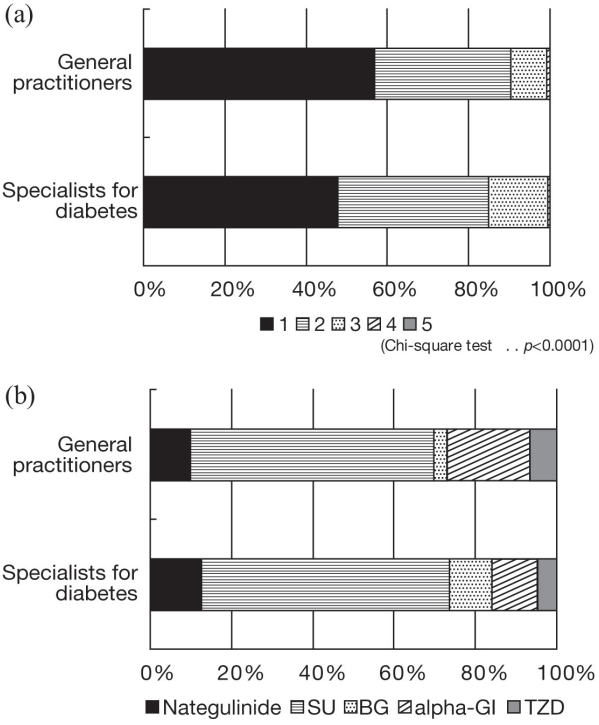

Fig. 1 Oral hypoglycemic agent (OHA) therapy for patients with type 2 diabetes mellitus (T2DM) being treated by general practitioners (GPs) or diabetes specialists in Japan. (a) The number of drugs used for OHA therapy differed significantly between GPs and specialists ($p<0.0001$, Chi-square test), with a larger proportion of GPs prescribing monotherapy. (b) OHAs used for monotherapy. Sulfonylureas were the most frequently used OHAs for the treatment of diabetes by both GPs and diabetes specialists.

(43.1% *vs*. 52.3%, respectively).

Various OHAs were used for the treatment of patients with T2DM, as shown in Fig. 1b. Sulfonylureas were the most frequently used drugs for the treatment of diabetes by both GPs and specialists. In the GP-treated group, sulfonylureas accounted for 35.4% of all OHAs used and were used in 60.0% of patients receiving monotherapy; in contrast, in the diabetes specialist-treated group, these figures were 29.2% and 61.2%, respectively. Sulfonylureas were used as part of combined OHA therapy by 79.6% and 85.6% of GPs and diabetes specialists, respectively.

Sulfonylurea agents used as monotherapy

Several sulfonylureas are available in Japan, with three sulfonylureas, namely glibenclamide, gliclazide, and glimepiride, most commonly used. The results of

the present study indicated that GPs and diabetes specialists used different sulfonylurea agents as monotherapy (p=0.001, Chi-square test), even after adjusting the difference of sex and the age of the patients treated between by a GP and a specialist with GLM (glibenclamide; p<0.0001, glimepiride; p=0.006, GLM), as shown in Fig. 2a Glibenclamide was used more frequently by GPs than by specialists (37.2% *vs*. 23.5%, respectively, p<0.0001 by GLM), whereas glimepiride was used more frequently by specialists than by GPs (54.0% *vs*. 43.6%, respectively, p=0.006 by GLM).

HbA1c levels of patients treated by sulfonylurea monotherapy

Mean HbA1c levels of patients treated with a sulfonylurea alone did not differ between those treated by GPs and those treated by diabetes specialists (6.9 ± 1.1% and 7.0 ± 1.1%, respectively). The rank of order of mean HbA1c levels according to treatment with glibenclamide, glimepiride, and gliclazide was 7.0 ± 1.2%, 6.9 ± 1.1%, and 6.7 ± 1.0%, respectively, in patients treated by GPs. The HbA1c levels in patients treated with glibenclamide were significantly higher than those in patients treated with either glimepiride (p=0.0001) or gliclazide (p<0.0001), with HbA1c levels in glimepiride -treated patients higher than those in patients treated with gliclazide (p=0.033; Fig. 2b). We had the same result with GLM for adjusting the age and sex of the patients treated between by a GP and a specialist. Although this rank order of mean HbA1c levels was the same for patients treated by specialists (7.1 ± 1.1%, 6.9 ± 1.1%, and 6.8 ± 1.3%, respectively), mean HbA1c levels did not differ significantly between the three sulfonylurea-treated groups. In addition, despite the trend for the prescription of different sulfonylureas by GPs and specialists, mean HbA1c levels in patients did not differ between the GP- and diabetes specialist-treated groups (Fig. 2b).

