JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Current status of oral antidiabetic drug prescribing patterns based on the body mass index for Japanese type 2 diabetes mellitus patients and yearly changes in diabetologists' prescribing patterns from 2002 to 2019 (JDDM61)

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Keywords
Antidiabetic drugs, Body mass index, Diabetes mellitus type 2

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J Diabetes Investig 2022; 13: 65–73

doi: 10.1111/jdi.13621

[Correction added on 4 September 2021, after first online publication: The article's title, corresponding author's email address, and reference 26 have been amended.]

ABSTRACT

Aims/Introduction: Type 2 diabetes mellitus is caused by a relative imbalance between insulin secretion and sensitivity related to the body mass index (BMI). Seven categories of oral antidiabetic drugs (OADs) are available in Japan. It is important to assess the OAD utilization patterns based on patients' BMI levels.

Materials and methods: OAD prescribing patterns from 2002 to 2019 were analyzed using the data collected in the computerized diabetes care database provided by the Japan Diabetes Clinical Data Management Study Group; OAD utilization patterns in 25,751 OAD-treated type 2 diabetes mellitus patients registered in 2019 were analyzed after classifying them into five categories of BMI.

Results: Comparing OAD usage between 2002 and 2019, sulfonylureas decreased from 44.5 to 23.2%, and biguanides (BGs) increased from 19.3 to 50.3%. Dipeptidyl peptidase-4 inhibitors (DPP4is) increased to 56.9% in 2019. Sodium–glucose cotransporter 2 inhibitors (SGLT2is) increased to 23.6% in 2019. About 90% of type 2 diabetes mellitus patients had BMI < 30 kg/m^2. DPP4is were the most used OADs in 2019. When BMI exceeded 30 kg/m^2, use of BGs and sodium–glucose cotransporter 2 inhibitors increased, and use of sulfonylureas and DPP4is decreased. Although DPP4is were the most used OADs for patients with BMI <30 kg/m^2, they were the third most prescribed OADs for patients with BMI >35 kg/m^2 after BGs and sodium–glucose cotransporter 2 inhibitors .

Conclusions: DPP4i usage was as high as that of BG in the analysis of Japanese type 2 diabetes mellitus patients with relatively low BMI. This was considered to be a treatment option appropriate for the pathophysiology in Japanese patients.

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Received 31 March 2021; revised 18 June 2021; accepted 27 June 2021

INTRODUCTION

The International Diabetes Federation reported in November 2019 that the number of adult diabetes mellitus patients reached 436 million worldwide, 90% of whom had type 2 diabetes mellitus[1]. It was also reported that the number of Japanese diabetes mellitus patients exceeded 10 million in 2016[2]. In contrast, the types of currently available oral antidiabetic drugs (OADs) are increasing, and their efficacy is improving[3]. The first OAD, phenformin, was used in Japan in 1954, and from then to around 1990, just two types of OADs, biguanides (BGs) and sulfonylureas (SUs), were available[4]. OADs with different actions, such as α-glucosidase inhibitors (αGIs), thiazolidinediones (TZDs) and glinides, were launched until 1999. Dipeptidyl peptidase-4 inhibitors (DPP4is) were launched in 2009, and sodium–glucose transporter 2 inhibitors (SGLT2is) were launched in 2014; now, seven types of OADs are available in Japan. However, general clinicians who do not specialize in diabetes often find it difficult to choose OADs.

Countries around the world are preparing their own diabetes mellitus treatment guidelines, useful for providing appropriate treatment. All guidelines, excluding the Japanese guidelines, positioned BGs, especially metformin, as the first-line OAD, and other OADs as the second-line agents for add-on therapy according to the presence of diabetic complications[5–7]. The guideline of the Japan Diabetes Society does not assume a specific OAD as a first-line or second-line drug, and recommends the appropriate selection of OADs according to the pathophysiology, metabolic status and patient's age[8]. Therefore, it becomes somewhat difficult for general clinicians to select appropriate drugs.

East Asian people, including Japanese people, develop type 2 diabetes mellitus despite having a lower BMI than white people. It is known that the pathophysiological characteristics of diabetes mellitus in East Asian people are low insulin secretion and better insulin sensitivity[9–13]. Therefore, diabetes treatment strategies might differ between white people and East Asian people, including Japanese people.

In the present study, the kinds of OADs selected by Japanese diabetologists according to the Japanese guideline for type 2 diabetes mellitus with lower BMI than in Western countries and the resulting glycemic control status were analyzed.

