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ORIGINAL ARTICLE

Time trends (2012–2020) in glycated hemoglobin and adherence to the glycemic targets recommended for elderly patients by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee among memory clinic patients with diabetes mellitus

Taiki Sugimoto[1,2]*, Hisashi Noma[3], Yujiro Kuroda[1], Nanae Matsumoto[2], Kazuaki Uchida[2,4], Yoshinobu Kishino[2,5], Naoki Saji[2], Shumpei Niida[6], Takashi Sakurai[1,2,5]

[1]Department of Prevention and Care Science, Research Institute, National Center for Geriatrics and Gerontology, Obu, Japan, [2]Center for Comprehensive Care and Research on Memory Disorders, Hospital, National Center for Geriatrics and Gerontology, Obu, Japan, [3]Department of Data Science, The Institute of Statistical Mathematics, Tokyo, Japan, [4]Department of Public Health, Graduate School of Health Sciences, Kobe University, Kobe, Japan, [5]Department of Cognition and Behavior Science, Nagoya University Graduate School of Medicine, Nagoya, Japan, and [6]National Center for Geriatrics and Gerontology, Research Institute, Obu, Japan

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***Correspondence**
Taiki Sugimoto
Tel.: +81-562-46-2311
Fax: +81-562-46-8394
E-mail address:
taiki-s@ncgg.go.jp

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ABSTRACT

Aims/Introduction: To investigate the changes in the glycated hemoglobin (HbA1c) levels and the relative status of the glycemic control related to the new glycemic targets recommended by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee in 2016 in patients with diabetes mellitus visiting a memory clinic from 2012 to 2020.

Materials and Methods: This cross-sectional study included 1,436 patients aged ≥65 years with diabetes. Patients were categorized into three categories as follows: category I, intact cognitive function and activities of daily living (ADL); category II, mild cognitive deficits or impaired instrumental ADL; and category III, moderate to severe cognitive impairment or impaired basic ADL. Trends in HbA1c levels, glycemic control status (optimally/poorly/excessively controlled) and proportion of individuals receiving drugs potentially associated with severe hypoglycemia among all patients and categories (I, II or III) from 2012 to 2020 were examined using linear, logistic and multinominal logistic regression models adjusted for confounding factors.

Results: Between 2012 and 2020, the HbA1c levels, as well as the proportion of patients with poor glycemic control, increased, whereas the proportion of patients with excessive glycemic control and those receiving drugs potentially associated with severe hypoglycemia decreased.

Conclusions: Increased levels of HbA1c and decreased proportions of individuals under excessive glycemic control might reflect recent treatment strategies that avoid hypoglycemia in older patients. Given the adverse complications associated with hyperglycemia, more flexible and individualized glycemic targets based on comprehensive assessments, including vascular complications and comorbidities, might be necessary.

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INTRODUCTION

The prevalence of diabetes mellitus among older adults is increasing[1]. In Japan, the prevalence of diabetes mellitus among adults aged ≥70 years is estimated to be 26.4% and 19.6% in men and women, respectively[2]. Diabetes mellitus is associated with an increased risk of cancer[3], depression[4], cognitive decline, dementia[5,6], and microvascular and macrovascular complications[7]. Developing successful strategies to prevent adverse health consequences and maintain the quality of life for patients with diabetes is considered an urgent priority nowadays.

Previous randomized controlled trials focused on the ability of intensive glycemic control to prevent adverse health outcomes among older adults; however, no reduction in major cardiovascular events[8–10] or microvascular complications[8,10] was observed. Furthermore, intensive interventions to reduce glycated hemoglobin (HbA1c) levels for 3.5 years elevated mortality with no reduction in major cardiovascular events[10]. In addition, it has been reported that a severe hypoglycemia associated with intensive glycemic control might increase the risk of falls, fall-related fractures, cognitive decline and dementia[11,12]. Based on this evidence, several guidelines and position statements[13–16] to date have suggested exercising care to avoid hypoglycemia, and have emphasized the importance of determining glycemic targets for older adults by considering patient characteristics, such as age, cognitive and physical function, ability to carry out activities of daily living (ADL), and comorbidities.