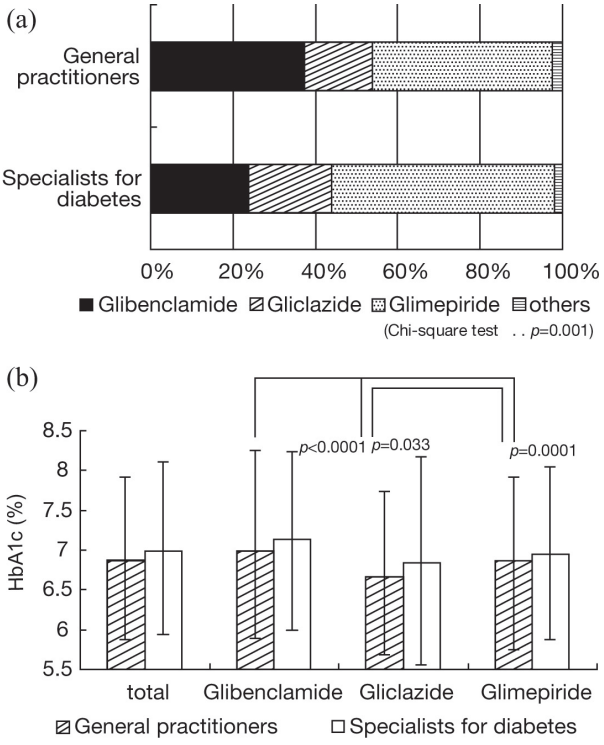

Fig. 2 Sulfonylurea monotherapy for patients with type 2 diabetes mellitus (T2DM) being treated by general practitioners (GPs) or diabetes specialists in Japan. (a) Sulfonylureas used for monotherapy. There was a significant difference in the types of sulfonylureas used as monotherapy by GPs and diabetes specialists (p=0.001, Chi-square test), with glibenclamide used more frequently by GPs than by specialists. (b) Mean (±SD) glycosylated hemoglobin (HbA1c) values in patients treated with different sulfonylureas. The rank order of mean HbA1c levels according to sulfonylurea treatment was glibenclamide > glimepiride > gliclazide, regardless of treatment by a GP or specialist. For patients under the care of a GP, mean HbA1c levels differed significantly between the three treatment groups. However, a significant difference was not seen in HbA1c levels for patients under the care of a diabetes specialist. There was no significant difference in mean HbA1c levels between patients treated by GPs and specialists across the treatment groups.

Patient characteristics according to HbA1c levels (≥8.0% or <6.5%)

Of the patients treated with sulfonylurea monotherapy, 1335 (35.2%) achieved HbA1c levels < 6.5%, whereas HbA1c levels were ≥8.0% in 531 (14.0%). Patients with HbA1c levels ≥8.0% had a higher BMI (24.7 ± 3.8 *vs*. 24.2 ± 3.6 kg/m^2; p=0.008) and were younger (66.0 ± 11.9 *vs*. 70.3 ± 10.5 years; p<0.0001) than patients with HbA1c levels<6.5% (Table 1). There was a significant difference in the frequency of the three sulfonylureas used as monotherapy in patients with HbA1c ≥8.0% compared with those in whom HbA1c levels were <6.5% (p<0.001, Chi-square test). The ratio of glibenclamide : gliclazide : glimepiride use in patients with HbA1c levels ≥8.0% was 43.9 : 11.5 : 45.2, compared with 32.7 : 38.5 : 45.2 in patients in whom HbA1c levels were <6.5% (Table 1). Moreover, the daily dose of each sulfony-