MATERIALS AND METHODS

Participants and study procedures

The data collected in the computerized diabetes care (CoDiC) database provided by the Japan Diabetes Clinical Data Management Study Group (JDDM) were analyzed cross-sectionally from 2002 to 2019. The JDDM is composed of Japanese diabetologists belonging to specialized facilities for diabetes treatment, and they established the CoDiC database in 2001[14]. The basic patient data are published on the JDDM homepage as basic research reports, and the content is updated annually[15]. The data of type 2 diabetes mellitus patients who visited JDDM facilities from May to July in each year were extracted from the CoDiC database and analyzed retrospectively.

The yearly course of OAD prescribing patterns was analyzed from 2002 to 2019. OADs were classified into seven categories: SUs, BGs, αGIs, glinides, TZDs, DPP4is and SGLT2is. When combination agents were used, each component was considered as a single OAD.

In 2019, 46,701 patients with type 2 diabetes mellitus were registered in CoDiC from 52 specialized facilities for diabetes treatment, and 25,751 patients treated with OADs and without either insulin or glucagon-like peptide-1 receptor agonists were recruited into the present study. The analyzed overall patient background included six clinical parameters (age, sex, duration of diabetes, BMI, glycated hemoglobin [HbA1c] and estimated glomerular filtration rate [eGFR]), OAD usage rate and the number of OADs used. Targeted patients were categorized into five groups according to their BMI, namely BMI <18.5 (underweight [UW], $n = 926$), $18.5 < \text{BMI} < 25$ (normal range, $n = 14{,}241$), $25 < \text{BMI} < 30$ (obese 1, $n = 7{,}962$), $30 < \text{BMI} < 35$ (obese 2 [OB2], $n = 2{,}037$), and BMI >35 kg/m^2 (obese 3 [OB3], $n = 585$), and the relationships between the OAD usage rate, the number of OADs used and five clinical parameters (sex, age, duration of diabetes, HbA1c and eGFR) were analyzed.

Statistical analysis

All statistical analyses were carried out with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[16]. As 17 analyzed parameters showed a non-parametric distribution (Kolmogorov–Smirnov test), these data are reported as medians (25–75th percentiles, interquartile range). A logistic regression analysis was carried out using six parameters (BMI, sex, age, age of onset, HbA1c and eGFR) to examine determinants of the use of each of the seven OADs, and each odds ratio (95% confidence interval) was calculated.

Ethics statement

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. The JDDM ethics committee, Approval No. JDDM2019-6 (12 May 2019). Written, informed consent was not required from patients because of the retrospective nature of this study. The option to 'opt out' and how to do it were made clear through a poster in each clinic describing the study[15].

RESULTS

Evaluation of the OAD prescribing patterns from 2002 to 2019

Five types of OADs were evaluated from 2002 to 2009, DDP4is were added to the evaluation from 2010, and seven types of OADs including SGLT2is were evaluated from 2014 to 2019. As shown in Figure 1, SUs were the most used OADs in 2002 (44.5%), but the usage rate decreased to 23.2% in 2019 ($P < 0.0001$, χ^2-test). BGs were prescribed to 19.3% of patients in 2002, but their usage increased to 50.3% in 2019 ($P < 0.0001$). The usage rates of αGIs, TZDs and glinides were 17.8, 5.5 and 3.9% in 2002, respectively, and they were 14.4, 8.9 and 7.0% in 2019, respectively. The usage of TZD peaked in 2010 (18.2%), but then decreased.

The DPP4i usage rate reached 44.5% in 2013, surpassing the usage rate of BGs and SUs, and became the most used OAD. The DPP4i usage rate decreased temporarily in 2016, but remained the most used OAD until 2019 (56.9%). Although the SGLT2i usage rate could not outpace the increasing DPP4i usage rate, the usage rate in 2019 exceeded the SU usage rate (23.6%).