In 2013, the Japan Diabetes Society (JDS) published practice guidelines for the treatment of diabetes and suggested a new concept for glycemic control[17]. In the declaration, the optimal HbA1c level was set at <7.0% to prevent microvascular complications. However, for individuals with treatment objectives aimed at normal glycemia, the HbA1c level was set at <6%, and for those with hypoglycemia as a potential intervention side-effect, the ideal level was set at <8.0%[17]. The JDS/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes proposed the "Glycemic Targets for Elderly Patients with Diabetes"[18] in 2016 and a Practical Guideline for the Treatment of Elderly Diabetes[19] in 2017. These reports proposed that the glycemic target, HbA1c, should be determined by classifying the patient into one of the following categories: category I, intact cognitive function and ADL; category II, mild cognitive impairment to mild dementia or impairment of instrumental ADL; and category III, moderate or severe dementia, impairment of basic ADL, or presence of multiple comorbidities. The lower limit of each glycemic target is specified for different drugs associated with a high risk of severe hypoglycemia[18].

This proposal of new glycemic targets has significantly affected clinical practices, especially for older patients with diabetes and cognitive impairment and/or disability[20]. However, there has been no study analyzing the impact of the new glycemic targets on patients with diabetes. Therefore, the present study aimed to examine the changes in HbA1c and the relative status of glycemic control associated with the new glycemic targets from 2012 to 2020 among patient with diabetes mellitus visiting a memory clinic.

MATERIALS AND METHODS

Study population

The present cross-sectional study included patients who met the following criteria: (i) visiting the National Center for Geriatrics and Gerontology memory clinic of Japan from January 2012 to December 2020; (ii) completed a comprehensive geriatric assessment (CGA) including cognitive and blood tests; (iii) aged ≥65 years; and (iv) had a self-reported history of diabetes, antidiabetic medications use, or HbA1c levels ≥6.5%. As patients usually undergo comprehensive geriatric assessment, including blood tests, on their first visit, almost all data were derived from their first visit. Only their first data, for both comprehensive geriatric assessment and blood test results, were assigned to the respective calendar year, even if the patients had multiple visits to the memory clinic.

All participants approved the use of their data in the study, and the Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol (approval number #1569).

Measurements and categorization of patients

General patient information, such as age, sex, education, body mass index, HbA1c levels, estimated glomerular filtration rate and current medications, was retrieved from patient clinical charts. The basic and instrumental ADL were assessed using the Barthel Index[21] and modified Lawton Index[22], respectively. Those with scores of <80 were considered as having disabled basic ADL. Three items of the Lawton Index ("preparing food," "housecleaning" and "laundry") were not applicable to many of the male patients; therefore, these three items were excluded from the calculation of the Lawton Index for men. Those who had a total score of <5 in men and <8 in women were considered as having disabled instrumental ADL.

Global cognitive function was assessed using the Mini-Mental State Examination (MMSE)[23]. The severity of cognitive impairment was operationally categorized into intact cognitive function (MMSE score, ≥28), mild cognitive deficits (MMSE score, 21–27) or moderate-to-severe impairment (MMSE score, 0–20)[24,25].

Ultimately, patients were categorized based on their combined cognitive function and ADL ability as follows: intact cognitive function and ADL (category I), mild cognitive deficits or impairment of instrumental ADL (category II) and moderate-to-severe cognitive impairment or impairment of basic ADL (category III)[18].

Status of glycemic control

To assess the status of glycemic control relative to the glycemic targets of the JDS/JGS Joint Committee[18], the patients were

Table 1 | Classification of patients' status of glycemic control (glycated hemoglobin) related to the "Glycemic Targets for Elderly Patients with Diabetes" by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee

	Category I	Category II	Category III
Patients not receiving drugs associated with high risk of severe hypoglycemia			
Optimally controlled	<7.0%	<7.0%	<8.0%
Poorly controlled	≥7.0%	≥7.0%	≥8.0%
Patients receiving drugs associated with high risk of severe hypoglycemia			
Optimally controlled	6.5–7.4% (65–74 years) 7.0–7.9% (≥75 years)	7.0–7.9%	7.5–8.4%
Poorly controlled	≥7.5% (65–74 years) ≥8.0% (≥75 years)	≥8.0%	≥8.5%
Excessively controlled	<6.5% (65–74 years) <7.0% (≥75 years)	<7.0%	<7.5%

Category I, intact cognitive function and activities of daily living (ADL); category II, mild cognitive deficits or impairment of instrumental ADL; category III, moderate or severe cognitive impairment, or impairment of basic ADL.

divided into optimally, poorly and excessively controlled groups, according to whether they were receiving insulin, sulfonylureas and/or glinides. HbA1c levels of each category are shown in Table 1.