Table 1 Patient characteristics according to glycosylated hemoglobin level

	HbA1c		*p* value
	<6.5%	≥8.0%	
No. patients (%)	1355 (35.2)	531 (14.0)	
BMI (kg/m^2)	24.2 ± 3.6	24.7 ± 3.8	0.008
Age (years)	70.3 ± 10.5	65.9 ± 11.9	<0.0001
Drugs for monotherapy			
Glibenclamide : gliclazide : glimepiride (%)	32.7 : 38.5 : 45.2	43.9 : 11.5 : 42.2	<0.0001
Mean dose of sulfonylurea (mg)			
Glibenclamide	2.3 ± 1.6	4.2 ± 2.2	<0.0001
Gliclazide	36.5 ± 18.6	62.0 ± 31.6	<0.0001
Glimepiride	1.4 ± 0.9	2.8 ± 1.6	<0.0001

Where appropriate, data are given as the mean ± SD.
HbA1c, glycosylated hemoglobin; BMI, body mass index.

Table 2 Mean glycosylated hemoglobin levels and sulfonylurea dose according to body mass index

	BMI (kg/m^2)		*p* value
	<25	≥25	
HbA1c (%)	6.85 ± 1.13	6.92 ± 1.10	0.058
Dose of sulfonylurea (mg)			
Glibenclamide	3.0 ± 2.0	3.0 ± 2.0	0.978
Gliclazide	41.7 ± 24.5	45.4 ± 24.5	0.072
Glimepiride	1.8 ± 1.2	1.8 ± 1.3	0.725

Data are given as the mean ± SD.
HbA1c, glycosylated hemoglobin; BMI, body mass index.

lurea used was significantly higher in patients with HbA1c levels ≥8.0% compared with patients in whom HbA1c levels were <6.5% (p<0.0001; Table 1).

Mean HbA1c levels and sulfonylurea doses in patients with BMI <25 or ≥25 kg/m^2

Mean HbA1c levels tended to be higher in patients with a BMI ≥25 kg/m^2 compared with patients with a BMI <25 kg/m^2 (p=0.058). However, the doses of the sulfonylureas used did not differ between patients with a BMI ≥25 and <25 kg/m^2 (Table 2).

Mean HbA1c levels and BMI in patients receiving combined OHA therapy including sulfonylureas

In the GP-treated group, mean HbA1c levels were significantly lower for patients treated with a sulfonylurea alone compared with patients treated with other OHAs. In addition, mean HbA1c levels were significantly lower for patients treated with a sulfonylurea alone in the specialist-treated group compared with those patients treated with a sulfonylurea plus biguanide or a sulfonylurea plus a TZD (Fig. 3a). The BMI of patients treated with a sulfonylurea alone was significantly lower than that of patients treated with a sulfonylurea plus biguanide, a sulfonylurea plus a TZD, and sulfonylurea plus biguanide and TZD in both the GP- and specialist-treated groups (Fig. 3b).

Discussion

The results of the present study indicate that, in Japan, both GPs and diabetes specialists largely use sulfonylureas, either as monotherapy or in combination therapy, for the treatment of patients with T2DM. The frequency of monotherapy with an OHA was significantly less for patients under the care of a diabetes specialist compared with patients being treated by a GP. However, the proportion of sulfonylureas used as monotherapy by specialists and GPs did not differ significantly. The use of sulfonylureas as monotherapy by diabetes specialists has reportedly decreased recently in Japan [8], with sulfonylurea monotherapy for T2DM accounting for 37.1% of entire OHA therapy in 2002. In the present study, sulfonylurea monotherapy was found to account for 29.2% and 35.4% of all OHA therapy administered by diabetes specialists and GPs,