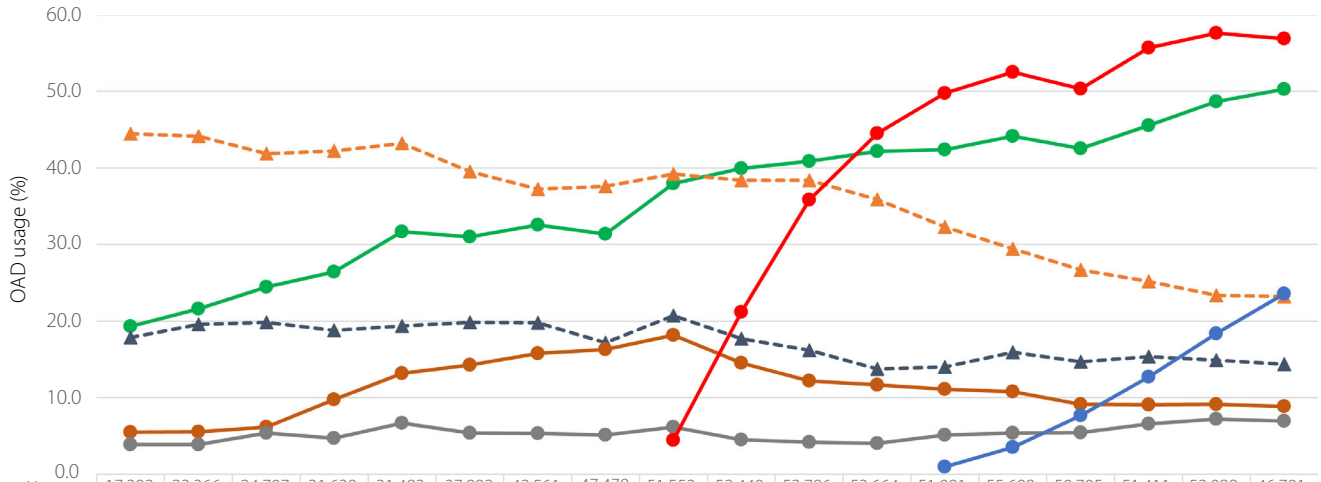
Clinical background of type 2 diabetes mellitus patients in 2019

In 2019, 46,701 patients with type 2 diabetes mellitus were registered in CoDiC. The results of 25,751 diabetes mellitus patients treated with OADs and without either insulin or glucagon-like peptide-1 receptor agonists are also shown in Table 1. The proportion of men was 64.6%, the median age was 69.0 years (60.0–75.0 years), disease duration was 14.7 years (8.2–19.5 years), the BMI was 24.1 kg/m^2 (22.0–26.9 kg/m^2) and HbA1c was 6.9% (6.5–7.4%). The OAD prescription rate was the highest for DPP4is at 75.6%, followed by BGs (64.4%), SUs (32.7%), SGL2s (27.0%), αGIs (15.9%), TZDs (11.1%) and glinides (7.3%).

OAD monotherapy was given to 25.8% of patients, 31.4% were treated with two OADs and 27.7% were given three OADs.

Logistic regression analysis of clinical parameters related to OAD prescribing patterns in 2019

Table 2 shows the results of logistic regression analysis using six parameters (BMI, sex, age, duration of diabetes, HbA1c and eGFR) as explanatory variables, and each OAD usage as the



No.	17,392	23,366	24,707	31,639	31,483	37,992	42,561	47,470	51,552	52,440	53,796	53,664	51,091	55,698	50,705	51,411	52,088	46,701
Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
BGs	19.3	21.6	24.5	26.4	31.7	31.0	32.5	31.4	37.9	39.9	40.9	42.2	42.4	44.2	42.5	45.6	48.7	50.3
SUs	44.5	44.1	41.9	42.2	43.2	39.5	37.2	37.6	39.2	38.4	38.4	35.9	32.3	29.5	26.7	25.2	23.4	23.2
αGIs	17.8	19.6	19.9	18.8	19.4	19.8	19.8	17.2	20.7	17.7	16.2	13.8	14.0	15.9	14.7	15.4	14.9	14.4
TZDs	5.5	5.5	6.2	9.7	13.2	14.3	15.8	16.3	18.2	14.6	12.2	11.7	11.1	10.8	9.1	9.1	9.1	8.9
Glinides	3.9	3.9	5.4	4.7	6.7	5.4	5.3	5.1	6.2	4.5	4.2	4.0	5.1	5.4	5.4	6.6	7.2	7.0
DPP4is									4.5	21.2	35.8	44.5	49.7	52.5	50.3	55.7	57.6	56.9
SGLT2is													1.0	3.5	7.7	12.7	18.4	23.6

BGs, biguanides : SUs, sulfonylureas : αGIs, α-glucosidase inhibitors ; TZDs, thiazolidinediones ; DPP4is, dipeptidyl peptidase-4 inhibitors ;SGLT2is, sodium-glucose cotransporter 2 inhibitors.

Figure 1 | Oral antidiabetic drug (OAD) prescribing patterns in patients with type 2 diabetes by year from 2002 to 2019. The number of patients with type 2 diabetes mellitus registered in the computerized diabetes care database from 2002 to 2019. The prescription rates of the oral hypoglycemic drugs used are shown for each year. αGIs, α-glucosidase inhibitors; BGs, biguanides; DPP4is, dipeptidyl peptidase-4 inhibitors; SGLT2is, sodium–glucose cotransporter 2 inhibitor; SUs, sulfonylureas; TZDs, thiazolidinediones.