Statistical analysis

Trends in mean HbA1c levels were analyzed using the Jonckheere–Terpstra trend test. Trends in the proportion of individuals receiving drugs that are potentially associated with severe hypoglycemia and that of those in the optimally, poorly and excessively controlled groups were analyzed using the Cochran–Armitage test and the multinominal Cochran–Armitage test[26], respectively. In addition, multivariate analysis using linear, logistic and multinominal logistic regression models were carried out by adjusting potential confounding factors of age, sex, education and body mass index for the continuous, dichotomous and multinominal outcomes, respectively. Statistical analyses comparing the three cognitive/ADL categories (I, II and III) and the prescription drugs associated with high risk of severe hypoglycemia were carried out.

Also, we analyzed the trends in the proportion of individuals receiving drugs that are not potentially associated with severe hypoglycemia (biguanides, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter 2 inhibitors) using the Cochran–Armitage test.

Differences in mean HbA1c levels between 2012–2015 and 2016–2020 were also compared to understand the influence of published glycemic guideline targets on glycemic levels.

All statistical analyses were carried out using Stata version 14.0 (Stata Corp, College Station, TX, USA) and R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). All *P*-values are two-tailed, and the significance level was set at 0.05.

RESULTS

Overall, 1,436 patients with diabetes aged ≥65 years were included in the present study. A flowchart of patient selection is shown in Figure S1. Patient characteristics by calendar year are shown in Table 2.

A significant positive trend was found ($P = 0.005$) for mean HbA1c across all patients from 2012 to 2020. An increasing HbA1c trend from 2012 to 2020 was only found in category III patients ($P < 0.001$; Figure 1). In linear regression analyses adjusted for the potential confounding factors, these trends remained significant in all patients ($P = 0.022$; Table 3) and in category III patients ($P = 0.002$; Table 3). Figure S2 shows time trends in HbA1c levels in patients with optimally, poorly or excessively controlled glycemic levels in each category. In category II patients, a decreasing HbA1c trend was significantly found in patients with poorly controlled HbA1c levels ($P = 0.012$; Figure S2b), whereas this trend was not significant after adjustment for the potential confounding factors ($P = 0.109$).

From 2012 to 2020, the percentage of patients with poorly controlled glycemic levels increased, whereas that of those with excessively controlled glycemic levels decreased (Figure 2a; $P < 0.001$). The proportion of individuals receiving drugs that are potentially associated with severe hypoglycemia deceased from 2012 to 2020 (Figure 2b; $P < 0.001$). These trends were found in categories II ($P = 0.002$; Table 3) and III patients ($P < 0.001$; Table 3).

Overall, the mean HbA1c levels significantly increased from 2012 to 2020 regardless of the medication status for hypoglycemia (not receiving medication, $P = 0.001$; receiving medication, $P = 0.025$), and the proportion of patients with poorly controlled glycemic levels increased significantly (not receiving medication, $P < 0.001$; receiving medication, $P = 0.001$; Table S1).

Figure S3 shows the trends in the proportions of patients receiving drugs that are not potentially associated with severe hypoglycemia. From 2012 to 2020, the percentage of patients receiving biguanides (Figure S3a, $P = 0.018$), glucagon-like peptide-1 receptor agonists (Figure S3e, $P = 0.006$) and SGLT2 inhibitors (Figure S3f, $P < 0.001$) significantly increased, whereas that of those receiving α-glucosidase inhibitors decreased (Figure S3b, $P = 0.005$).