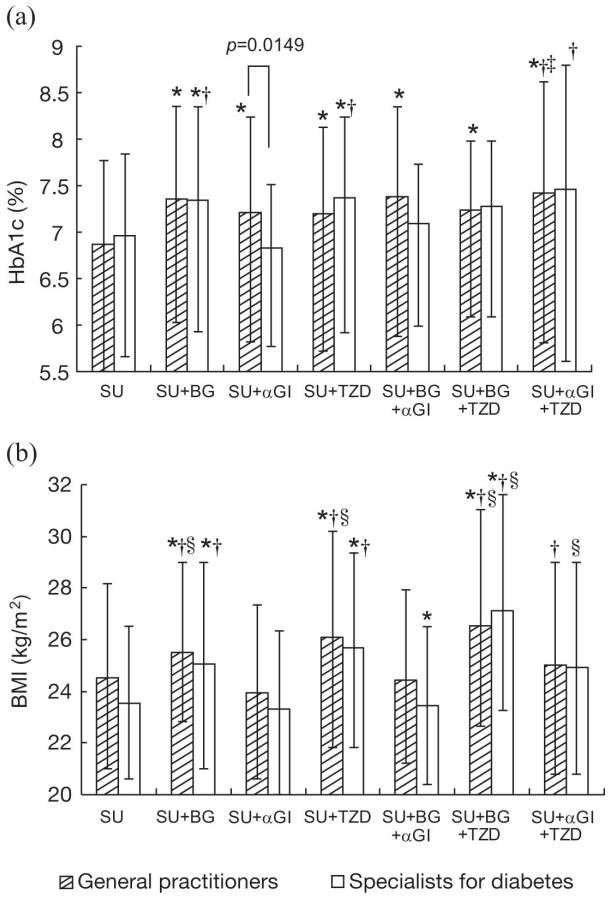

Fig. 3 Mean (a) glycosylated hemoglobin (HbA1c) levels and (b) body mass index (BMI) in patients receiving sulfonylurea monotherapy or combination OHA therapy. SU, sulfonylurea; BG, biguanide; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor. The mean HbA1c levels of patients receiving SU+α-GI therapy were higher for patients under the care of a general practitioner (GP) than for those under the care of a diabetes specialist (P=0.0149). Data are the mean ± SD. *p<0.05 compared with monotherapy by the same health care professional (i.e. GP or diabetes specialist); †p<0.05 compared with SU+α-GI prescribed by the same health care professional; ‡p<0.05 compared with SU+TZD prescribed by the same health care professional; §p<0.05 compared with SU+BG+α-GI prescribed by the same health care professional.

respectively. These figures suggest that the use of sulfonylurea monotherapy continues to decline in Japan.

Different OHAs are used to treat T2DM depending on the individual pathogenesis in each patient. For example, α-glucosidase inhibitors (α-GI) are used to treat postprandial hyperglycemia; biguanide or TZDs are used in cases of insulin resistance; and nateglinide or sulfonylureas are used in patients with deficient insulin secretion. Impaired insulin secretion and insulin resistance both contribute to the pathogenesis of T2DM. Most diabetic patients in Japanese begin with decreased insulin secretion, but a small group of diabetic patients, especially obese subjects, may start with insulin resistance [12]. The fact that sulfonylureas were the most frequently used drugs in the present study, either as monotherapy or in combination with other OHAs, may be due to their particular suitability for use in Japanese patients based on the pathogenesis of their diabetes. In conjunction with our results, sulfonylureas continue to be the most commonly used OHA worldwide for the treatment of T2DM [19] because they are reliable, efficacious, cause very few side effects (mainly hypoglycemia), and are relatively inexpensive.

Despite the extensive use of sulfonylureas, concerns have grown over the past decade regarding the risk of hypoglycemia, body weight gain, and β-cell exhaustion following the use of sulfonylureas, as well as their limited specificity for β-cell K_{ATP} channels. It has been reported that modest weight gain occurs following sulfonylurea therapy and that excess insulin remaining in the circulation causes insulin-dependent fatty acid synthesis, which further contributes to weight gain [20]. Conversely, glimepiride has been reported to be neutral with respect to body weight gain, so a more considered choice of agent may allow for easier control of body weight, even in overweight patients [21]. In the present study, there were no significant differences in mean HbA1c levels and the dose of sulfonylureas administered between patients with a BMI <25 and those with a BMI ≥25 kg/m^2. Also the patients with HbA1c levels ≥8.0% tended to have a higher BMI than patients in whom HbA1c levels were <6.5%. For this reason, there are two possible explanations. One may be the adverse effect of the sulfonylureas, and the other may be inappropriate use in obese patients.