Table 1 | Clinical characteristics of patients with type 2 diabetes mellitus treated with oral antidiabetic drugs, but not insulin or glucagon-like peptide-1 receptor agonists

Variables	Median (IQR) or (%)	*n*
Age (years)	69.0 (60.0–75.0)	25,751
Men/women (%)	64.6/35.4	16,644/9,107
Duration of diabetes (years)	14.7 (8.2–19.5)	25,415
Body mass index (kg/m^2)	24.1 (22.0–26.9)	25,751
Glycated hemoglobin (%)	6.9 (6.5–7.4)	25,751
Estimated glomerular filtration rate (10 mL/min/1.73 m^2)	6.9 (5.7–8.1)	22,473
Biguanide usage	64.4	16,582
Sulfonylurea usage	32.7	8,424
α-Glucosidase inhibitor usage	15.9	4,094
Thiazolidinedione usage	11.1	2,864
Glinide usage	7.3	1,878
Dipeptidyl peptidase-4 inhibitor usage	75.6	19,470
Sodium–glucose cotransporter 2 inhibitor usage	27.0	6,954
One oral antidiabetic drug monotherapy	25.8	6,648
Two oral antidiabetic drugs combination therapy	31.4	8,078
Three oral antidiabetic drugs combination therapy	27.7	7,141
Four oral antidiabetic drugs combination therapy	13.2	3,400
Five oral antidiabetic drugs combination therapy	1.8	465
Six oral antidiabetic drugs combination therapy	0.1	19

Data are presented as median (interquartile range [IQR]) or percentage.

objective variable. The odds ratios of clinical parameters for each OAD usage were compared. BMI was positively associated with BGs (odds ratio 1.05, $P < 0.001$), TZD (odds ratio 1.12, $P < 0.001$) and SGLT2is use (odds ratio 1.15, $P < 0.001$), and negatively associated with SUs (odds ratio 0.98, $P < 0.001$), αGIs (odds ratio 0.93, $P < 0.001$), glinides (odds ratio 0.91, $P < 0.001$) and DPP4is use (odds ratio 0.94, $P < 0.001$). Female sex was negatively associated with SGLT2is use (odds ratio 0.88, $P < 0.001$). Age was positively associated with SU (odds ratio 1.01, $P < 0.001$), αGIs (odds ratio 1.01, $P < 0.001$), TZDs (odds ratio 1.01, $P = 0.001$), glinides (odds ratio 1.01, $P < 0.001$) and DPP4is (odds ratio 1.01, $P < 0.001$) use, and negatively associated with BGs (odds ratio 0.95, $P < 0.001$) and SGLT2is (odds ratio 0.96, $P < 0.001$) use. Duration of diabetes was positively associated with all OADs. HbA1c had a positive correlation with all OADs except αGIs, with a particularly high correlation with SUs (odds ratio 2.40, $P < 0.001$). The eGFR was positively associated with BGs (odds ratio 1.12, $P < 0.001$), SUs (odds ratio 1.05, $P < 0.001$) and SGLT2is (odds ratio 1.03, $P = 0.003$) use, and negatively associated with αGIs (odds ratio 0.89, $P < 0.001$) and glinides (odds ratio 0.94, $P < 0.001$) use.

Analysis of the OAD prescribing patterns in 2019 by BMI

Of the 25,751 patients treated with OADs in 2019, the numbers (%) of UW, normal range, obese 1, OB2 and OB3 were 926 (3.6%), 14,241 (55.3%), 7,962 (30.9%), 2,037 (7.9%) and 585 (2.3%), respectively (Table 3). Although the proportion of women was 35.4% in total, UW, OB2 and OB3 had higher proportions of women. The median age decreased with increased BMI ($P < 0.001$, Kruskal–Wallis test). With higher current BMI, the duration of diabetes was shorter ($P < 0.001$), and HbA1c was higher ($P < 0.001$). With the increase of BMI, eGFR increased. BGs, TZDs and SGLT2is use each increased with BMI ($P < 0.0001$, χ^2-test). In contrast, SUs, αGIs, DPP4is and glinides use decreased with BMI.

DPP4is (83.3%, 79.8%) were the most prescribed for the UW and NW groups, followed by BGs (42.8%, 60.2%) and SUs (32.5%, 34.9%).