Table 2 | Characteristics of patients from 2012 to 2020

Years	2012	2013	2014	2015	2016	2017	2018	2019	2020
Sample (*n*)	190	170	194	141	138	161	165	125	152
First visit, *n* (%)	183 (96.3)	164 (96.5)	190 (97.9)	132 (93.6)	131 (94.9)	157 (97.5)	164 (99.4)	125 (100.0)	140 (92.1)
Mean age, years (SD)	77.7 (5.7)	78.2 (6.2)	78.8 (6.0)	78.1 (5.6)	77.9 (5.8)	78.5 (6.0)	78.1 (6.3)	79.0 (5.3)	79.2 (5.4)
Female, *n* (%)	121 (63.7)	108 (63.5)	109 (56.2)	77 (54.6)	73 (52.9)	80 (49.7)	80 (48.5)	73 (58.4)	97 (63.8)
Mean education, years (SD)	10.1 (2.5)	10.5 (2.7)	10.3 (2.8)	10.6 (2.5)	10.8 (2.6)	10.5 (2.9)	10.8 (3.0)	10.5 (2.2)	11.1 (2.3)
Mean BMI, kg/m^2 (SD)	23.4 (3.9)	23.2 (3.5)	23.1 (4.1)	22.9 (3.9)	23.5 (4.0)	23.2 (3.7)	23.1 (3.8)	23.5 (3.5)	22.9 (3.4)
Mean eGFR, mL/min/1.73 m^2 (SD), *n* = 1,428	63.9 (20.2)	63.0 (18.8)	63.9 (20.3)	63.5 (23.0)	61.3 (18.6)	64.8 (20.9)	65.7 (17.6)	64.6 (19.5)	62.1 (18.6)
Barthel Index, mean (SD)	92.6 (13.5)	90.6 (16.8)	93.4 (13.0)	93.3 (13.3)	94.1 (12.2)	95.3 (10.0)	95.5 (9.6)	94 (11.5)	94.1 (11.3)
Lawton Index, mean (SD)									
Female (/8)	5.3 (2.2)	5.2 (2.5)	5.3 (2.3)	5.5 (2.4)	5.7 (2.1)	5.9 (2.1)	6.0 (2.2)	5.7 (2.0)	5.7 (2.3)
Male (/5)	3.0 (1.6)	3.1 (1.6)	3.3 (1.6)	3.3 (1.5)	3.3 (1.6)	3.7 (1.3)	3.6 (1.4)	3.4 (1.5)	3.3 (1.6)
Mean MMSE (SD)	20.2 (5.1)	19.9 (6.0)	20.6 (6.0)	20.8 (5.6)	21.1 (5.2)	20.9 (6)	21.0 (4.6)	20.0 (5.0)	21.3 (5.3)
Category, *n* (%)									
Category I	11 (5.8)	8 (4.7)	21 (10.8)	11 (7.8)	13 (9.4)	21 (13.0)	12 (7.3)	5 (4.0)	8 (5.3)
Category II	75 (39.5)	69 (40.6)	78 (40.2)	66 (46.8)	62 (44.9)	72 (44.7)	77 (46.7)	51 (40.8)	85 (55.9)
Category III	104 (54.7)	93 (54.7)	95 (49.0)	64 (45.4)	63 (45.7)	68 (42.2)	76 (46.1)	69 (55.2)	59 (38.8)

Category I, intact cognitive function and activities of daily living (ADL); category II, mild cognitive deficits or impairment of instrumental ADL; category III, moderate or severe cognitive impairment, or impairment of basic ADL. BMI, body mass index; eGFR, estimated glomerular filtration rate; MMSE, Mini-Mental State Examination; SD, standard deviation.

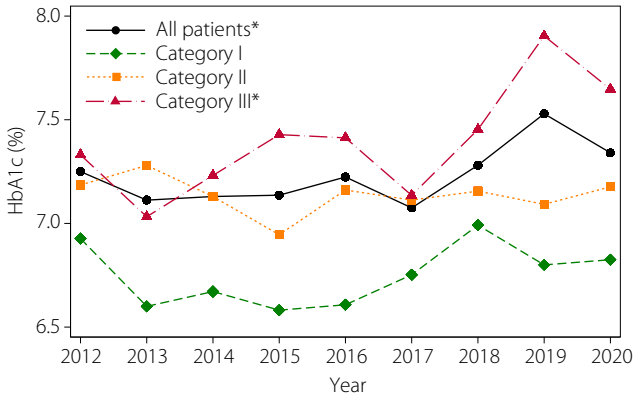

Figure 1 | Time trends in glycated hemoglobin (HbA1c) among all patients and each category between 2012 and 2020. *Increase in HbA1c levels among all patients and those in category III was statistically significant (P = 0.022 and 0.002 respectively) after adjusting the confounding factors. Category I, intact cognitive function and activities of daily living (ADL); category II, mild cognitive deficits or impairment of instrumental ADL; category III, moderate or severe cognitive impairment, or impairment of basic ADL.