In Japan, three sulfonylureas, namely second-generation agents glibenclamide and gliclazide and the third-generation sulfonylurea glimepiride, are widely used for the treatment of T2DM. There appear to be some differences in the pharmacological properties of these three drugs. The plasma insulin-increasing and blood glucose decreasing activity among these sulfonylureas are the order of glimepiride < gliclazide < glibenclamide [5], and the rate of secondary sulfonylurea failure has been reported to be greatest for glibenclamide and least for gliclazide [22]. Glimepiride

may be expected to have lower rate of secondary failure, because of lower binding affinity and highly dissociation rate for the beta cell receptor compared with other sulfonylureas [23]. However, the rate of secondary failure in glimepiride has not been elucidated yet. The pharmacological characteristics of these agents may have had some bearing on the greater use of glibenclamide in patients with HbA1c levels ≥8.0%.

The maximum daily dose of a sulfonylurea is recommended by each manufacturer. However, several studies have demonstrated that the maximum effective doses of sulfonylureas are much lower than the recommended maximum daily dose [24, 25]. Consistent with these reports, the daily dose of each sulfonylurea in the present study was found to be lower in patients with HbA1c levels <6.5% compared with patients with HbA1c levels ≥8.0% (Table 1). These results suggest that therapeutic strategies need to be modified if effective glycemic control is not achieved despite the use of the maximum daily dose of sulfonylureas.

When desirable HbA1c levels cannot be achieved by sulfonylurea monotherapy, the next therapeutic choice may be either the addition of another oral agent or the initiation of insulin therapy. However, in the present study, regardless of whether patients were being treated by a GP or diabetes specialist, mean HbA1c levels and BMI were higher in patients receiving combination therapy with a sulfonylurea with either biguanide or TZD than in patients receiving sulfonylurea monotherapy (Fig. 3a). This suggests that, for Japanese T2DM patients, the addition of either biguanide or TZD to sulfonylurea does not necessarily improve glycemic control. It has been reported that the metformin monotherapy reduced body weight and reversed the weight gain by sulfonylurea in combination with sulfonylurea, while BMI of the patients treated with sulfonylurea alone compared with sulfonylurea plus metformin was variable [26, 27]. Our study was not longitudinal and could not detect the changes in body weight, therefore, we could not discuss the desirable effect of metformin on BMI. In contrast, in the diabetes specialist-treated group, mean HbA1c levels and BMI did not differ between patients treated with a combination of sulfonylureas plus α-GI and those treated with sulfonylurea monotherapy. Also in a combination of sulfonylureas plus α-GI, mean HbA1c levels and BMI of the patients treated by a spcialsit was lower than those treated by a GP, even after adjusting the difference of age and sex with GLM (p=0.002). Previous studies have reported that α-GI treatment in combination with sulfonylurea or TZD prevents the body weight gain seen in patients treated with sulfonylurea or TZD alone [28, 29]. Thus, combination therapy with α-GI may be potentially useful in preventing body weight gain. Furthermore, in the present study mean HbA1c levels tended to increase with the number of agents used. This suggests that even combination OHA therapy has limitations in terms of satisfactory glycemic control. The results of our study may reflect the difficulty in glycemic control of the patients without enhancement of lifestyle intervention or initiation of insulin therapy. This observation may also depend on the difference in lifestyle intervention between diabetes specialist and GP, and the fact that some patients or GP still hesitate to initiate insulin therapy despite poor glycemic control.

This study has some limitations. First, this study is cross-sectional and observational. Second, the clinics and the hospitals that participated in this study compromised approximately 10% of all practitioners in Japan. It is likely that only practitioners who have an interest in diabetes care may have agreed to take part in this study, because participation was voluntary. Third, the duration of the diabetes have not be surveyed, because the query was intended to be easier for general practitioners.

In conclusion, sulfonylureas still occupy a central position in the treatment of T2DM in Japan. However, 14% of patients receiving sulfonylurea monotherapy had HbA1c levels ≥8.0%. To achieve good glycemic control, careful consideration of suitable patients, agents, and doses is necessary. Unless satisfactory glycemic control has been achieved by monotherapy with a maximum dose of sulfonylureas or combined OHA therapy, other therapeutic strategies, such as intensification of lifestyle interventions or initiation of insulin therapy, should be considered.

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No potential conflicts of interest relevant to this article were reported.

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