In the obese 1 group, the prescription of SUs decreased, and the order was DPP4is (71.7%), BGs (71.0%) and SGLT2is (36.9%). In the OB2 group, the prescriptions for DPP4is and BGs were reversed, resulting in BGs (74.0%), DPP4is (63.8%) and SGLT2is (52.1%). Furthermore, in the OB3 group, the prescriptions of DPP4is and SGLT2is were reversed, so that the order was BGs (77.1%), SGLT2is (65.5%) and DPP4is (56.1%). In terms of the number of drugs, monotherapy was the most common for the UW group, and the combination of two drugs was common from the normal range to OB3 groups. The patients with four or more combinations had a higher proportion of patients with higher BMI.

DISCUSSION

The present study investigated OAD prescribing patterns in a large number of Japanese type 2 diabetes mellitus patients registered in the CoDiC database from 2002 to 2019, and further analyzed the details of OAD prescribing patterns in 2019. This was an analysis of OAD utilization patterns, as prescribed by Japanese diabetologists. As in reports outside Japan[17–20], in the present study, the usage rate of SUs, which were prescribed the most in 2002, decreased significantly until 2019, and the BG usage rate increased instead. The decrease in the use of SUs is thought to be due to the high efficacy of metformin shown in the UK Prospective Diabetes 34 Study (UKPDS34)[21] and the increase in severe hypoglycemia in diabetes patients in Japan caused by the combination of SUs and sitagliptin, which was launched in 2009[22]. Furthermore, it is believed that the inhibition of ischemic preconditioning by glibenclamide[23,24] and the results of the Action to Control Cardiovascular risk in Diabetes (ACCORD) study[25] raised awareness of the severe hypoglycemia risk and led to a decrease in the SU usage rate.

Since its first appearance in 2009, DPP4i usage has continued to grow, with DPP4is becoming the most prescribed OADs in 2013. After that, the DPP4i usage rate decreased temporarily in

Table 2 | Logistic regression analysis of clinical parameters related to oral antidiabetic drugs prescribing patterns in 2019

	BGs		SUs		αGIs		TZDs		Glinides		DPP4is		SGLT2is	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
BMI (kg/m^2)	1.05 (1.05-1.06)	<0.001	0.98 (0.98-0.99)	<0.001	0.93 (0.92-0.94)	<0.001	1.12 (1.11-1.13)	<0.001	0.91 (0.90-0.93)	<0.001	0.94 (0.93-0.94)	<0.001	1.15 (1.14-1.16)	<0.001
Sex[†]	1.07 (1.00 −1.14)	0.037	1.00 (0.94-1.07)	0.935	1.01 (0.94-1.09)	0.704	0.86 (0.78-0.94)	0.001	0.95 (0.86-1.06)	0.396	1.01 (0.95-1.09)	0.664	0.88 (0.82-0.94)	<0.001
Age (years)	0.95 (0.95-0.96)	<0.001	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	0.001	1.01 (1.01-1.02)	<0.001	1.01 (1.01-1.01)	<0.001	0.96 (0.96-0.96)	<0.001
Duration of diabetes (years)	1.04 (1.03-1.04)	<0.001	1.07 (1.06-1.07)	<0.001	1.01 (1.00-1.01)	<0.001	1.04 (1.03-1.05)	<0.001	1.02 (1.01-1.02)	<0.001	1.02 (1.01-1.02)	<0.001	1.01 (1.01-1.02)	<0.001
HbA1c (%)	1.39 (1.33-1.46)	<0.001	2.40 (2.29-2.51)	<0.001	0.93 (0.89-0.98)	0.005	1.06 (1.01-1.12)	0.024	1.13 (1.06-1.21)	<0.001	1.45 (1.39-1.52)	<0.001	1.51 (1.44-1.57)	<0.001
eGFR (10 mL/min/1.73 m^2)	1.12 (1.10-1.14)	<0.001	1.05 (1.03-1.07)	<0.001	0.89 (0.87-0.91)	<0.001	1.02 (1.00-1.05)	0.058	0.94 (0.92-0.97)	<0.001	0.99 (0.97-1.00)	0.139	1.03 (1.01-1.05)	0.003

$P < 0.05$ was considered significant. [†]Men (0), women (1). αGIs, α-glucosidase inhibitors; BGs, biguanides; BMI, body mass index; DPP4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; OR, odds ratio; SGLT2is, sodium–glucose cotransporter 2 inhibitors; SUs, sulfonylureas; TZDs, thiazolidinediones.

2016. The decrease was thought to be due to increased SGLT2i use based on the results of the Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose published in 2015[26]. DPP4is and SGLT2is are expensive OADs in Japan, and it is thought that SGLT2is were used alone, avoiding combined use from the perspective of cost.