Comparisons between 2012–2015 and 2016–2020 showed a small significant increase in HbA1c levels (7.2% ± 1.3% vs 7.3% ± 1.3%; P = 0.043), a significant decrease in the percentage of individuals receiving medications that are associated with high risk of severe hypoglycemia (34.0% vs 20.1%, P < 0.001), and significant increase and decrease in the proportions of patients with poorly and excessively controlled glycemic levels (22.5% vs 31.6%, P = 0.002; 15.3% vs 6.5%; P < 0.001; respectively, Table S2).

DISCUSSION

This is the first study to report changes in HbA1c levels and status of glycemic control relative to the glycemic targets set by the JDS/JGS Joint Committee between 2012 and 2020 among patients with diabetes mellitus visiting a memory clinic. The present findings show that the glycemic targets proposed in April 2016 had a significant impact on diabetes treatment diabetes treatment and clinical practices.

We reported a significant decreasing trend in the proportion of patients with excessively controlled glycemic levels and those receiving drugs that are potentially associated with severe hypoglycemia between 2012 and 2020. In contrast, the proportion of patients receiving biguanides and SGLT2 inhibitors increased during the study period. A retrospective nationwide study including 1,136,723 patients with type 2 diabetes in Japan showed that the use of biguanides and SGLT2 inhibitors increased from 2014 to 2017, whereas the use of other drugs, including sulfonylureas, decreased[27]. Another study that analyzed the data provided by the Japan Diabetes Clinical Data Management Study Group also showed that the usage of sulfonylureas decreased, whereas the usage of biguanides increased

Table 3 | Time trends in the status of glycemic control related to the glycemic targets recommended for elderly patients by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee

Years	2012	2013	2014	2015	2016	2017	2018	2019	2020	*P* for trend	*P* for trend*
All patients (*n* = 1436)											
Sample, *n*	190	170	194	141	138	161	165	125	152	–	–
HbA1c, mean (SD)	7.3 (1.5)	7.1 (1.2)	7.2 (1.1)	7.1 (1.4)	7.2 (1.4)	7.1 (1.1)	7.3 (1.3)	7.5 (1.6)	7.3 (1.1)	0.005	0.022
SU/insulin/glinides, *n* (%)	63 (33.2)	53 (31.2)	74 (38.1)	46 (32.6)	39 (28.3)	33 (20.5)	25 (15.2)	26 (20.8)	26 (17.1)	<0.001	<0.001
Status of glycemic control, *n* (%)											