The present study found that 58.9% of Japanese people with type 2 diabetes mellitus have a BMI <25, 30.9% have a BMI of 25 to <30 and just 10.2% have a BMI ≥30 kg/m^2. The OAD prescribing trend in Japanese patients with type 2 diabetes mellitus is characterized by the fact that DPP4is prescriptions exceed those of BGs, unlike reports in other countries[17–20,27]. Previous reports have stated that the reason for DPP4is being the most prescribed OADs in Japan is their pharmacological characteristic of a low risk of hypoglycemia[27]. However, SGLT2is prescriptions, which have the same low risk of hypoglycemia as DPP4is, do not produce the same results as DPP4is prescriptions.

Among OADs other than αGIs, the proportion of insulin-secretory OADs, such as DPP4is, SUs and glinides, decreased as BMI increased, and that of non-insulin-secretory OADs, such as BGs, TZDs and SGLT2is, increased as BMI increased.

The present study also showed that DPP4is, categorized as insulin secretagogues, were used at a high rate in patients with BMI <25 kg/m^2. DPP4is, categorized as insulin secretagogues, and BGs, categorized as non-insulin secretory secretagogues, were used in patients with 25 ≤ BMI < 30 kg/m^2. Usage of DPP4is and BGs was reversed between BMIs of 30 and 35 kg/m^2, and BGs and SGLT2is were used for patients with BMI >35 kg/m^2.

Furthermore, OAD monotherapy was given to 25.8%, two OADs were given to 31.4% and three OADs were given to 27.7%. SGLT2is were selected for obese patients, and DPP4is were selected for non-obese patients. From these results, it was clarified that the change in the OAD trends in Figure 1 is the result of prescription by Japanese diabetologists according to the pathophysiology of type 2 diabetes mellitus.

There are many factors, such as efficacy, safety and economics, involved in the selection of OADs for diabetes patients. It is known that type 2 diabetes mellitus is caused by an increase in BMI that reduces insulin sensitivity, resulting in an imbalance between insulin secretion and sensitivity[28–30]. Metformin, a main BG, is an excellent OAD that meets all of the aforementioned criteria for drug selection[6,21]. Although there is a strong correlation between BMI and the onset of type 2 diabetes mellitus[28], it has been reported that East Asian people, including Japanese people, develop type 2 diabetes mellitus at lower BMIs than white people[9–13]. It has also been reported that Asian people obtain a stronger HbA1c lowering effect with DPP4is than non-Asian people[31]. Including the present study, many studies have reported that DPP4i usage was higher than that of BGs for the treatment of type 2 diabetes mellitus in Japan[27,32]. Seino *et al.* stated that DPP4is have potential as

Table 3 | Analysis of oral antidiabetic drug prescribing patterns in 2019 according to body mass index categories

Variables	BMI category (kg/m^2) (n = 25,751)					$P^{\dagger}$
	BMI <18.5 (Underweight)	18.5 ≤ BMI < 25 (Normal range)	25 ≤ BMI < 30 (Obese 1)	30 ≤ BMI < 35 (Obese 2)	BMI ≥35 (Obese 3)	
No. patients	926	14,241	7,962	2,037	585	
Men : women	403:523	9328:4913	5,361:2,601	1,221:816	331:254	
Age (years)	73.0 (68.0–80.0)	71.0 (64.0–77.0)	66.0 (57.0–73.0)	59.0 (49.0–69.0)	52.0 (45.0–62.0)	<0.001
Duration of diabetes (years)	16.9 (11.3–24.1)	14.7 (9.3–21.1)	12.5 (7.4–17.5)	10.1 (5.8–15.4)	8.7 (4.7–13.5)	<0.001
Glycated hemoglobin (%)	6.8 (6.4–7.3)	6.9 (6.5–7.3)	7.0 (6.6–7.5)	7.0 (6.6–7.6)	7.1 (6.5–7.7)	<0.001
eGFR (10 mL/min/1.73 m^2)	6.9 (5.8–8.2)	6.8 (55.9–79.7)	6.9 (5.7–8.1)	7.2 (5.9–8.6)	7.7 (6.3–9.2)	<0.001
Biguanide usage	396 (42.8)	8,576 (60.2)	5,652 (71.0)	1,507 (74.0)	451 (77.1)	<0.001
Sulfonylurea usage	301 (32.5)	4,970 (34.9)	2,521 (31.7)	497 (24.4)	135 (23.1)	<0.001
α-Glucosidase inhibitor usage	232 (25.1)	2,611 (18.3)	1,002 (12.6)	197 (9.7)	52 (8.9)	<0.001
Thiazolidinedione usage	61 (6.6)	1,212 (8.5)	1,050 (13.2)	383 (18.8)	158 (27.0)	<0.001
Glinide usage	153 (16.5)	1,224 (8.6)	407 (5.1)	73 (3.6)	21 (3.6)	<0.001
DPP4i usage	771 (83.3)	11,365 (79.8)	5,707 (71.7)	1,299 (63.8)	328 (56.1)	<0.001
SGLT2i usage	57 (6.2)	2,518 (17.7)	2,934 (36.9)	1,062 (52.1)	383 (65.5)	<0.001
One OAD monotherapy	322 (34.8)	3847 (27.0)	1892 (23.8)	460 (22.6)	127 (21.7)	<0.001
Two OADs combination therapy	276 (29.8)	4613 (32.4)	2407 (30.2)	626 (30.7)	156 (26.7)	
Three OADs combination therapy	224 (24.2)	3926 (27.6)	2272 (28.5)	564 (27.7)	155 (26.5)	
Four OADs combination therapy	96 (10.4)	1657 (11.6)	1210 (15.2)	322 (15.8)	115 (19.7)	
Five OADs combination therapy	7 (0.8)	191 (1.3)	175 (2.2)	64 (3.1)	28 (4.8)	
Six OADs combination therapy	1 (0.1)	7 (0.0)	6 (0.1)	1 (0.0)	4 (0.7)	

Data are presented as median (interquartile range [IQR]) or patent number (%). †Statistical analysis was carried out using the Kruskal–Wallis test χ^2-test. $P < 0.05$ was considered significant. BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; OADs, oral antidiabetic drugs; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

first-line OADs for type 2 diabetes mellitus patients in East Asia, including Japan[33].

In contrast, 59% of type 2 diabetes mellitus patients had a BMI ≥30 kg/m^2 in the Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes (SHIELD), and 51% of them had a BMI ≥30 kg/m^2 in National Health and Nutrition Examination Surveys (NHANES)[34]. This is a large difference from the results of the present study with Japanese type 2 diabetes mellitus patients, of whom 10.2% had a BMI ≥30 kg/m^2. Such a difference in BMI leads to selection of different OADs between Japan and USA. It is very important to focus on the difference in BMI of type 2 diabetes mellitus patients between Japan and Western countries. Iwahashi *et al.* found that insulin secretion was lower in Japanese type 2 diabetes mellitus patients than in white patients, but Japanese patients with a BMI ≥25 kg/m^2 maintained their insulin secretory capacity compared with those with BMI <25 kg/m^2[35]. The main cause of type 2 diabetes mellitus in Japanese people is lesser insulin secretion than in white people[36], but the present study showed that insulin resistance was very much involved in the pathophysiology of Japanese diabetes patients with high BMIs.

The American Diabetes Association and the European Association for the Study of Diabetes have set guidelines for diabetes treatment that 'metformin should be started when type 2 diabetes is diagnosed unless contraindicated' because of its efficacy, safety and economy[5,6]. It was reported that metformin accounted for 77% of the first-line OADs in the USA in 2016. At the same time, however, an SU was prescribed as an OAD in combination therapy[17]. It is interesting that an SU was used more than SGLT2is in the USA, where more than half of type 2 diabetes mellitus patients had a BMI ≥30 kg/m^2.

There were several strengths of the present study. First, the target patients for this study were collected from all over Japan, including an extremely large number of patients in the analysis. Second, OAD prescribing patterns of Japanese diabetologists, rather than general clinicians, were analyzed. It is considered that Japanese diabetologists are familiar with not only the Japan Diabetes Society guidelines, but also guidelines for diabetes mellitus treatment in Western countries. Third, Japanese patients can select any clinician for treatment of their diseases, and Japanese clinicians can freely select any drugs according to their evaluation of the status of each patient[8], because the Japanese public health insurance system imposes no limitations. Japanese type 2 diabetes mellitus patients can receive any type of OADs, paying <30% of the cost. Therefore, the disparity in type 2 diabetes treatment available to individual patients is small in Japan[37]. Finally, the American Diabetes Association guidelines published in 2021 were changed to reflect that additional or alternative OADs to BGs can be considered in special circumstances, such as in individuals with established or increased

risks of cardiovascular or renal complications[38]. These changes are exactly in line with the results of the present study.