Optimally controlled	111 (58.4)	109 (64.1)	128 (66.0)	85 (60.3)	85 (61.6)	106 (65.8)	111 (67.3)	73 (58.4)	84 (55.3)	<0.001	<0.001
Poorly controlled	50 (26.3)	32 (18.8)	38 (19.6)	36 (25.5)	38 (27.5)	43 (26.7)	47 (28.5)	45 (36)	61 (40.1)		
Excessively controlled	29 (15.3)	29 (17.1)	28 (14.4)	20 (14.2)	15 (10.9)	12 (7.5)	7 (4.2)	7 (5.6)	7 (4.6)		
Category I (*n* = 110)											
Sample, *n*	11	8	21	11	13	21	12	5	8	–	–
HbA1c, mean (SD)	6.9 (0.8)	6.6 (0.5)	6.7 (0.6)	6.6 (0.4)	6.6 (0.4)	6.8 (0.5)	7.0 (0.8)	6.8 (0.7)	6.8 (0.5)	0.455	0.464
SU/insulin/glinides, *n* (%)	3 (27.3)	2 (25.0)	6 (28.6)	2 (18.2)	3 (23.1)	4 (19.1)	3 (25.0)	1 (20.0)	1 (12.5)	0.404	0.601
Status of glycemic control											
Optimally controlled	6 (54.6)	4 (50.0)	19 (90.5)	8 (72.7)	12 (92.3)	16 (76.2)	6 (50)	4 (80.0)	4 (50.0)	0.442	0.212
Poorly controlled	4 (36.4)	2 (25.0)	1 (4.8)	2 (18.2)	1 (7.7)	5 (23.8)	5 (41.7)	1 (20.0)	3 (37.5)		
Excessively controlled	1 (9.1)	2 (25.0)	1 (4.8)	1 (9.1)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (12.5)		
Category II (*n* = 635)											
Sample, *n*	75	69	78	66	62	72	77	51	85	–	–
HbA1c, mean (SD)	7.2 (1.2)	7.3 (1.4)	7.1 (1.1)	6.9 (1.0)	7.2 (1.2)	7.1 (1.2)	7.2 (1.3)	7.1 (1.1)	7.2 (1.0)	0.731	0.806
SU/insulin/glinides, *n* (%)	26 (34.7)	20 (29.0)	31 (39.7)	24 (36.4)	17 (27.4)	17 (23.6)	13 (16.9)	9 (17.7)	10 (11.8)	<0.001	<0.001
Status of glycemic control, *n* (%)											
Optimally controlled	43 (57.3)	43 (62.3)	45 (57.7)	37 (56.1)	32 (51.6)	41 (56.9)	50 (64.9)	28 (54.9)	44 (51.8)	0.006	0.002
Poorly controlled	23 (30.7)	22 (31.9)	24 (30.8)	20 (30.3)	23 (37.1)	23 (31.9)	25 (32.5)	20 (39.2)	40 (47.1)		
Excessively controlled	9 (12.0)	4 (5.8)	9 (11.5)	9 (13.6)	7 (11.3)	8 (11.1)	2 (2.6)	3 (5.9)	1 (1.2)		
Category III (*n* = 691)											
Sample, *n*	104	93	95	64	63	68	76	69	59	–	–
HbA1c, mean (SD)	7.3 (1.7)	7.0 (1.1)	7.2 (1.2)	7.4 (1.7)	7.4 (1.7)	7.1 (1.1)	7.5 (1.4)	7.9 (1.8)	7.6 (1.3)	<0.001	0.002
SU/insulin/glinides, *n* (%)	34 (32.7)	31 (33.3)	37 (39.0)	20 (31.3)	19 (30.2)	12 (17.7)	9 (11.8)	16 (23.2)	15 (25.4)	<0.001	0.001
Status of glycemic control, *n* (%)											
Optimally controlled	62 (59.6)	62 (66.7)	64 (67.4)	40 (62.5)	41 (65.1)	49 (72.1)	55 (72.4)	41 (59.4)	36 (61.0)	<0.001	<0.001
Poorly controlled	23 (22.1)	8 (8.6)	13 (13.7)	14 (21.9)	14 (22.2)	15 (22.1)	17 (22.4)	24 (34.8)	18 (30.5)		
Excessively controlled	19 (18.3)	23 (24.7)	18 (19.0)	10 (15.6)	8 (12.7)	4 (5.9)	4 (5.3)	4 (5.8)	5 (8.5)		