The present study had several limitations. First, among the clinical parameters, the focus was on the BMI, as OAD prescribing patterns were analyzed according to BMI. However, prescribing patterns could not be analyzed by other clinical parameters, such as blood pressure and eGFR. The relationships between other parameters and OAD usage will need to be considered in the future. In particular, OAD utilization patterns based on the prevalence of cardiovascular disease and heart failure could not be analyzed, because cardiovascular disease and heart failure were not included in the JDDM basic research data extracted from CoDiC. In the latest guidelines of Western countries, the presence or absence of cardiovascular disease and that of heart failure are also one of the bases for OAD selection[6,38]. Second, it was not possible to compare the OAD prescription patterns between diabetologists and general clinicians in the present study. The CoDiC database, used in the present study, is not available to general clinicians, because it is a database specialized for diabetologists registered in JDDM. Murayama *et al*., however, reported that general clinicians tended to consider BMI as the basis for selection more than diabetologists when selecting metformin[37]. We hope that OAD prescription pattern analysis of general clinicians will be carried out in the future.

In the treatment of diabetes, it is important to pay attention to the patients' comorbidities and prevent diabetic complications. The present study focused on BMI among the patients' comorbidities and analyzed the OAD prescribing patterns. We believe that the results of the present study will be accepted by many Japanese diabetologists as a general prescription pattern for Japanese type 2 diabetes patients, and at the same time will be an opportunity for many diabetologists to confirm the appropriateness of their treatment strategies. In addition, we believe that the present study provides valuable suggestions for the treatment of Japanese patients with type 2 diabetes when different combination patterns of OADs must be selected due to comorbidities and diabetic complications. These findings have important implications for the treatment of type 2 diabetes mellitus patients, not only in Japan, but also in Asian countries where the number of type 2 diabetes mellitus patients continues to increase[39,40].

ACKNOWLEDGMENTS

The authors thank the following members of JDDM who participated in this study (by prefecture, in alphabetical order): (Hokkaido) Dr Atsushi Hasegawa, Dr Masakazu Kato, Dr Yoshio Kurihara, Dr Naoki Manda, Dr Kazuhiro Miyazawa, Dr Tetsuya Moriai, Dr Kenichi Tsuchida, Dr Daishiro Yamada and Dr Haruhiko Yoshimura; (Aomori) Dr Makoto Nakazono; (Iwate) Dr Yasushi Ishigaki and Dr Yoshihiko Takahashi; (Miyagi) Dr Fuminobu Okuguchi; (Yamagata) Dr Hiroshi Yamaguchi; (Hukushima) Dr Takashi Ajihara; (Ibaraki) Dr Takeshi Osonoi, Dr Miyoko Saito, Dr Akimitsu Takahashi and Dr Koichi Kawai; (Chiba) Dr Shigetake Ko, Dr Susumu Nakamura, Dr Akira Tsuruoka and Dr Daigaku Uchida; (Tokyo) Dr Mitsutoshi Kato, Dr Hiroshi Takamura, Dr Osamu Tomonaga and Dr Akio Ueki; (Kanagawa) Dr Koichi Hirao, Dr Kotaro Iemitsu, Dr Akira Kanamori, Dr Hajime Maeda, Dr Masahiko Takai and Dr Hiroshi Takeda; (Niigata) Dr Masato Takaki; (Toyama) Dr Hikari Suzuki; (Nagano) Dr Yuki Kono; (Shizuoka) Dr Sumio Kato; (Mie) Dr Hiroshi Hayashi, [Shiga] Dr Atsunori Kashiwagi and Dr Ituko Miyazawa; (Nara) Dr Akiko Hosokawa and Dr Takashi Noto; (Yamaguchi) Dr Koichi Iwasaki; (Kagawa) Dr Masahiro Iwamoto; (Fukuoka) Dr Masae Minami, Dr Hiroshi Ninomiya, Dr Kokichi Tanaka and Dr Yoshifumi Yokomizo; (Kumamoto) Dr Kohei Yamaguchi; (Oita) Dr Katsushige Abe and Dr Nobuyuki Abe; (Miyazaki) Dr Nobuki Yano; (Kagoshima) Dr Michiko Chosa; and (Okinawa) Dr Takako Arakaki.

DISCLOSURE

SS has received lecture fees from Novo Nordisk Pharma, Eli Lilly Japan and Sanofi K.K. HM has received research support unrelated to this study from Astellas Pharma Inc., Astra Zeneca K.K., Ono Pharmaceutical, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Daiichi Sankyo, Mitsubishi Tanabe Pharma, and Sano, and lecture fees from Astellas Pharma, Taisho Toyama Pharmaceutical, Ono Pharmaceutical, Novo Nordisk Pharma, Eli Lilly Japan, MSD, Daiichi Sankyo, Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Sano, Kowa Pharmaceutical and Takeda Pharmaceutical. NY, IK, KA, MO, YF, HY, KY and H.S. declare no conflict of interest.

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