Category I, intact cognitive function and activities of daily living (ADL); category II, mild cognitive deficits or impairment of instrumental ADL; category III, moderate or severe cognitive impairment, or impairment of basic ADL. *Adjusted for age, sex, education, body mass index. HbA1c, glycated hemoglobin; JDS/JGS, Japan Diabetes Society/Japan Geriatrics Society; SD, standard deviation; SU, sulfonylurea.

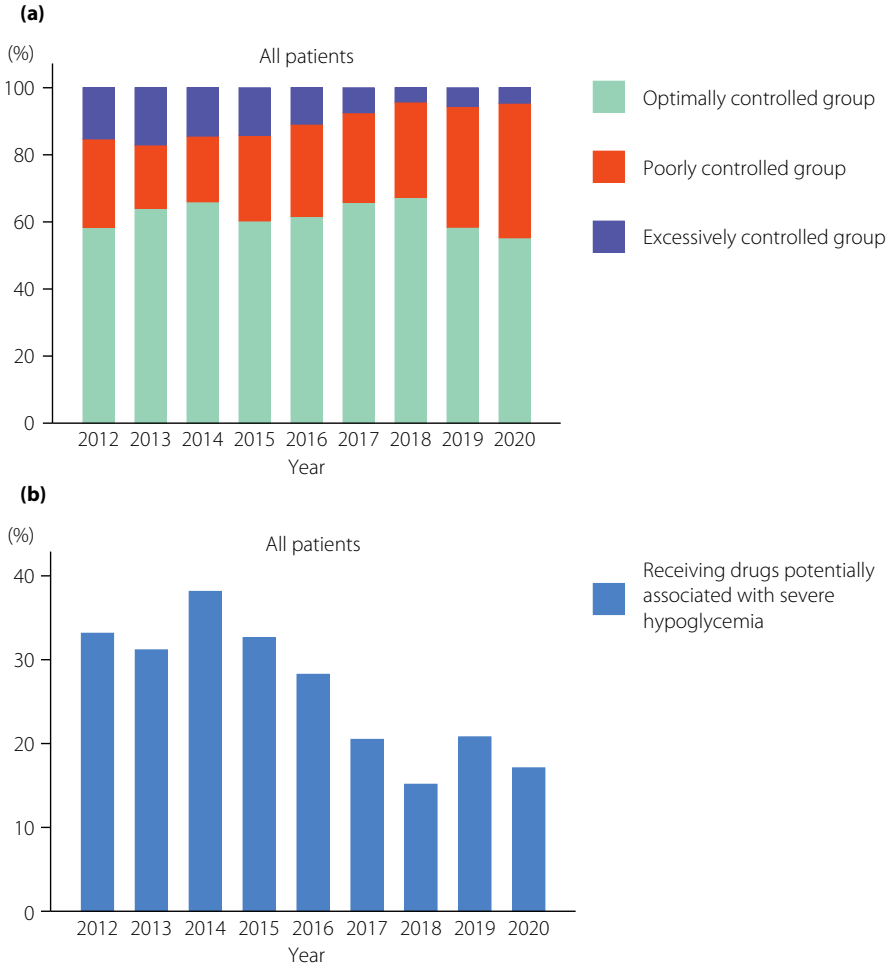

Figure 2 | Time trends in the (a) status of glycemic control relative to the glycemic targets recommended for elderly patients by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee and (b) proportion of patients receiving drugs associated with a high risk of severe hypoglycemia between 2012 and 2020 among all patients.

from 2002 and 2019 among 25,751 patients treated with oral antidiabetic drugs and without insulin or glucagon-like peptide-1 receptor agonists[28]. The current study supported these findings in older patients with diabetes and cognitive impairment. These findings are important given that severe hypoglycemia can lead to adverse health outcomes, such as cognitive decline, disability and mortality[12,29]. In Japan, it was previously shown that patients with excessively and poorly controlled glycemic levels were at a higher risk of basic ADL disability over a 1-year follow up compared with optimally controlled patients[30].

An analysis including 136,931 patients with type 2 diabetes from Germany, Austria, Switzerland and Luxembourg reported that the proportion of patients treated with intrinsic hypoglycemic medications, including insulin, sulfonylurea and glinides, alone or in combination, decreased over the past 15 years[31]. Similar trends were also observed in the USA[32] and Hong Kong[32]. It was reported that such declines in hypoglycemic treatments tend to correspond with decreased severe hypoglycemic events[31,33].

A previous study investigating the association between diabetes medications and metrics from continuous glucose monitoring showed that the use of drugs with a high risk of severe hypoglycemia was associated with time below range (<70 mg/dL) in 172 older adults with type 2 diabetes.[34] Nevertheless, in this study[34] carried out after the proposal of the new glycemic target[18], older patients had a mean time below range of 0.1%, and just two patients received a higher dose of sulfonylureas. These results might be attributed to wide recognition of the Joint Committee's guidelines[34]. Although the current study lacked information about the incidence of hypoglycemic events, our findings suggest that the Joint Committee's guidelines are helpful for reducing hypoglycemia and associated complications in older adults with diabetes mellitus and cognitive impairment.

The current study showed a general increase in HbA1c levels for the entire population, particularly in category III patients (Figure 1). Additionally, regardless of whether receiving drugs associated with a high risk of severe hypoglycemia, HbA1c levels increased over time. The present findings are consistent with a recent cross-sectional analysis investigating trends in HbA1c levels between 2001 and 2018 among 3,539 older Americans aged ≥65 years using the National Health and Nutrition Examination Survey[35]. This analysis showed that the mean HbA1c levels increased slightly from 6.8% (2001–2004) to 7.0% (2013–2018), but this increase did not vary with patient's health status[35]. Conversely, a trend analysis in Germany, Austria, Switzerland and Luxembourg showed that HbA1c levels decreased slightly from 7.3% in 2005 to 7.2% in 2019[31]. That study found that decreases in HbA1c levels did not differ among older patients with or without cognitive impairment[31]. Additionally, HbA1c levels of 719,438 patients with diabetes in Hong Kong (aged ≥20 years) decreased from 7.6% in 2002 to 7.2% in 2016[33]. However, increased mean HbA1c was observed from 2014 to 2016 in that study[33], which may suggest concerns that the trend of HbA1c might rise in more recent years[33]. In the current study, HbA1c levels for all patients remained relatively constant for the first 6 years of the study (from 2012 to 2017), and increases were only observed for the last 3 years of the study (from 2018 to 2020; Figure 1). Thus, increases in HbA1c levels reported in the current study might reflect large increases observed in recent years.

We found a significant increase in the proportion of patients with poorly controlled glycemic levels from 2012 to 2020 (Figure 2a). In this context, Nakanishi *et al.*[36] showed that a poor glycemic control with HbA1c level ≥8.5% increased the risk of microangiopathy, including retinopathy and neuropathy, among Japanese patients aged ≥65 years. In addition, hyperglycemia defined as HbA1c levels ≥8.0% is associated with increased risks of frailty, decreased muscle quality, impaired physical performance, injurious falls requiring hospitalization and mortality in older adults[37–40]. Although the disadvantages of poor glycemic control in older adults is apparent, it might be difficult to archive more stable glycemic targets in patients at risk of developing side-effects from multidrug combination therapies or with serious comorbidities. More flexible and individualized glycemic targets based on comprehensive assessments, including vascular complications and comorbidities, might be necessary.

Intriguingly, despite a clear increase in the percentage of patients with poorly controlled glycemic levels and a dramatic decrease in the percentage of patients with excessively controlled glycemic levels, HbA1c levels of patients in category II remained unchanged during the study period (Table 3). These findings might be attributable to a decreasing HbA1c trend in patients in the poorly controlled group in category II (Figure S2b), showing a possibility that excessive hyperglycemia is decreasing among this population. To examine the impact of the increase of patients with poorly controlled glycemic levels on their health outcomes, further studies investigating the trend in the incidence rate of serious hyperglycemic emergencies, such as diabetic ketoacidosis and hyperglycemic hyperosmolar state, are required.

The current study had several limitations. First, this study focused on older adults with diabetes and cognitive impairment; this might limit its applicability to the general population. Nevertheless, because most of the patients in the current study were first-visit patients who were referred by their general practitioners or family members to our memory clinic, our findings seemed to show a change in glycemic management by their general practitioners. Second, the study focused on patients from Aichi prefecture in Japan and, therefore, might not reflect the glycemic trends nationwide. Third, the current study lacked some information about the duration of diabetes, doses of antidiabetic drugs and diabetic complications that could have impacted glycemic control measurements. Furthermore, the current study lacked information about the annual incidence rates of serious hyperglycemic emergencies and severe hypoglycemic events. Finally, the analyses were descriptive, and could not examine directly how the guideline of the JDS/JGS Joint Committee affected the changes in HbA1c and glycemic control over time.

In conclusion, the HbA1c levels increased, and the proportion of patients under excessive glycemic control decreased in 1,436 patients with diabetes visiting a memory clinic from 2012 to 2020. Over the same period, the proportion of patients categorized as having poor glycemic control increased. These findings might reflect a treatment shift to less stringent glycemic control for older patients to avoid severe hypoglycemia. Given the adverse complications associated with hyperglycemia, flexible and individualized glycemic targets based on a comprehensive patient assessment might be necessary. Further studies providing evidence about optimal glycemic control for older adults with diabetes must be carried out. We hope that the guidelines would be revised and improved in the near future for achieving and maintaining patients' good quality of life.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol (approval number #1569).

Informed consent: All participants provided their written informed consent to participate in this study.
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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 | Patient selection flowchart for analysis.

Figure S2 | Time trends in glycated hemoglobin levels in each status of glycemic control in each category from 2012 to 2020.

Figure S3 | Time trends in the proportions of patients receiving (a) biguanides, (b) α-glucosidase inhibitors, (c) thiazolidinediones, (d) dipeptidyl peptidase-4 inhibitors, (e) glucagon-like peptide-1 receptor agonists and (f) sodium–glucose cotransporter 2 inhibitors from 2012 to 2020.

Table S1 | Time trends in the status of glycemic control related to the glycemic targets recommended for elderly patients by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee among patients not receiving or receiving drugs associated with high risk of severe hypoglycemia.

Table S2 | Difference in status of glycemic control related to the glycemic targets recommended for elderly patients by the Japan Diabetes Society/Japan Geriatrics Society Joint Committee between 2012–2015 and 2016–2020.